Cardiology Research and Practice

Cancer and Cardiovascular Disease

Guest Editors: Syed Wamique Yusuf, Carlo Cipolla, Jean-Bernard Durand, and Daniel J. Lenihan

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Editorial Board

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Editorial

Cancer and Cardiovascular Disease

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Cancer and cardiovascular disease (CVD) are the two most common causes of mortality and morbidity worldwide. The incidence of both cancer and cardiovascular disease increases with age. With increased life expectancy, the burden of both these diseases will increase substantially over the next generation. Advancement in cancer therapy and supportive care has led to increasing number of survivors of childhood cancer. Seventy percent of the children diagnosed with malignancy before the age of 15 years will have a disease-free 5-year survival from diagnosis. Cancer is now being recognized as a chronic disease as evidenced by a growing number of cancer survivors that currently exceeds 11 million. With further improvement in cancer therapy, this number will likely increase in years to come. As the numbers of survivors grow so does the number of patients living with the late effects of cancer-related cardiotoxicity. Amongst Hodgkin lymphoma patients who have received radiation, CVD is one of the most common causes of death.

Physicians and ancillary staff frequently have to take care of patients with concomitant cancer and cardiovascular disease. Some cardiac diseases predates the diagnosis of cancer, whereas other conditions like chemotherapy-induced cardiomyopathy and radiation-related heart disease are directly related to the cardiotoxic side effects of cancer therapy. The cardiotoxic side effects of agents like 5-fluouracil, adriamycin, and tyrosine kinase inhibitors are well known. However, the cardiotoxic profiles of newer investigational chemotherapeutic agents are largely unknown.

Chemotherapy frequently induces thrombocytopenia, which in itself poses therapeutic challenge in the management of conditions like acute coronary syndrome, atrial fibrillation, stroke, and prosthetic valves. Evidence-based treatment of cardiovascular disease in cancer patients is lacking largely because all cardiology trials have excluded patients with cancer and similarly cancer trials have excluded patients with significant cardiovascular comorbidity.

While recently some single-center studies have shown the efficacy of medications like ace inhibitors and beta blockers for the treatment of chemotherapy-induced cardiomyopathy, evidence-based treatment of other major cardiovascular diseases in cancer patients is not well established.

In this issue of cancer and cardiovascular disease, we have covered some common conditions like venous thrombosis, cardiovascular effects of radiation therapy, cardiovascular effects of anthracycline in childhood cancer survivors, and management of aortic aneurysm in cancer patients. The use of newer modality, like computed tomographic angiography, may provide a pivotal role in the investigation of cancer patients with concomitant cardiac problem, as outlined in a clinical investigation in this journal. The case reports presented are some conditions that are unique to cancer population. Cardio-oncology is a growing field, and we are encouraged by the number of submissions to our special edition. We hope that the readers will find this special edition useful in their clinical practice.

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Clinical Study

Impact of Cardiac Computed Tomographic Angiography Findings on Planning of Cancer Therapy in Patients with Concomitant Structural Heart Disease

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Background. Exclusion of underlying coronary artery disease (CAD) is essential in the diagnosis of chemotherapy-induced cardiomyopathy. Presence and severity of CAD can also impact the choice of therapy in cancer patients. The value of cardiac computed tomographic angiography (CCTA) in this setting has not been reported. *Methods*. We collected data on the clinical presentation and indications for CCTA performed from January to December 2008 at the University of Texas MD Anderson Cancer Center (MDACC). All examinations were performed using a 64-detector scanner. CCTA results and subsequent treatment decisions were examined. *Results*. A total of 80 patients underwent CCTA during the study period for the following indications (not mutually exclusive): cardiomyopathy of unknown etiology in 33 pts (41.3%), chest pain in 32 (40.0%), abnormal stress test in 16 (20.0%), abnormal cardiac markers in 8 (10.0%), suspected cardiac mass or thrombus in 7 (8.8%). Chemotherapy-induced cardiomyopathy was diagnosed in 18 pts (22.5%). Severe CAD was detected in 22 pts (27.5%); due to concomitant advanced cancer or patient refusal, only 12 underwent coronary angiogram. Of these, 4 pts (5% of total) underwent coronary artery bypass grafting. A total of 41 pts (51.3%) had their cancer management altered based on CCTA findings. *Conclusion*. CCTA is useful in evaluating cancer pts with structural heart disease and can have an impact on the management of cancer and cardiac disease.

1. Introduction

Suspected coronary artery disease (CAD) in patients with a concurrent malignancy greatly impacts prognosis and treatment decisions. Faced with both diseases, appropriate prioritization of care is needed, as some cancer treatments may be cardiotoxic [1] or lead to blood dyscrasias that could discourage the use of commonly prescribed cardiac medications, such as aspirin or heparin products. On the other hand, planning of cardiac invasive testing requires clinicians to take into account cancer status and possible delays in care. Noninvasive coronary anatomical imaging could therefore help with accurate treatment planning prior to using invasive strategies.

Exclusion of significant obstructive CAD in patients with left ventricular (LV) dysfunction and a prior history of exposure to cardiotoxic chemotherapy agents are both needed for the diagnosis of chemotherapy-induced cardiomyopathy (CIC) [2]. In addition, some cancer patients presenting with other findings suggestive of structural heart disease may need an accurate anatomical coronary evaluation. While invasive coronary angiography (ICA) remains the procedure of choice in patients with high pretest probability of CAD, it is not always justified in those with low to intermediate suspicion of CAD [3]. It also carries a risk of bleeding or infectious complications, which may be more likely in cancer patients because of blood dyscrasias or immunosuppression. Ongoing chemotherapy or radiation treatment may also further delay ICA. There is therefore a need for an accurate noninvasive modality to define the coronary anatomy in some cancer patients. Cardiac computed tomographic angiography (CCTA) is such a modality, and has been shown to correlate well with ICA [4–6]. Specifically, its negative predictive value in excluding CAD in the presence

Table 1: Baseline cardiac CT angiogram population characteristics.

Population characteristics	
Age in years (mean ± SD*)	58.8 ± 12.8
Male gender (%)	45 (56.3)
Known coronary artery disease (%)	7 (8.8)
Hypertension (%)	38 (47.5)
Hyperlipidemia (%)	29 (36.3)
Diabetes mellitus (%)	10 (12.5)
Smoking (%)	5 (6.3)
Previous chest/mediastinal radiation (%)	11 (13.8)
Hematologic malignancy (%)	36 (45.0)

*SD: standard deviation.

Table 2: Indications for cardiac computed tomographic angiography.

CCTA* indications	*N* (%)
Left ventricular dysfunction	33 (41.3)
Chest pain/dyspnea	32 (40.0)
Abnormal stress test	16 (20.0)
Abnormal cardiac biomarkers	8 (10.0)
Miscellaneous†	13 (16.3)

*CCTA: cardiac computed tomographic angiography.
†Miscellaneous indications included suspected tumor and/or thrombus (7 patients) and suspected pulmonary embolism (6 patients).
Indications were not mutually exclusive.

of a normal scan is very high [7]. We sought to investigate the impact of CCTA findings on cancer treatment decisions.

2. Methods

This retrospective data review study was approved by the Institutional Review Board (IRB). The clinical presentation and baseline characteristics of patients who underwent CCTA between January and December 2008 at the University of Texas MD Anderson Cancer Center (MDACC) were reviewed. The indications for CCTA were collected, as well as contraindications to invasive angiography, when explicitly documented. The downstream impact of CCTA results on patient care decision-making was ascertained for both cardiac and cancer treatment by review of the medical records. Specific diagnostic or therapeutic steps were considered to be based on CTA results only when medical records explicitly referenced the CTA results and directly linked those decisions with these findings. All statistical analysis was performed using NCSS2001 (Kaysville, Utah).

Prior to CCTA, patients with heart rates above 65 beats per minute on breath holding received beta-blockers (metoprolol, up to 100 mg orally and/or up to 20 mg intravenously). Patients needing heart rate control, but with contraindications to beta-blockers were managed with oral calcium-channel blockers. When blood pressure allowed, patients were also given sublingual nitroglycerin spray 0.4 mg immediately prior to undergoing scan. All studies were performed using a 64-detector scanner (Lightspeed VCT, General Electric Healthcare (GEHC), Milwaukee, WI). A calcium scoring scan was performed using 2.5 mm collimation and 25 cm display field of view with prospective cardiac triggering without intravenous contrast material. 150 mL of 320 mgI/mL contrast material (iodixanol, Visipaque 320, GEHC) was administered at 5 mL/sec, followed by 50 mL of normal saline at 5 mL/sec. A fixed scan delay of 30 seconds was used. Cardiac scanning was performed with 0.625 mm collimation using retrospective cardiac gating and electrocardiographic (ECG) dose modulation. In patients with significant beat to beat heart rate variability or frequent ectopic beats, ECG dose modulation was not used. Data was reconstructed at 0.625 mm slice thickness and 0.4 mm interval at 70%, 75%, and 80% of the R-R interval for coronary analysis and a second series at 1.25 mm slice thickness and 1.25 mm interval with 10 cardiac phases from 5% to 95% of the R-R interval for functional analysis. Additional coronary analysis phases were reconstructed as needed to address motion artifacts on the standard phases. Examinations were interpreted by a thoracic radiologist (GG) with 5 years experience in cardiac CT in conjunction with a cardiologist (ID). Interpretation and postprocessing were performed using an Advantage workstation (GEHC) or an iNtuition workstation (TeraRecon, Inc., San Mateo, CA).

Severe CAD was defined as luminal diameter narrowing estimated to be greater than 70% in at least one vessel or more than 50% left main coronary stenosis. Coronary stenosis that did not meet the defined criteria for severe was termed mild to moderate CAD. A diagnosis of chemotherapy-induced cardiomyopathy was established by LV dysfunction with prior cardiotoxic chemotherapy exposure and absence of significant obstructive CAD. Thrombocytopenia was defined as platelet count less than 50,000 per μL, and leucopenia as white blood cell count below 4,000 per μL.

Table 3: Relative contraindications for invasive coronary angiography.

Invasive angiography contraindications	*N* (%)
Low to moderate probability for CAD*	49 (61.3)
Leucopenia/thrombocytopenia	15 (19.2)
Concomitant chemotherapy or radiation	20 (25.0)
≥1 above contraindication	72 (90)

*CAD: coronary artery disease.
Contraindications are not mutually exclusive.

Table 4: Coronary findings of cardiac computed tomographic angiography.

CCTA* results	*N* (%)
Normal coronary arteries	21 (26.3)
Mild to moderate CAD†	37 (46.2)
Severe‡ CAD	22 (27.5)

*CCTA: cardiac computed tomographic angiography.
†CAD: coronary artery disease.
‡Severe CAD defined as luminal narrowing estimated to be greater than 70% in at least one vessel or more than 50% left main coronary stenosis.

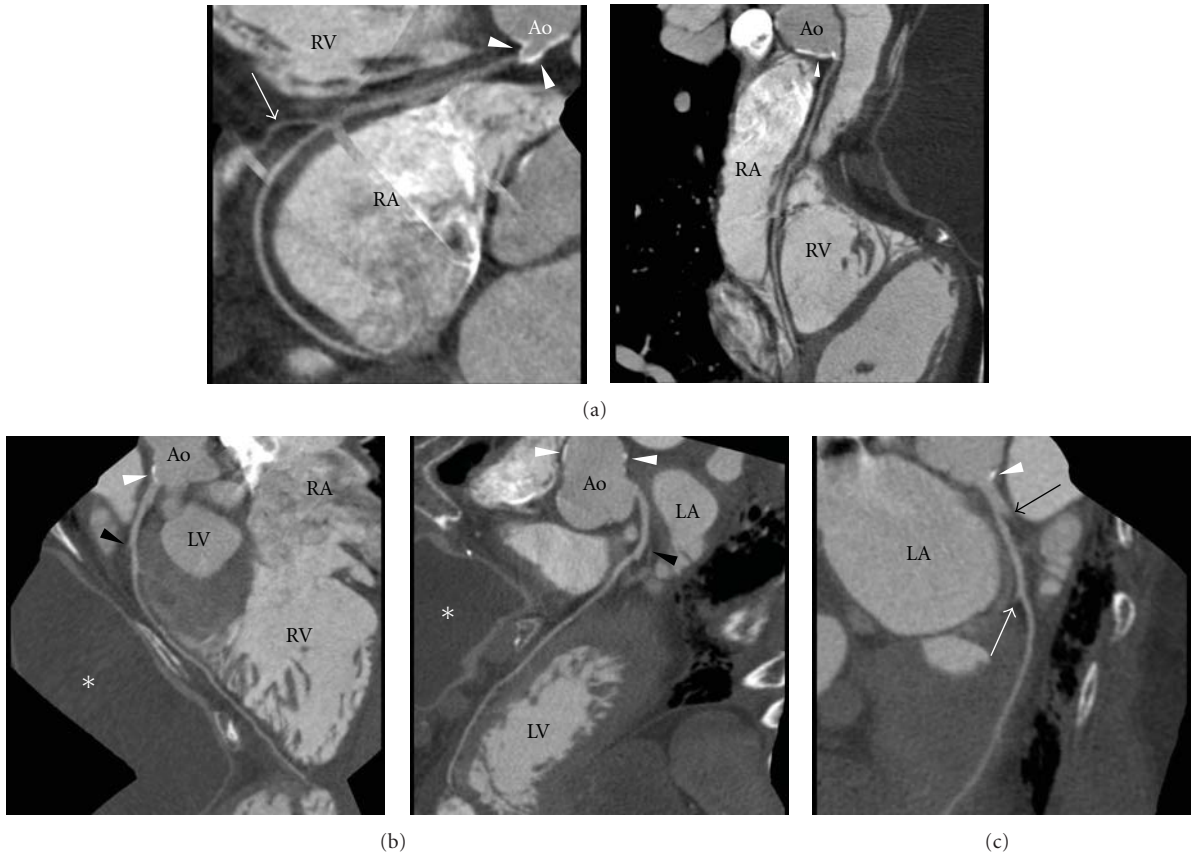


Figure 1: 48-year-old female with history of childhood lymphoma treated with mediastinal radiation therapy and anthracycline chemotherapy at age 12, presented with fatigue and decreased left ventricular ejection fraction by echocardiogram. Coronary CT angiography shows nonobstructive coronary plaques and supports the diagnosis of chemotherapy-induced cardiomyopathy. (a) Curved reformat view of the right coronary artery (RCA) shows nonocclusive calcific ostial plaque (arrowheads) calcific plaque in the aortic root. The first acute marginal branch is identified (arrow). Also noted are misregistration artifacts. (b, c) Curved reformat views of the left anterior descending (LAD) (b) and circumflex (c) coronary arteries show calcific plaque (white arrowhead) in the aortic root at the origin of the left main coronary artery. The first diagonal artery (black arrowhead) is identified on the LAD view (b). The LAD origin (black arrow) and distal circumflex artery continuation (white arrow) are identified on the circumflex view (c). No significant narrowing is seen in any of the major coronary arteries. LA = left atrium. LV = left ventricle. RA = right atrium. RV = right ventricle. Ao = Aortic root. $*$ = breast prosthesis.

Medical management of CAD was defined as treatment based on coronary calcification and/or the presence of plaque (which defines atherosclerotic disease and therefore identifies more aggressive secondary prevention targets).

CAD risk factor modification was defined as primary prevention step in absence of demonstrated CAD, which, for nondiabetic patients, has less stringent criteria.

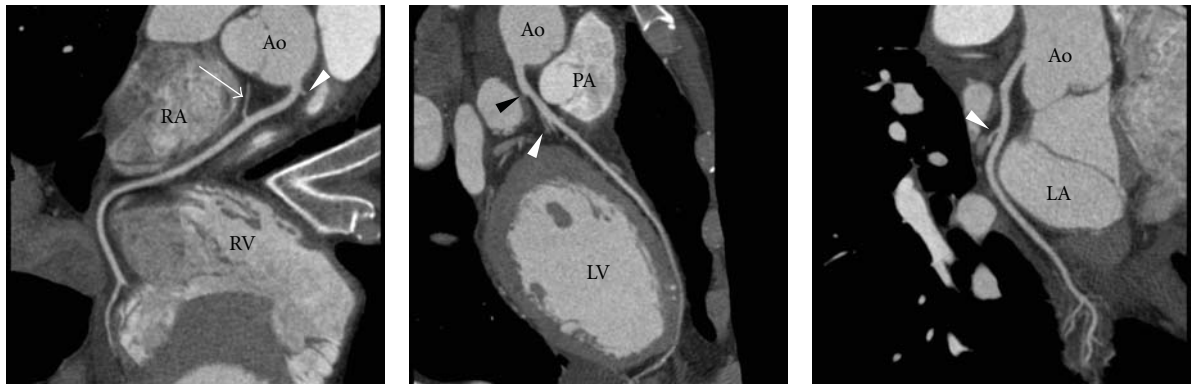
3. Results

Eighty CCTAs were performed during the first year at our center. Baseline demographics, CAD risk factors and proportions of hematological malignancies are shown in Table 1.

The mean age of the patient population was 58.8 ± 12.8 years with 56% males. Hypertension was found in 48% of the cases, hyperlipidemia in 36% of cases, diabetes mellitus in 13% and established CAD in 9% of cases. About 45% of patients had hematological malignancy (leukemia and lymphoma) whereas the rest had a solid tumor.

The most common indication for obtaining a CCTA was LV dysfunction (41% of cases) followed by chest pain and or dyspnea in 40% of the cases (Table 2). About 20% CCTA was obtained for atypical symptoms with abnormal stress test and 10% were for atypical symptoms with abnormal biomarkers. Miscellaneous indications were present in 13 patients (16.3%), including suspected cardiac tumor and/or thrombus or pulmonary embolism. Indications were not mutually exclusive and some patients had more than one at the time of CCTA.

Overall, 72 pts (90%) had at least one relative contraindication to ICA (Table 3). The majority of the patients (61%) who underwent a CCTA had a low to moderate pretest probability for CAD. Concomitant radiation or chemotherapy was present in 25% of cases and rest (19%) had leucopenia and/or thrombocytopenia.



(a) (b) (c)

Figure 2: 53-year-old male with metastatic melanoma underwent testing prior to Interleukin-2 (IL-2) therapy. Resting electrocardiogram and echocardiogram are normal. Dobutamine stress echocardiogram shows inferior wall inducible ischemia. IL-2 is held while coronary CT angiography is performed. Based on CT findings, IL-2 is started and given uneventfully. (a) Curved reformat view of the right coronary artery shows no atherosclerotic plaque. The conus branch (arrowhead) and sinoatrial nodal branch (arrow) are identified. (b) Curved reformat view of the left anterior descending artery shows no atherosclerotic plaque. The circumflex artery origin (black arrowhead) and first diagonal artery (white arrowhead) are identified. (c) Curved reformat view of the circumflex coronary artery shows no atherosclerotic plaque. The first obtuse marginal branch (arrowhead) is identified. LA = left atrium. LV = left ventricle. RA = right atrium. RV = right ventricle. Ao = Aortic root. PA = pulmonary artery root.

Table 5: Cardiac treatment decisions based on cardiac computed tomographic angiography findings.

Cardiac treatment decisions	*N* (%)
ICA* only	8 (10)
ICA followed by CABG†	4 (5)
Medical management of nonobstructive CAD‡	30 (37.5)
CAD risk factors modification	20 (25)
Management of chemotherapy-induced cardiomyopathy	18 (22.5)

*ICA: invasive coronary angiography.
†CABG: coronary artery bypass grafting.
‡CAD: coronary artery disease.

Table 6: Impact of cardiac computed tomographic angiography on cancer-related treatment decisions.

Cancer treatment decisions	*N* (%)
Proceed with chemotherapy	19 (23.8)
Proceed with stem cell transplant evaluation	8 (10.0)
Proceed with cancer surgery	3 (3.8)
Proceed with radiation therapy	2 (2.5)
Change chemotherapy agents due to cardiomyopathy	7 (8.8)
Hold chemotherapy for invasive coronary angiography	2 (2.5)

Coronary findings in CCTA are detailed in Table 4. Normal coronaries were found in 26.3% of patients, while mild to moderate CAD was found in 46% and severe CAD in 28%.

Cardiac treatment decisions based on CCTA findings are outlined in Table 5.

Due to concomitant advanced cancer or patient refusal, only 12 out of 22 patients with severe CAD by CCTA underwent ICA, including 4 patients who eventually underwent coronary artery bypass grafting (CABG). The majority of the patients were managed medically, with 38% of the patients treated medically for nonobstructive CAD and 23% of patients treated for chemotherapy-induced cardiomyopathy (Figure 1). In 25% of the cases the result of CCTA led to CAD risk factor modifications.

A total of 41 pts (51.3%) had their cancer management altered based on CCTA findings (Table 6). In 24% of cases, these findings directly influenced the decision to restarting chemotherapy (Figure 2), while in 9% of cases, they led to a change in chemotherapy agents based on a diagnosis of chemotherapy-induced cardiomyopathy. In 2.5% of cases, chemotherapy was temporarily discontinued in order to proceed with invasive angiography (Figure 3). In 10% of cases, exclusion of significant CAD by CCTA allowed for stem cell transplant evaluation to proceed. In 4% of cases, cancer surgery was performed without further cardiac testing, and 2.5% of cases subsequently started radiation therapy.

4. Discussion

The present study shows that CCTA can have important consequences in evaluating cancer patients with suspected coronary disease, often leading to important decision in the care of both cancer and heart disease. For more than half the patients in our study, CCTA had a significant impact on their cancer care. Coexistence of CAD and malignancy often creates a therapeutic and diagnostic challenge: faced with two potentially life-threatening conditions, prioritization of care is paramount. This is because cancer, its treatment, and complications may render commonly used cardiac tests and

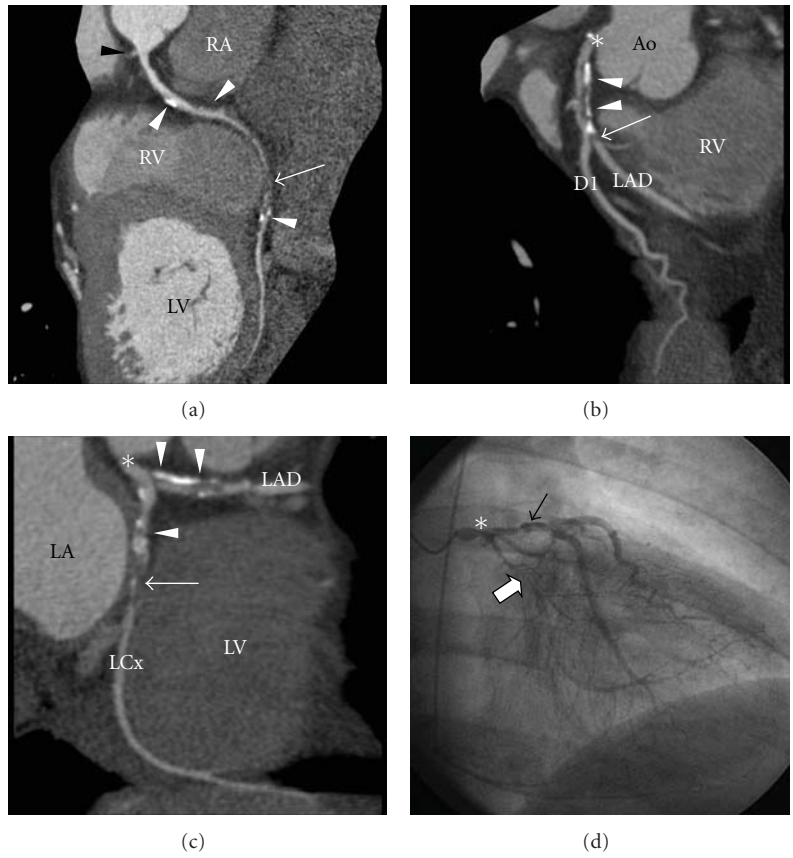


Figure 3: 61-year-old male with aggressive large B-cell lymphoma developed chest pain after the first cycle of chemotherapy. Electrocardiogram and cardiac enzyme measurements are consistent with NSTEMI. Echocardiography demonstrated a decrease in left ventricular ejection fraction from a normal baseline to 40%. Due to postchemotherapy thrombocytopenia and leucopenia, an invasive coronary angiogram could not be obtained. Based on the coronary CT angiogram results, further chemotherapy was placed on hold. Invasive coronary angiography was performed after recovery of blood counts, followed by coronary artery bypass grafting. Two weeks later, the patient restarted chemotherapy. (a) Curved reformat view of the right coronary artery shows scattered calcific and noncalcified atherosclerotic plaque (white arrowheads) with possible occlusion (arrow) near the junction of the mid and distal segments. The conus branch origin (black arrowhead) is identified. (b) Curved reformat view of the left anterior descending artery (LAD) shows calcific and noncalcified atherosclerotic plaque (white arrowheads) in the proximal LAD, with focal near occlusion (arrow) of the LAD at the origin of the first diagonal (D1). Also noted is a mixed ostial left main artery plaque (asterisk). (c) Curved reformat view of the circumflex coronary artery (LCx) and proximal LAD shows calcific and noncalcified atherosclerotic plaque (arrowheads) in the proximal segments of both vessels. The LCx appears occluded at the junction of the proximal and middle segments (arrow). The ostial left main artery plaque in this projection appears noncalcified and significantly stenotic (asterisk). LA = left atrium. LV = left ventricle. RA = right atrium. RV = right ventricle. Ao = Aortic root. (d) Invasive angiogram demonstrating same findings with good correlation. The left main coronary is significantly stenosed (asterisk). The left anterior descending artery shows multiple high grade stenoses (thin arrow) and the left circumflex artery is occluded (thick arrow).

therapies difficult, if not contraindicated. Cancer patients receiving chemotherapy and experiencing bone marrow suppression are at higher risk of procedural complications should they undergo ICA routinely. In other instances, postoperative status, ongoing infections, or radiation therapy may also preclude an invasive approach. In fact, a large majority of our patients had at least one relative contraindication to ICA, and as such would have been less likely to be fully assessed without CCTA. This often leads to the use of noninvasive stress imaging, traditionally echocardiography and nuclear imaging for a functional assessment of the coronaries. However, neither technique is able to show nonobstructive CAD, nor are they free of false positives [8] (which could lead to unnecessary ICA [9]) and false negatives (which could fail to correctly identify cancer patients with significant CAD).

CCTA also allowed the accurate diagnosis of CIC, which has important implications in ongoing cancer care. Current guidelines for the diagnosis of CIC recommend a coronary angiogram to exclude the presence of significant CAD. The ACC/AHA guidelines for the diagnosis and management of heart failure updated in 2009 [2] recognize the use of noninvasive imaging for detection of ischemia in patients presenting with heart failure, if revascularization is contemplated, with the caveat that stress testing may not reliably distinguish between ischemic and nonischemic etiologies.

This emphasizes the need for coronary anatomic assessment in these patients. In our practice in a tertiary cancer center, most patients with exposure to potentially cardiotoxic chemotherapy who experience a decrease in LV function are considered for angiography. Prior to the use of CCTA, however, many could not undergo ICA, and a conclusive diagnosis was often lacking. As we have shown, however, significant CAD in the setting of a cardiomyopathy could accurately be excluded, therefore confirming a suspicion of CIC in a quarter of our patients (Figure 1).

Noninvasive coronary artery imaging is therefore appealing in many instances in this patient population, particularly because of its high negative predictive value. Indeed, CCTA can conclusively demonstrate a normal coronary tree, therefore alleviating the need for ICA [10]. By accurately defining the coronary anatomy, CCTA in fact allowed the prioritization of cancer and cardiac care in our patients, in some cases, by excluding significant CAD suspected either based on cardiac biomarkers, symptoms, or previous testing (Figure 2). The advantage of adequate identification of underlying severe CAD in certain circumstances would allow stratification of patients who need modification of their chemotherapeutic regimen or who may benefit from concurrent treatment with cardioprotective therapeutic agents that promote positive remodeling, such as β-adrenergic blockers, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers. In others, by identifying patients who needed their cancer care to be put on hold until more pressing cardiac issues could be addressed, CCTA also prevented undue delays in cancer care by seamlessly integrating with the flow of care.

Our results in a group of cancer patients with low to intermediate pretest probability for CAD on the basis of risk factors alone suggest that it may be more prevalent than suspected. Indeed, we found that nearly a third of pts had severe CAD, and 5% of total population underwent CABG. This emphasizes the importance of coordinating cancer and cardiac care, as both can coexist with equal severity in the same patients. In fact, some cases will require the interruption of chemotherapy until the patient has undergone coronary revascularization (Figure 3). The addition of noninvasive coronary imaging therefore adds an invaluable tool in the approach to these difficult cases.

Our study describes a single center experience, and included patients referred for CCTA. In particular, there is no control group, and therefore no direct comparison to other noninvasive modalities (stress testing) can be drawn. Whether CCTA as a first step would compare favorably to other noninvasive modalities needs further study, particularly as a cost and radiation reduction measure. Although we reported short-term outcomes in terms of cancer and cardiac care, long-term followup will be needed to show definitive improvement in overall outcomes.

5. Conclusions

Cardiac computed tomographic angiography is an attractive imaging modality in cancer patients with suspected structural heart disease when invasive coronary angiography may be too risky or impractical and allows improved coordination of cancer and cardiac care.

Abbreviations

CABG: coronary artery bypass grafting
CIC: chemotherapy-induced cardiomyopathy
CCTA: cardiac computed tomographic angiography
CAD: coronary artery disease
ECG: electrocardiogram
ICA: invasive coronary angiography
LV: left ventricular.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Review Article

Preclinical Research into Basic Mechanisms of Radiation-Induced Heart Disease

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Radiation-induced heart disease (RIHD) is a potentially severe side effect of radiotherapy of thoracic and chest wall tumors if all or part of the heart was included in the radiation field. RIHD presents clinically several years after irradiation and manifestations include accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and injury to cardiac valves. There is no method to prevent or reverse these injuries when the heart is exposed to ionizing radiation. This paper presents an overview of recent studies that address the role of microvascular injury, endothelial dysfunction, mast cells, and the renin angiotensin system in animal models of cardiac radiation injury. These insights into the basic mechanisms of RIHD may lead to the identification of targets for intervention in this late radiotherapy side effect.

1. Introduction

The worldwide number of long-term cancer survivors is growing fast with ongoing improvements in cancer therapies [1, 2]. However, long-term cancer survivors may suffer from late side effects of cancer therapy. One of these late side effects is radiation-induced heart disease (RIHD), which may occur after radiotherapy of thoracic and chest wall tumors whenever all or part of the heart is situated in the radiation field. RIHD has been described to occur, for instance, among survivors of Hodgkin's Disease [3, 4] and breast cancer [5, 6]. Radiotherapy planning has undergone many improvements over the last decades, with modalities such as Intensity-Modulated Radiation Therapy (IMRT), image-guided radiation therapy, and proton therapy, leading to reduced exposures of the heart. Nonetheless, recent studies indicate that problems may persist. For instance, patients with Hodgkin's Disease, lung cancer, and esophageal and proximal gastric cancer may still receive either a high dose of radiation to a small part of the heart or a lower dose to the whole heart [7–11]. In addition, although there is increasing use of concomitant therapies, the extent to which these therapies affect radiotherapy side effects such as RIHD is largely unknown.

Manifestations of RIHD include accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and injury to cardiac valves [4, 12]. The disease is progressive and both incidence and severity increase with a higher radiation dose volume, younger age at the time of radiotherapy, a greater time elapsed since treatment, and concomitant use of cardiotoxic chemotherapeutic agents such as anthracyclines. Although RIHD is widely acknowledged as an impediment to quality of life for certain long-term cancer survivors, from a clinical perspective the only current way to reduce RIHD is through efforts to improve radiotherapy treatment planning, as other methods to prevent or reverse RIHD are not yet available. Hence, pre-clinical studies seek to unravel basic mechanisms of RIHD, with the ultimate goal to identify potential targets for intervention.

2. Pre-Clinical Models of Radiation-Induced Heart Disease

Pre-clinical animal models have long been used to study RIHD [13–18]. While transgenic mouse models are being used in investigations of radiation-accelerated atherosclerosis

[19, 20], wild type rodents are usually not atherosclerosis prone. Hence, studies that use rodents to investigate radiation-induced coronary artery disease are limited in number [21, 22]. On the other hand, many laboratory animals, including rodent, have been used successfully as models of radiation-induced cardiomyopathy [16, 23–27]. Common doses used in these pre-clinical models of localized heart irradiation are either a single dose between 5 Gy and 25 Gy, or fractionated schedules of, for instance, 5 daily fractions of 9 Gy. Some of the histopathological changes in pre-clinical models, such as myocardial degeneration and fibrosis, are also commonly described in human cases of RIHD, mainly after exposure to doses of ~30 Gy and above [3, 4, 28–30]. Although clinical and pre-clinical data on the cardiovascular effects of lower radiation doses are growing [11, 31], the focus of this review will be on myocardial injury and cardiac function changes after exposure to higher doses of radiation. Table 1 summarizes some of the main pre-clinical studies reviewed.

3. Vascular Injury and Endothelial Dysfunction

Previous paper indicate the important role of vascular injury and endothelial dysfunction (loss of thromboresistance and increased expression of adhesion molecules and cytokines) in the pathogenesis of normal tissue radiation injury [42, 43]. Endothelial dysfunction may contribute to profibrotic and proinflammatory environments, which are common aspects of normal tissue radiation injury [42, 44]. Although the role of endothelial dysfunction in RIHD has not been studied in detail, experimental RIHD is known to be associated with reduced myocardial capillary density [32, 33], focal loss of endothelial alkaline phosphatase [14, 34], and increased expression of von Willebrand factor [35]. Hence, microvascular injury and the resulting local ischemic injury are considered to be some of the underlying mechanisms of RIHD.

Radiation-induced vascular injury and endothelial dysfunction are mediated in part by Transforming Growth Factor-β (TGF-β) [45, 46], a pluripotent growth factor that is part of many normal tissue radiation responses [47–49]. Previous studies have shown cardiac upregulation of TGF-β in rat models of RIHD after localized heart irradiation with 20 Gy or 5 fractions of 9 Gy [36–38]. A TGF-β-inducing compound was used to investigate the role of TGF-β in RIHD in the rat. Cardiac radiation fibrosis was more severe in animals that had been administered the TGF-β-inducing compound during the 6-month followup time after irradiation (unpublished data). Pre-clinical studies involving TGF-β receptor inhibition are being undertaken.

4. Mast Cells

Mast cells, cells that belong to the hematopoietic myeloid lineage, reside in many organs and tissues including the heart. Although best known for their role in hypersensitivity reactions, mast cells are also intimately involved in wound healing and tissue remodeling [50–52]. Mast cells store and release a wide range of cellular mediators, both via degranulation and via constitutive pathways that do not involve degranulation [53]. Increased mast cell numbers are commonly found in coronary atherosclerosis, myocardial fibrosis [54, 55], and also in animal models of RIHD [40, 56], where mast cell numbers correlate with myocardial radiation injury.

The development and maturation of mast cells depend on the c-kit receptor, which is specific for stem cell factor. Several mast cell deficient animal models, based on a mutation in the c-kit receptor or stem cell factor, are available [57–59]. Our laboratories have made use of a rat model that is homozygous for a 12-base deletion in the c-kit receptor gene [60, 61]. Both mast cell-deficient rats and their mast cell-competent wild type litter mates were exposed to localized heart irradiation with a single dose of 18 Gy. Although mast cell-deficiency was associated with reduced radiation-induced myocardial inflammation and degeneration, other manifestations of cardiac radiation injury such as myocardial fibrosis and *ex vivo* measures of myocardial stiffness were exacerbated in the absence of mast cells [41]. These studies suggest that mast cells, in contrast to what had been the prevailing assumption but similar to what has been found in some other cardiac disease models [62, 63], play a predominantly protective role in RIHD.

5. Mast Cell Interactions

Mast cells interact with many cellular and molecular systems in the heart. Mast cell-derived proteinases, for instance, have been shown to contribute to both the formation and degradation of endothelin-1 (ET-1) [64–68]. ET-1 is a 21-amino acid peptide that was first discovered as a potent vasoconstrictor but also has proinflammatory and pro-fibrotic properties [69, 70]. The role of ET-1 in cardiovascular pathology has been studied extensively [71, 72]. Both ET-1 receptors, ET_A and ET_B are expressed by a wide variety of cell types in the heart [70, 73]. Short-term upregulation of ET-1 and its receptors may serve as a mechanism to maintain cardiac function in certain cardiovascular diseases [74, 75]. Long-term up-regulation of the endothelin system, on the other hand, may have detrimental effects due to the vasopressor, prohypertrophic, and pro-fibrotic properties of ET-1 [73, 76].

Mast cells express the receptor ET_A, which upon activation by ET-1 induces mast cell degranulation [77], a pathway by which ET-1 may enhance the activity of matrix metalloproteinases (MMPs) in the heart [78, 79]. Dual inhibition of ET_A and ET_B prevented mast cell degranulation and the associated increase in cardiac MMP levels, interstitial collagen degradation, and ventricular dilatation in a rat model of chronic volume overload [80]. On the other hand, in a preliminary study of a rat model of RIHD, dual inhibition of ET_A and ET_B did not alter radiation-induced functional or structural cardiac changes [81]. Moreover, vascular injury seemed aggravated by selective ET_A inhibition in a rat model of localized intestine irradiation [82]. Dosing of receptor antagonists and opposing cardiovascular effects of

Table 1: Summary of pre-clinical studies into basic mechanisms of RIHD.

Main Observation or Study Outcome	References
Reduced myocardial capillary density, focal loss of endothelial alkaline phosphatase, and increased expression of von Willebrand factor indicate vascular injury in rat models of RIHD.	[14, 32–35]
Coronary artery disease has been observed after localized heart irradiation in hypertensive rats or rats on a high-fat diet.	[21, 22]
Increased myocardial levels of TGF-β1, Ang II, and aldosterone have been found after localized heart irradiation in rats.	[36–39]
ACE inhibitor captopril reduced myocardial fibrosis and prevented left ventricular capillary density loss after localized heart irradiation in rats.	[40]
Mast cell-deficient rats showed reduced radiation-induced myocardial inflammation and degeneration, but increased myocardial fibrosis when compared to mast cell-competent rats.	[41]

the ET_A and ET_B,receptors [83, 84] warrant further studies to clarify the role of ET-1 and its two receptors in RIHD.

Mast cells are one of the main cell types involved in neuroimmune interactions [85]. They are found in close proximity to nerve terminals or axons in many organs, including the heart [86, 87], and interact with nerves on the molecular level in many ways [85, 88, 89]. Mast cells express α- and β-adrenergic receptors [90, 91]. In normal rat myocardium, β-blockade is associated with increased mast cell degranulation and decreased collagen deposition [92]. Some sensory neuropeptides such as calcitonin gene-related peptide (CGRP), substance P, and neuropeptide Y are able to induce or enhance mast cell degranulation [93–100] while others have been shown to inhibit mast cell degranulation [101, 102]. Mast cells, in turn, affect neuronal growth and function by producing nerve growth factor [103] and by activating proteinase-activated receptor-2 on the surface of neurons [104, 105]. Cardiac sensory nerves play a protective role in the heart via the release of nitric oxide and CGRP [106, 107]. For instance, CGRP plays a protective role in myocardial injury such as from ischemia reperfusion and the cardiotoxic chemotherapeutic agent doxorubicin [108, 109]. CGRP is a potent vasodilator but also has beneficial effects in the heart by local downregulation of tumor necrosis factor-alpha (TNF-α) and upregulation of insulin-like growth factor-1 (IGF-1) [110, 111]. Interestingly, both downregulation of TNF-α and upregulation of IGF-1 are associated with reduced normal tissue radiation injury [112, 113]. In line with this evidence, CGRP has been shown to protect in a rat model of radiation enteropathy [114]. Its role in RIHD has not yet been studied extensively.

6. The Renin-Angiotensin System

The role of the renin angiotensin system (RAS) in normal tissue radiation injury has been well defined [115, 116]. Inhibitors of angiotensin-converting enzyme (ACE) and antagonists of angiotensin type 1 receptors reduce injury in animal models of localized kidney, lung, and brain irradiation [117–119]. Although the role of RAS in RIHD is less well defined, RAS mediators may be upregulated in the heart after irradiation [39]. However, while the ACE inhibitor captopril reduced radiation injury in kidney, lung, and skin of rats [119–121], captopril did not prevent cardiac function loss after localized heart irradiation with 20 Gy in a rat model. Captopril, on the other hand, did reduce myocardial fibrosis and prevented left ventricular capillary density loss after local heart irradiation. It is not known whether these effects were due to properties of captopril other than its inhibition of ACE [40].

Inhibition of ACE is considered to be cardioprotective in part by suppressing the breakdown of bradykinin by ACE [122]. Bradykinin, a small peptide hormone that is sometimes considered to aggravate cardiac disease with a significant inflammatory component such as myocardial infarction [123], is also known to mediate cardioprotection via induction of nitric oxide and prostacyclin [124–126]. Bradykinin is formed in the kallikrein-kinin system by proteolytic cleavage of both high- and low-molecular weight kininogen by kallikrein enzymes, but also by the mast cell-derived enzyme tryptase [127, 128]. Interestingly, the mast cell proteinases chymases are one of the main converters of angiotensin I into angiotensin II [129]. Mast cells seem to hereby provide a particularly large contribution to local extravascular generation of Ang II [130]. The roles of RAS and bradykinin in cardiac radiation injury and the potential influence of mast cells herein need further investigation.

7. Conclusions

Radiotherapy planning has undergone many improvements over the last decades, leading to improved targeting and reduced normal tissue radiation exposure. Nonetheless, some patients with Hodgkin's Disease, lung cancer, and esophageal and proximal gastric cancer may still receive either a high dose of radiation to a small part of the heart or a lower dose to the whole heart, which may lead to late manifestations of RIHD. Some of the basic mechanisms of RIHD have begun to emerge from recent pre-clinical studies and include the involvement of vascular injury, mast cells, and the RAS. Future studies will elucidate the significance of these mechanisms for clinical RIHD and their usefulness as targets for intervention in RIHD.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Review Article

Radiation-Induced Heart Disease: A Clinical Update

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Cardiovascular diseases and cancer are the two leading causes of morbidity and mortality worldwide. Improvement in cancer therapy has led to increasing number of cancer survivors, some of whom may suffer from adverse cardiovascular effects of radiation therapy. Longterm followup is essential, as the cardiac complication may manifest years after completion of radiation therapy. In this paper, we have discussed the cardiovascular effects of radiation therapy.

1. Introduction

Cardiovascular disease and cancer are the two leading causes of morbidity and mortality worldwide [1]. Over the last half century, radiation therapy (RT) has evolved to become one of the cornerstones of treatment for various types of cancers. It is estimated that more than 50% of patients with cancer are treated with radiotherapy. Along with the development of novel chemotherapeutic agents, radiation therapy (RT) has revolutionized the prognosis of patients with various cancers. Many childhood and adolescent years cancers are now successfully treated and these patients go on to live an active and normal adult life, as evident by an increasing number of cancer survivors [2]. Late cardiovascular effects are seen often in cancer survivors. Amongst Hodgkin lymphoma (HL) patients who have received radiation, cardiovascular disease (CVD) is of the most common causes of death. Studies have shown that these patients have an increased risk for Coronary Artery Disease (CAD), valvular heart disease, congestive heart failure (CHF), pericardial disease and sudden death. The risk is particularly high in patients treated before the age of 40 years [3–6].

The reported relative risk of death from a fatal myocardial infarction in patients treated with mediastinal RT is increased from 1.5 to 3.0 times that of unirradiated patients [7, 8]. In young patients undergoing mediastinal irradiation, myocardial ischemia and CAD is very prevalent [9]. A meta-analysis of eight randomized trials found a 62% increase in cardiac deaths among women who were treated with radiation therapy [10]. Even at lower radiation doses, there appears to be of excess risk of cardiovascular disease as shown in the Japanese atomic bomb survivors [11]. Due to improvement in radiation technique, the risk of cardiovascular complications in relation to radiation may have declined over time, but even in patients treated as lately as between 1979 and 1986 the risk congestive heart failure and valvular dysfunction remained increased [12]. Radiation damage to the heart can involve the pericardium, myocardium, valves, and coronary vessels with pericardium being most frequently involved [13, 14]. Radiation damages the vascular endothelium, and hence radiation-induced vascular injury occurs in the field of radiation exposure. Damage to the capillary vessels manifests as telangiectasia, whereas thrombotic, inflammatory, and fibrogenic complications in larger vessels can result in peripheral, coronary and carotid artery disease. Table 1 lists the possible radiation induced cardiovascular complications.

Figure 1 illustrates the case of a patient who had multiple cardiovascular complications in relation to radiation therapy. Patient had Hodgkin's disease and completed radiation therapy (total of 40 Gy) to the mediastinum and neck in 1984. In 2005, a permanent pacemaker was inserted for complete heart block. In March 2007, he underwent pericardiocentesis, followed by a pericardial window. Subsequently he underwent pericardial stripping for pericardial constriction in April 2007. He also developed CAD and was

Table 1: Spectrum of radiation induced heart disease.

(1) Radiation-induced atherosclerosis
(a) *Symptomatic*
(b) *Asymptomatic*
(2) Pericardial disease
(a) *Acute pericarditis*
(b) *Delayed pericarditis*
(c) *Pericardial effusion*
(d) *Constrictive pericarditis*
(3) Myocardial and Endocardial disease
(a) *Pancarditis*
(b) *Cardiomyopathy*
(4) Valvular disease
(5) Conduction disturbances
(a) *RBBB*
(b) *Atrioventricular nodal block*

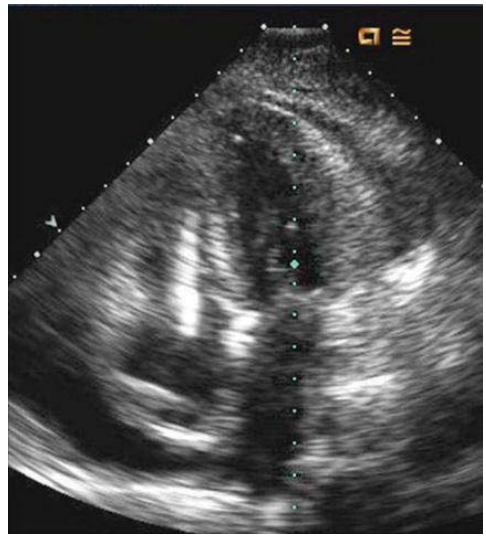

Figure 1: Echocardiogram image (apical 4-chamber view) shows thickened pericardium, small pericardial effusion, and a pacemaker lead in the right ventricle.

found to be 50% disease of the left anterior descending artery. His other radiation-included complications included hypothyroidism and restrictive lung disease.

2. Possible Mechanism of Radiation-Induced Vascular Disease

The exact primary mechanisms by which radiation-induces or promotes atherosclerosis have not been identified. A number of acute effects, including endothelial damage, lipid and inflammatory cell infiltration, and lysosomal activation, have been described [15, 16]. Primary basic mechanism behind radiation induced vascular damage appear to be endothelial dysfunction [17]. However certain risk factors like smoking and hyperlipidemia appears to act as accelerating agents. Radiation itself can cause fibrotic changes in the coronary arteries [14], but cholesterol feeding of the animals markedly increased the degree of atherosclerosis in the rabbits [18]. These findings suggest that the combined effect of irradiation and some other risk factor is necessary to produce significant radiation-induced atherosclerosis [18].

Though previously initiation of atherosclerosis was attributed mainly to lipid accumulation within the arterial walls, it is now widely accepted that inflammation plays a vital role in the initiation and progression of the disease [19, 20]. In animal model irradiation accelerates the development of macrophage-rich, inflammatory atherosclerotic lesions prone to intraplaque hemorrhage [21] and enhances the atherogenic effects of a high-fat diet [22]. It is postulated that radiation promotes short-lived changes in oxidative stress conditions (O2 concentrations) in the artery wall and that atherogenic lipoproteins, which are elevated in response to the high-fat diet, must be available during this period to participate in the initiation of the disease process [22]. Another mechanism of radiation-induced endothelial dysfunction is via production of reactive oxygen species [23]. Significant increases in superoxide and peroxides were observed in the microvessels of rats exposed to radiation [23].

A proposed mechanism of inflammatory vascular damage due to radiation in humans is also via oxidative stress and activation of nuclear factor-kappa B (NF-kB) [24].

Certain cytokines and growth factors, such as TGF-beta1 and IL-1 beta, may stimulate radiation-induced endothelial proliferation, fibroblast proliferation, collagen deposition, and fibrosis leading to advanced lesions of atherosclerosis [25].

Indirect association of inflammation with radiation-induced vascular damage comes from studies showing elevated levels of the proinflammatory cytokines IL-6, CRP, TNF-α, and INF-γ and also increased levels of the anti-inflammatory cytokine IL-10, in the Japanese atomic bomb survivors [26, 27]. There was also dose-related elevation in erythrocyte sedimentation rate and in levels of IgG, IgA and total immunoglobulins in this cohort, all markers of systemic inflammation [27]. In experimental atherosclerosis model it has been shown that following multiple small radiation doses the chemoattractant (MCP-1) concentration increases proportionally to cumulative dose; this increase in MCP-1 is largely driven by radiation-induced monocyte death [28]. In an animal model, following a single dose of radiation to the heart, from 3 months onwards changes in coronary arteries of the irradiated hearts included endothelial cell loss, a loss of smooth muscle cells, and fibrosis in media and adventitia [29].

Endothelial cell injury markers secreted after irradiation includes thrombomodulin [30]. Following radiation, the endothelial cell neutrophil chemotactic activity is increased, with greater adherence of polymorphonuclear leucocytes to irradiated endothelial cells [31]. In women with breast cancer, it has been shown that endothelium-dependent vasodilatation was significantly impaired in the irradiated axillary arteries compared with the contra lateral, nonirradiated arteries [32]. In irradiated human cervical arteries,

the impaired nitric oxide-mediated relaxation was associated with a lack of endothelial nitric oxide synthase expression, suggesting the importance of impaired endothelial function in irradiated human blood vessels [33]. Endothelial cell swelling, increased permeability, interstitial fibrin deposition, and development of platelet thrombi ultimately lead to fibrosis. Various local and systemic factors, implicating endothelial cell damage and inflammation, eventually lead to the development of symptomatic CAD.

3. Radiation-Induced CAD

Due to high prevalence of CAD, the precise incidence of radiation induced accelerated atherosclerosis is difficult to confirm. However it occurs in a number of patients without traditional risk factors for CAD [9, 34]. In these patients, conventional risk factors like CAD, diabetes mellitus, hyperlipidemia, and smoking were uncommon and insensitive indicators of coronary risk after mediastinal irradiation [9].

3.1. Pathology. Intimal proliferation of mainly fibrous tissue leads to luminal narrowing [14]. Histologically there may be some overlap and it may be difficult to distinguish between radiation-induced CAD (RICAD) and typical atherosclerotic CAD. However media is more severely destroyed and the adventitia is markedly thickened and fibrotic in radiation-induced CAD as compared with nonradiation CAD [35]. In irradiated coronary vessels, there also appears to be loss of smooth muscle cells from the media and adventitial fibrosis [14].

3.2. Clinical Presentation. Symptoms of CAD may include chest discomfort with or without radiation to the arm, back, neck, jaw, or epigastrium, shortness of breath, weakness, diaphoresis, nausea, and lightheadedness, all with or without exertion. Women and the elderly are more likely to present with "atypical features" [36]. Clinically patients with radiation induced CAD (RICAD), most commonly, present with angina, dyspnea or heart failure [34]; however there are reports of sudden death in patients treated with radiotherapy [14]. Sudden death in these patients is thought either to diffuse fibrointimal hyperplasia of all coronary vessels or left main stenosis and ostial lesions [14, 34]. Mean time interval for the development of RICAD in relation to radiotherapy is approximately 82 months (range 59–104) [13]. Patients with RICAD generally present at younger age than general population, especially survivor of childhood and adolescence malignancies treated with mediastinal radiation [37]. Hancock et al. followed a total of 2232 consecutive Hodgkin's disease patients treated from 1960 through 1991 for an average of 9.5 years to assess the risk of death from heart disease after Hodgkin's disease therapy. The relative risk (RR) for cardiac death was found to be 3.1 (CI; 2.4–3.7) and the RR for acute myocardial infarction was the highest after irradiation before 20 years of age and decreased with increasing age at treatment ($P < .0001$ for trend) [8]. The proximal coronary vessels, which are in the range of radiation, are mainly involved [13, 14].

Occasionally in patient with myocardial infarction due to previous radiation therapy, no obstructive CAD is found and provocative tests for coronary artery spasm response are normal [38]. Spontaneous recanalization of the thrombus may have occurred as this patient was treated with aspirin and heparin and coronary angiogram was done 3 days later [38].

Asymptomatic disease is also prevalent in patients with previous radiation. New perfusion defects occurred in 50% to 63% of women 6 to 24 months after RT [39, 40]. Marks et al. demonstrate 27%, 29%, 38%, and 42% incidence of myocardial perfusion abnormalities in asymptomatic patients with breast cancer at 6, 12, 18, and 24 months after RT, respectively [41]. The incidence of perfusion defects was strongly correlated with the volume of left ventricle (LV) in the RT field occurring in 25% of patients with 1% to 5% of the LV within the tangent fields, and in 55% of patients with more than 5% of the LV within the field [41]. The clinical significance of these perfusion defects is unknown. However, they appear to be associated with abnormalities in wall motion and episodes of chest pain [41, 42]. A nonsignificant change in ejection fraction is apparent only in patients with relatively large fractions of the LV affected by perfusion defects [41]. In patients with distal esophageal cancer, RT is associated with a high prevalence of inferior left ventricular ischemia, as detected by gated myocardial perfusion images (GMPIs) [43]. Most perfusion defects are encompassed within an isodose line $\geq$45 Gy in the RT plan, and most patients have mild degree of ischemia [43]. A wall motion abnormality was seen in only few patients; such finding is likely due to the presence of only mild degree of ischemia [43]. In a small group of patients with esophageal and lung carcinoma, myocardial perfusion abnormalities were frequently seen after radiation but were not predictive of future cardiac events [44]. Due to small number of patients in these series and short duration of followup [41, 42, 44], the long-term clinical significance of these mild perfusion defects is unknown.

3.3. Diagnosis and Treatment. Diagnosis and treatment of radiation-induced CAD (RICAD) is similar to CAD in general population [45]. There are no specific guidelines or significant difference in the acute initial stabilization and management of these patients. Generally the treatment of both acute and chronic RICAD would follow the same lines as management of atherosclerotic CAD either with medical therapy or revascularization, considering the patient's symptoms, cancer stage, expected survival, and comorbidities.

For patients with RICAD, both percutaneous intervention and coronary artery bypass graft (CABG) have been used [34]. Surgical intervention and CABG may pose difficulties in these patients because of mediastinal fibrosis, with high incidence of complications [34]. In addition, the use of internal mammary artery as a graft may not always be possible due to radiation disease with this vessel itself.

Figure 2 represents a CT coronary angiogram showing left main disease in a 60-year-old female who had received radiation therapy to the mediastinum.

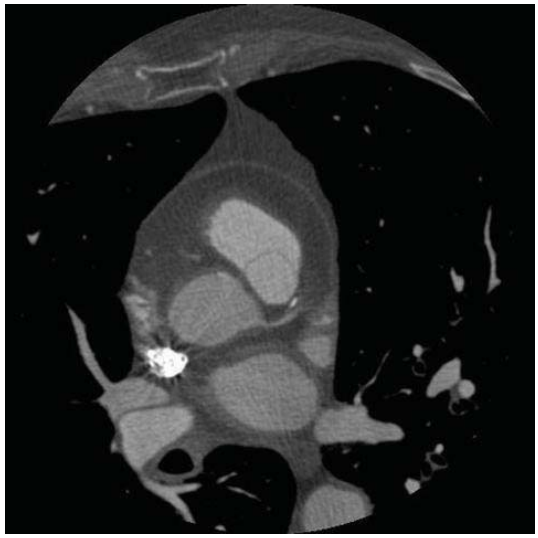

Figure 2: CT coronary angiogram showing left main disease in a 60-year-old female who had received radiation therapy the mediastinum.

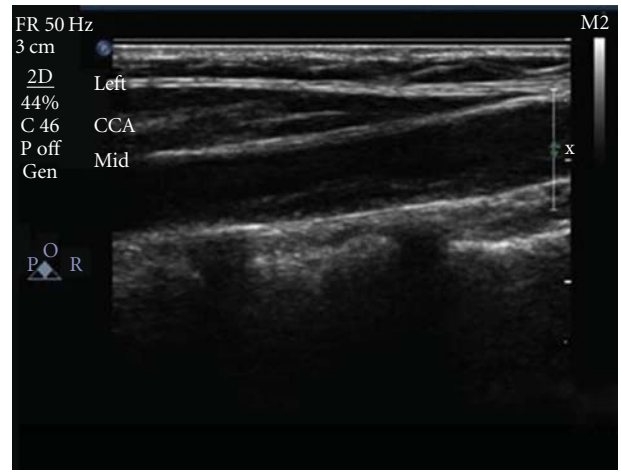

Figure 3: A carotid Doppler shows moderate disease in the left common carotid artery of a 33-year-old female who had received head and neck radiation for nasopharyngeal carcinoma 18 years ago.

4. Radiation-Induced Carotid Artery Disease

In patients with Hodgkin's disease, when compared to controls, the irradiated cases had a greater intima-media thickness in the carotid artery distribution [46]. During a 3-year followup, it was noted that despite improvement in intima-media thickens at 3 years, there was persistently reduced flow-mediated dilatation in the irradiated carotid artery, suggesting that early endothelial damage persists [47]. Radiation-induced carotid disease differs from traditional carotid disease. Radiotherapy often produces carotid lesions that are more extensive than the traditional bifurcation stenosis, often involving atypical areas such as long segments of carotid artery [48].

The treatment of radiation-induced carotid disease is similar to those in general population with both percutaneous intervention and surgery used in selective cases [49].

In patients with extensive fibrosis due to radiation, carotid stenting may be preferable.

Figure 3 represents a carotid Doppler of a 33-year-old female who had received head and neck radiation for nasopharyngeal carcinoma 18 yrs ago, showing moderate disease in the left common carotid artery. The patient also had evidence of occlusion of the left subclavian artery.

5. Radiation-Induced Pericardial Disease

Pericardial disease is a common manifestation of radiation-induced heart disease and is most frequently involved. In an autopsy study of radiation-induced heart disease, radiation-induced pericardial disease was noted in 70% of cases in whom pericardium was available [13].

5.1. Pathophysiology. Fibrosis is a common sequel of radiotherapy. It is a multicellular process involving various interacting cell systems in the heart resulting in the fibrotic phenotype of the fibroblast/fibrocyte cell system, which usually causes fibrous thickening of the pericardium [50]. In the pericardium, parietal surfaces are more severely damaged, with dense collagen and fibrin deposition on the mesothelial surfaces [51].

5.2. Clinical Presentation, Diagnosis, and Treatment. Pericardial disease with radiotherapy can present as pericarditis, pericardial effusion with or without constrictive pericarditis [13]. Pericardial effusion with or without constriction is the most commonly observed type of pericardial disease [13].

In patients with radiation-induced pericardial disease, the interval from radiation therapy to symptom development is variable and ranges between 2 and 145 months (mean time: 58 months) [13]. Patients presenting earliest were those with effusions, whereas those with constriction all became symptomatic after 18 months [13]. The development of disease 12 years after treatment emphasizes the importance of long-term followup in these patients [13].

Pericardial disease with radiotherapy can present as the following cases.

(1) Acute pericarditis during radiation treatment: the signs and symptoms are those of nonspecific pericarditis with chest pain, fever, and sometimes nonspecific ECG abnormalities. (Figure 4 represents an ECG showing pericarditis in a 60-year-old female who presented with chest pain 7 days after starting radiation therapy for breast carcinoma). Acute pericarditis during radiation treatment generally responds to bed rest and nonsteroidal anti-inflammatory drugs (NSAIDs). Treatment of primary malignancy should not be withheld because of this.

(2) Delayed pericardial disease: it can occur from months to several years after radiotherapy [52, 53]. Patients

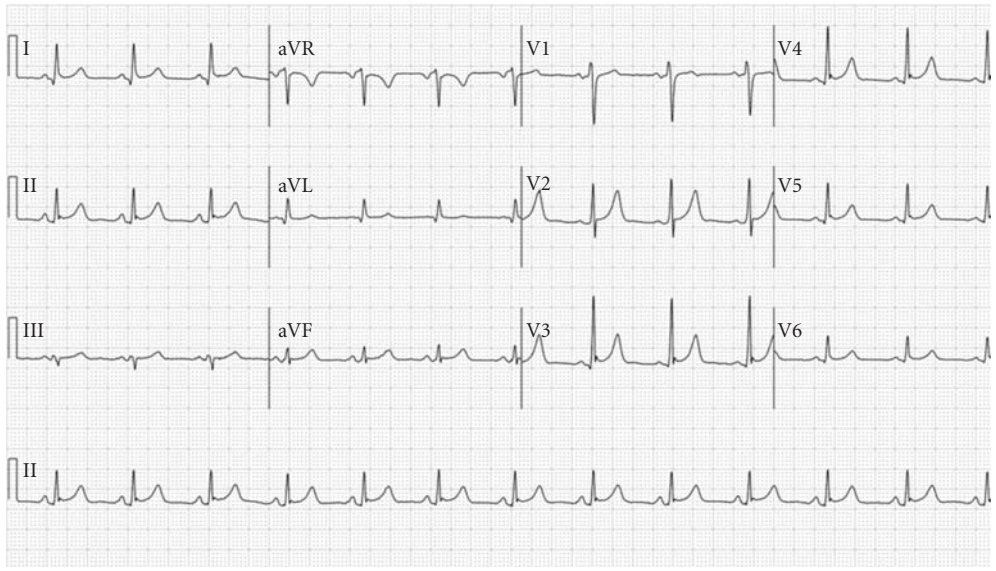

Figure 4: ECG showing ST elevation suggestive of pericarditis.

may present with pericardial pain, but dyspnea is the commonest presenting symptom [52, 53].
Delayed chronic pericardial effusion: it may present within 4–26 months and is usually detected by chest X ray showing an enlarging cardiac silhouette [52]. Radiographic evidence of cardiomegaly usually precedes the development of dyspnea and other signs of tamponade [52]. Some patients may present with tamponade. When delayed pericardial disease presents with a cardiac tamponade like clinical picture, needle pericardiocentesis is usually the initial treatment of choice. Recurrent, large, and hemodynamically significant pericardial effusions require surgical pericardiectomy, if no contraindications exist [52].

(3) Pancarditis: the most severe form of radiation-induced pericardial disease is pancarditis. In addition to pericardial fibrosis, there is myocardial fibrosis with or without endocardial fibrosis or fibroelastosis. Clinical picture is that of intractable congestive heart failure. When radiation-induced pancarditis presents as acute decompensated heart failure, besides early risk stratification, patients should be treated with loop diuretics, nitroglycerin, ACE inhibitors, vasodilators, inotropic agents, and supportive device as indicated.

(4) Constrictive Pericarditis: mediastinal radiation is a common cause of constrictive Pericarditis [54]. The majority of the patients present many years after radiation therapy with congestive heart failure [54]. Congestive heart failure is treated with conventional medications like diuretics, beta blockers and ACE inhibitors. The definite treatment is pericardiectomy, but radiation therapy is associated with poor survival in these patients, and hence pericardiectomy may not be curative for patients with radiation-induced constrictive pericarditis [54].

(5) In clinical practice some asymptomatic patients may have minimal to small pericardial effusion on routine echocardiogram. Except for followup, no active intervention is needed in these cases.

6. Radiation-Induced Cardiomyopathy

A large number of patients with previous radiation therapy develop cardiomyopathy. In a retrospective cohort study involving 14,358 five-year survivors of various cancers diagnosed and treated under the age of 21 between 1970 and 1986, Mulrooney et al. found that survivors of cancer were significantly more likely than siblings to report congestive heart failure (hazard ratio (HR) 5.9, 95% confidence interval 3.4 to 9.6; $P < .001$). Exposure to 250 mg/m2 or more of anthracyclines and radiation dose of more than 1200 cGy to the heart increased the relative hazard of congestive heart failure by two to sixfold as compared to nonirradiated survivors [55].

Overall, heart failure is a rare sequel of mediastinal radiation therapy and mostly associated with a restrictive hemodynamic pattern in the absence of a history of treatment with an anthracycline [56]. At a microscopic level collagen not only increases as a whole but the proportion of type I collagen increases proportionally to type 111. This marked alteration in collagen synthesis may contribute to impaired diastolic distensibility of the ventricles seen in this group of patients [57]. Most patients with myocardial involvement have interstitial fibrosis [13]. The most common pattern of fibrosis is pericellular and perivascular, with replacement fibrosis seen infrequently [13]. The loss of myocardium results in renin-angiotensin-aldosterone (RAA) and adrenergic system-driven myocardial remodeling, which is progressive and results in end-stage symptoms.

Multiple case series have reported myocardial perfusion defects in patients receiving mediastinal radiation therapy [39, 58–60]. The significance of these perfusion defects is unclear. However, they likely represent microvascular damage to the myocardium, which over time may lead to myocardial fibrosis and diastolic dysfunction [61]. Even if acute myocardial damage is only moderate, the process of myocardial remodeling can lead to progressive myocardial dysfunction over years and eventually induce myocardial dysfunction and heart failure. Treatment with ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, and beta blockers is usually recommended as per guidelines for treatment of heart failure in general population [62]. In animal model, captopril (an ACE inhibitor) ameliorated many of the structural changes but failed to influence or prevent the late functional deterioration after irradiation of the heart [63].

7. Radiation-Induced Valvular Heart Disease

Valvular disease is frequently seen in patients with radiation-induced heart disease. In one postmortem series, the incidence was high with 81% of patients showing evidence of valvular damage [14]. The aortic and mitral valves are more commonly involved than the tricuspid and pulmonary valves [14, 64]. The reason for preponderance of left-sided lesion and the rarity of pulmonary valve involvement despite its anterior position is not known. This may be related to higher pressure across left-side valves. Only a minority of patients with radiation-associated valvular disease (RAVD) have clinically moderate or severe dysfunction [14]. Vast majority (71%) of patients with RAVD exhibit no symptoms of valvular dysfunction [65]. The mean time from radiation to the onset of symptoms in RAVD is approximately 98 months (range 18–252) [13]. In an individual patient exposed to radiation, it is difficult to assess the time period for conversion of asymptomatic to symptomatic valvular heart disease, as radiation-associated valvular heart disease represents a continuum progressing from asymptomatic valvular thickening to symptomatic valvular dysfunction. However, it has been noted that diagnosis of asymptomatic RAVD occurred at a mean of 11.5 years after irradiation compared with 16.5 years for symptomatic patients [65]. Thus, 5 years appear to be the interval required for progression from asymptomatic to symptomatic RAVD.

The valve leaflets are fibrotic with focal dystrophic calcification and marked thickening. In the pathological findings, certain rheumatic endocarditis changes such as endocardial reduplication and vascularization are not found [64]. The cusps or leaflets of the valves thicken fibrose and on occasion partially calcify [66, 67]. The treatment of valvular disease in cancer patients and those related to radiotherapy is the same as in general population. The issue of endocarditis prophylaxis should be individualized.

Figure 5 represents Doppler echocardiogram of the aortic valve in a 46-year-female showing moderate aortic stenosis and aortic regurgitation. The patient had received radiation therapy for Hodgkin's disease 29 years ago. Some degree of regurgitation was noted in all 4 valves.

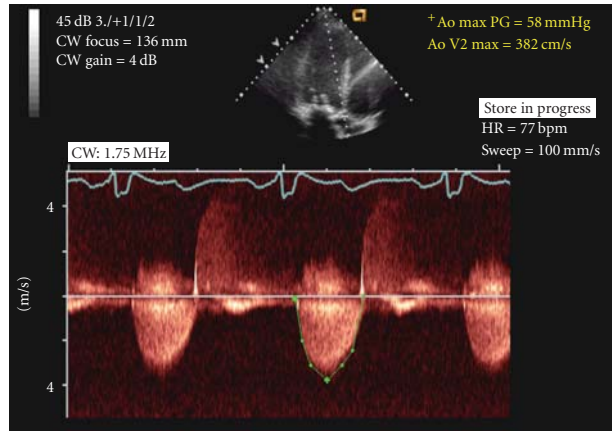

Figure 5: Doppler echocardiogram of the aortic valve (done in 2005) shows moderate aortic stenosis and aortic regurgitation in a 46-year-female who had received radiation therapy for Hodgkin's disease in 1976. Some degree of regurgitation was noted in all 4 valves.

8. Radiation-Induced Conduction System Disease

The conduction system is the least commonly involved of all the cardiac structures and its true incidence is not known. ECG changes after irradiation range from nonspecific ST-T changes to low voltage and right bundle branch block (RBBB) [14]. RBBB is commonly associated with mediastinal irradiation because the right bundle lies close to the endocardium on the right side [68]. Injury to bundle may occur either directly from radiation or indirectly from associated myocardial fibrosis and ischemia. One of the common serious manifestations is complete atrioventricular (AV) block [69]. Dual chamber pacing has been found to be somewhat more efficacious in symptom improvement in such patients [70]. A postmortem study in a 20-year-old man with Hodgkin's disease and previous radiation who had earlier developed heart block revealed marked arteriosclerosis with fibrosis of the epicardium, myocardium, and endocardium. Examination of the conduction system revealed extensive arteriolosclerosis of the sinoatrial node and its approaches. In addition, there was marked fibrosis of the approaches to the AV node, the AV bundle, and both bundle branches [71]. Complete heart block has been reported to occur at an interval of less than 1 year from radiation to 23 years after completion of radiation therapy [72]. Hence these patients should be followed up for life.

9. Role of Biomarkers in Patients Undergoing Radiation Therapy

There are only few studies of biomarkers in patients undergoing radiation and have shown conflicting results. In a study of 50 women with breast cancer, no change in serum troponin was found after a total dose of 45 to 46 Gy [73]. In this study, however, the cardiac dosimetric data was not provided [73]. In another study of 30 patients receiving

thoracic chemoradiation, no significant elevation in creatine kinase-myocardial band (CK-MB), troponin, or NT-pro BNP was detected with radiation therapy [74]. In one study both troponin and BNP increased significantly during the study; however, the absolute and mean values remained on a relatively low level (mean preradiation and postradiation troponin I: 0.007 ± 0.008, 0.014 ± 0.01 ng/mL; mean preradiation and post radiation BNP: 123 ± 147, 159 ± 184 pg/mL) [75]. Hence based on current knowledge, cardiac biomarkers are not recommended for evaluation of radiation-induced cardiotoxicity but remain a useful research tool.

10. Prevention and Future Direction

Subclinical cardiac damage occurs in >50% of breast cancer survivors treated with radiation therapy [39]. Alteration in radiotherapy field or targeted radiation, with avoidance and/or shielding of the heart, remains one of the most important things in prevention of radiation-induced cardiac damage. In the absence of risk factors, the value of primary and secondary prevention in these cases is debatable. Patients with classical risk factors like hypertension, smoking, and hyperlipidemia may be at increased risk of radiation-related cardiovascular complications, and these risk factors should be treated aggressively. Younger patients should be screened, because this patient population at risk usually have a considerable life expectancy. The role of routine stress test and biomarkers like troponin and B-type natriuretic peptide (BNP) in identifying high risk patients or predicting future cardiovascular events remains to be determined in large studies.

Similarly, in the absence of risk factors, the role of prevention therapy like use of antiplatelets, ACE inhibitors, and lipid lowering agents remains unclear. Recently CT scan of the coronary artery has been identified as a useful tool in identifying RICAD in asymptomatic patients [76]. Studies of myocardial perfusion in patients with previous radiation therapy indicate that the majority have mild myocardial perfusion defects. In patients with good long-term prognosis, the finding of the ischemia due to the RT may be significant as this is a reversible and treatable stage of RICAD, and halting its progression may decrease the incidence of future cardiovascular events.

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Conflict of Interests

There is no conflict of interests.

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Review Article

Cardiovascular Effects in Childhood Cancer Survivors Treated with Anthracyclines

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Anthracyclines are commonly used to treat childhood leukemias and lymphomas, as well as other malignancies, leading to a growing population of long-term childhood cancer survivors. However, their use is limited by cardiotoxicity, increasing survivors' vulnerability to treatment-related complications that can markedly affect their quality of life. Survivors are more likely to suffer from heart failure, coronary artery disease, and cerebrovascular accidents compared to the general population. The specific mechanisms of anthracycline cardiotoxicity are complex and remain unclear. Hence, determining the factors that may increase susceptibility to cardiotoxicity is of great importance, as is monitoring patients during and after treatment. Additionally, treatment and prevention options, such as limiting cumulative dosage, liposomal anthracyclines, and dexrazoxane, continue to be explored. Here, we review the cardiovascular complications associated with the use of anthracyclines in treating malignancies in children and discuss methods for preventing, screening, and treating such complications in childhood cancer survivors.

1. Introduction

Cancer is diagnosed in more than 12,000 children in the United States every year [1]. Over the past 25 years, the 5- and 10-year survival rates for childhood cancers have substantially improved, from less than 50% in the 1970s to almost 80% today [2, 3]. Some of this improvement comes from the use of anthracycline chemotherapeutic agents, which are widely used to treat childhood leukemias and lymphomas, as well as other malignancies. Their use has helped create a growing population of long-term childhood cancer survivors of more than 325,000 in the United States alone [4]. However, this growing population of survivors is at a substantial risk for treatment-related complications that can markedly affect their quality of life. Increasingly, survivors and their clinicians are realizing the importance of continuous monitoring long after their cancer treatment has been completed.

Within the first 30 years after diagnosis, 75% of childhood cancer survivors will suffer from a chronic health condition [5]. Recent 5-year estimates indicate that the leading non-cancer-related cause of morbidity and mortality in long-term survivors of childhood cancer is cardiovascular-related disease [5–10]. Survivors are 8 times more likely than the general population to die from cardiovascular-related disease, and compared to sibling controls, they are 15 times as likely to suffer from heart failure (HF), more than 10 times as likely to have coronary artery disease, and more than 9 times as likely to have had a cerebrovascular accident during the first 30 years after cancer diagnosis [5].

Anthracyclines, such as doxorubicin, are among the leading causes of these cardiovascular events. The cardiotoxic nature of anthracyclines, coupled with their widespread use, may explain the large impact they have made on survivor morbidity and mortality [11]. Childhood cancer survivors exposed to anthracyclines are at a significantly increased

risk of HF, and this risk increases as the cumulative dose increases; 30 years after diagnosis, more than 7.5% will have experienced HF [7]. The risks of cardiac events persist up to 45 years beyond treatment and are the second most common cause of death, after secondary malignancy [12]. Cardiotoxicity from childhood cancer treatments is a cause for heart transplantation in young adults [13]. In addition to clinical outcomes, detailed cardiac evaluations have shown that more than half of anthracycline-exposed childhood cancer survivors have subclinical cardiac abnormalities, including decreased left ventricular (LV) mass and wall thickness, increased LV afterload, and decreased LV contractility [14].

The severity of the cardiotoxic effects of anthracyclines vary and are categorized by time of onset as acute, occurring during or immediately after treatment, early, occurring within 1 year of exposure, and late, occurring 1 or more years after initial exposure (Table 1) [11, 15]. Severe cardiotoxicity, during or shortly after treatment, is strongly associated with HF later in life, despite an initial asymptomatic interval. In a followup study of long-term survivors of childhood cancer who were treated with anthracyclines and who experienced acute HF, all had a temporary recovery though nearly half of these patients later had recurrent HF [14]. Understanding the early- and late-onset cardiovascular complications of long-term survivors of childhood cancer is important for oncologists, cardiologists, and other health care providers involved in the care of such patients, not only after cancer treatment but also when selecting treatments at the time of diagnosis.

Here, we review the cardiovascular complications associated with the use of anthracyclines in treating malignancies in children and discuss methods for preventing, screening, and treating such complications in childhood cancer survivors.

2. Anthracyclines and Mechanisms of Cardiotoxicity

Anthracyclines are commonly used to treat a variety of solid and hematologic tumors in both adults and children. However, because they have clinically relevant dose-dependent cardiotoxicity, lower doses are used in treating childhood cancer [18, 19]. Anthracyclines express their anticancer effects through two major mechanisms: (1) their intercalation between base pairs of DNA prevents cancer cells from replicating and (2) their inhibition of topoisomerase-II activity prevents the uncoiling process of DNA that is necessary for replication and transcription.

However, the specific mechanisms of anthracycline cardiotoxicity are complex and, despite decades of research, remain unclear. The oxidative stress hypothesis is among the most widely studied and accepted cellular mechanism thought to cause cardiotoxicity [20–23]. Once administered, anthracyclines are believed to enter cells through passive diffusion, where they can reach intracellular concentrations several hundred times higher than that in extracellular compartments. Once inside the cell, anthracyclines may form complexes with intracellular iron, leading to the production of free radicals, which can cause DNA damage and lipid peroxidation. The damage caused by free radicals, and by reactive oxygen species (ROS), can eventually lead to cell death and larger-scale organ damage.

Why the heart is particularly vulnerable to oxidative stress caused by anthracyclines is not clear, but the abundance of mitochondria found in cardiomyocytes [5] may be involved. Increasingly, the importance of mitochondria as key mediators of anthracycline-induced cardiotoxicity has been reported [24]. Cardiolipin, a phospholipid found in high concentrations on the inner cell membrane of cardiac mitochondria, has a high affinity for anthracyclines. This affinity allows increased concentrations to enter cardiac mitochondria [25, 26], which may impair membrane stability or lead to mitochondrial DNA damage by intercalation. Anthracycline effects on the mitochondria may also impair the cell's ability to produce energy and to handle the added oxidative stress of cancer and its treatments [21, 27–29]. In addition, one of the heart's key antioxidants, glutathione peroxidase, is depleted in the presence of anthracyclines [30].

Several other mechanisms have been suggested for anthracycline cardiotoxicity, including the induction of apoptosis, abnormal creatine kinase activity, the production of vasoactive amines, the formation of toxic metabolites, upregulation of nitric oxide synthetase, and the inhibition of transcription and translation [31–33]. Anthracyclines cause uncoupling of the electron transport chain, which creates highly reactive oxygen species, and can impair oxidative phosphorylation and adenosine triphosphate (ATP) synthesis [24]. Anthracyclines can also impair mitochondrial calcium homeostasis, leading to the loss of stability of the mitochondrial membrane, decreased ATP, and cell death.

In addition, several other changes have been observed in anthracycline-exposed cardiomyocytes, for which the underlying mechanisms have yet to be fully explained. These changes include depleted cardiac stem cells [34], impaired DNA synthesis [35], impaired cell signaling that triggers cell death [36], altered gene expression [37], inhibited calcium release from the sarcoplasmic reticulum [38], impaired formation of the protein titin in sarcomeres [39], and impaired mitochondrial creatine kinase activity and function [40]. None of these findings, however, are necessarily completely dependent or independent of an oxidative stress pathway. The fact that many of these subcellular consequences continue to progress for weeks after anthracycline exposure may provide insight into the mechanisms of chronic cardiomyopathy [41].

Finally, understanding cardiovascular cell signaling proteins may prove useful by clarifying both the pathway of toxicity and the early detection of anthracycline-induced cardiotoxicity. Because of the synergistic cardiotoxic potential of anthracyclines and the ErbB2 antibody, trastuzumab, interest in the role of neuregulin (NRG-1) is growing. Neuregulin is a growth factor that is an endogenous ligand for the protein ErbB2 and is possibly involved in a signaling pathway that regulates sarcomere functioning [33]. Neuregulin levels are decreased with anthracycline use, suggesting a potential mechanism of toxicity. However, this decrease has not

Table 1: Characteristics and course of anthracycline-induced cardiotoxicity [15].

Characteristics	Acute cardiotoxicity	Early-onset, chronic progressive cardiotoxicity	Late-onset, chronic progressive cardiotoxicity
Onset	Within the first week of anthracycline treatment	<1 year after the completion of anthracycline treatment	≥1 year after the completion of anthracycline treatment
Risk factor dependence	Unknown	Yes[a]	Yes[a]
Clinical features in adults	Transient depression of myocardial contractility	Dilated cardiomyopathy	Dilated cardiomyopathy
Clinical features in children	Transient depression of myocardial contractility	Restrictive cardiomyopathy and/or dilated cardiomyopathy	Restrictive cardiomyopathy and/or dilated cardiomyopathy
Course	Usually reversible on discontinuation of anthracycline	Can be progressive	Can be progressive

From Adams et al. [15]. Reprinted with permission from John Wiley & Sons, Inc.
[a]Data from Giantris et al. [16], and Grenier and Lipshultz [17].

been clearly associated with serum and echocardiographic markers of cardiac dysfunction [42].

3. Risk Factors for Anthracycline-Related Cardiac Abnormalities

Not all children exposed to anthracyclines experience cardiac abnormalities, and the clinical severity of the abnormalities that do occur varies greatly between individuals. Hence, determining the factors that may increase susceptibility to the cardiotoxic effects of anthracyclines is of great importance. First, ascertaining which patients are most likely to experience cardiotoxicity can guide treatment, especially as long-term health becomes a more prominent treatment focus. Second, identifying risk factors may help to determine the mechanisms directly responsible for cardiac damage and potentially lead to novel strategies for cardioprotection and treatment. Third, risk stratification may help guide the efficient use of followup screening [22].

One of the main risk factors for anthracycline cardiotoxicity is high cumulative dose. Since the 1970s, studies have shown that higher cumulative doses of anthracyclines [43] and higher infusion rates are risk factors for anthracycline cardiotoxicity [10, 19]. The strong association between cumulative anthracycline dose and cardiotoxicity appears to be more important with increasing time from treatment [44, 45]. This relationship was revealed in a study of nearly 15,000 long-term survivors of childhood cancer treated with anthracyclines who described their cardiac health at up to 30 years after cancer treatment (Figure 1) [7]. Other known risk factors for anthracycline cardiotoxicity include younger age at treatment, female sex, the use of concomitant cardiotoxic therapies (such as mediastinal radiation), increasing time since treatment, cardiac injury, as indicated by elevations of serum cardiac troponin-T (cTnT), neurohormonal activation of cardiac myocytes in response to pressure and stress, as indicated by elevations of N-terminal probrain natriuretic peptide (NT-proBNP), during anthracycline therapy, and HF during anthracycline therapy [5, 10, 14, 19, 28, 45].

Although not completely understood, genetic predisposition may also be an important factor in determining the risk of anthracycline cardiotoxicity [46–48]. Genetic polymorphisms may alter membrane permeability, antioxidant capacity, or metabolism that favors the creation of cardiac damage. Hereditary hemochromatosis, a genetic disorder prevalent in individuals of European descent that can lead to iron overload, is of particular interest because doxorubicin's cardiotoxic effects depend, at least in part, on its interaction with iron. In mice, Hfe deficiency, the defective gene in hereditary hemochromatosis, increases the susceptibility to doxorubicin-induced cardiotoxicity, including mitochondrial degradation and increased mortality, when compared to that found in wild-type mice [49]. This fact suggests that genetic mutations related to defects in iron metabolism may contribute to cardiotoxicity in humans although there is currently no literature on the effect in humans. The concept of genetic predisposition as a risk factor for cardiotoxicity is further supported by findings of greater cardiac susceptibility in patients with trisomy 21 and black race [50, 51].

Despite the identification of these population-based risk factors, determining the risk for a specific patient is still difficult. Therefore, it is important that all children who receive anthracycline therapy be followed closely, both during and after treatment for cardiotoxicity. As a guide, the "Long-term Follow Up Program Resource Guide" [52], developed by Children's Oncology Group's Nursing Discipline Committee in collaboration with the Late Effects Committee, provides recommendations for screening and management of late effects of therapeutic exposures used during treatment for pediatric malignancies.

4. Monitoring Long-Term Cancer Survivors

4.1. Biomarkers. Although identifying multiple risk factors has helped to characterize groups at high risk for cardiac injury, both tolerance of chemotherapy and predisposition to cardiac damage still vary substantially between patients. This difference has led to an increasing interest in the use of monitoring serum biomarkers as a means of evaluating cardiotoxicity during and after treatment with anthracyclines.

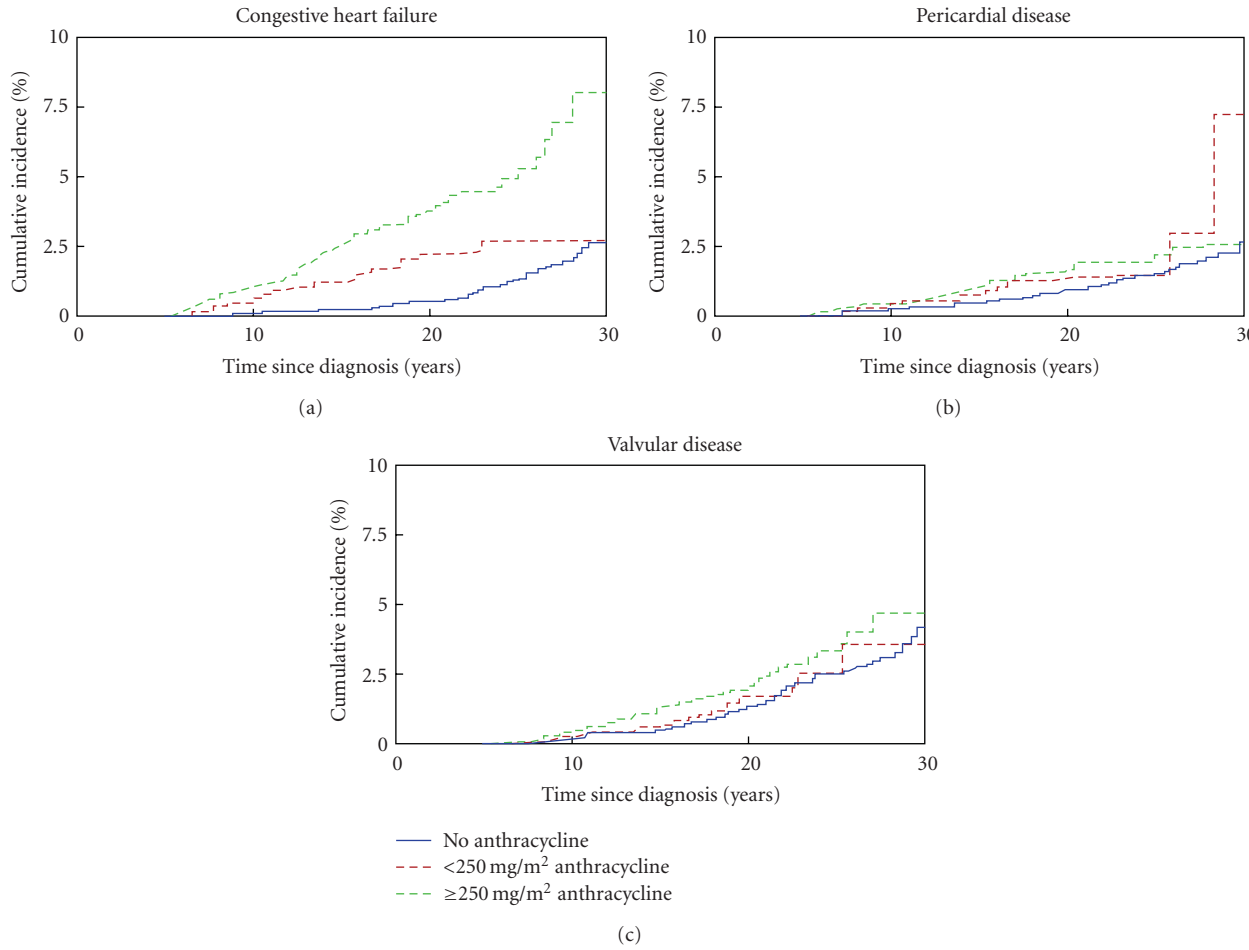

Figure 1: Cumulative incidence of cardiac disorders among childhood cancer survivors by anthracycline dose. From Mulrooney et al. [7]. Reprinted with permission from BMJ Publishing Group, Ltd.

4.1.1. Serum Cardiac Troponins. Elevations in cardiac troponin-T and I (cTnT and cTnI) accurately indicate cardiac damage, and their presence in serum in any detectable amount may indicate irreversible cellular necrosis [45, 54, 55]. Cardiac troponin-T is a cardiac-specific isoform that is present in cardiac myocytes in both the contractile unit and the cytoplasm. Serum cardiac troponins are widely used in diagnosing and managing ischemic heart disease in adults and also provide valuable clinical information in many other types of cardiac damage in children [56].

Initial investigations in animal models found dose-dependent cTnT elevations in response to doxorubicin administration, elevations that were related to the severity of histopathologic findings in cardiac tissue. This relationship is consistent with the hypothesis that anthracyclines damage cardiomyocytes, leading to the release of intracellular cTnT into the circulation [57].

The Dana-Farber Cancer Institute childhood acute lymphoblastic leukemia (ALL) consortium protocol 95-001 study found that elevated serum cTnT levels during the first 90 days of anthracycline therapy were significantly associated with reduced LV mass and LV end-diastolic posterior wall thickness as measured by echocardiography 4 years later [58, 59].

The cardiac contractile protein, cTnI, when present in the serum, is related to LV dysfunction and increased cardiovascular risk in adults receiving high-dose chemotherapy [54, 55]. These findings provide evidence of the value of serum troponin measurements in childhood cancer patients receiving anthracyclines.

4.1.2. Serum NT-proBNP. N-terminal probrain natriuretic peptide is produced during the cleavage of proBNP, a prohormone released from the cardiac ventricles in response to pressure overload and stretching [60, 61]. Chronic elevations in NT-proBNP indicate increased ventricular wall stress, in association with pressure overload and elevated diastolic pressure [62, 63].

The aforementioned Dana-Farber Cancer Institute protocol 95-001 study also assessed serum NT-proBNP measurements during and after therapy as possible predictors of cardiac damage. Elevations in NT-proBNP during the first 90 days of therapy were associated with an abnormal LV thickness-to-dimension ratio 4 years later, suggesting

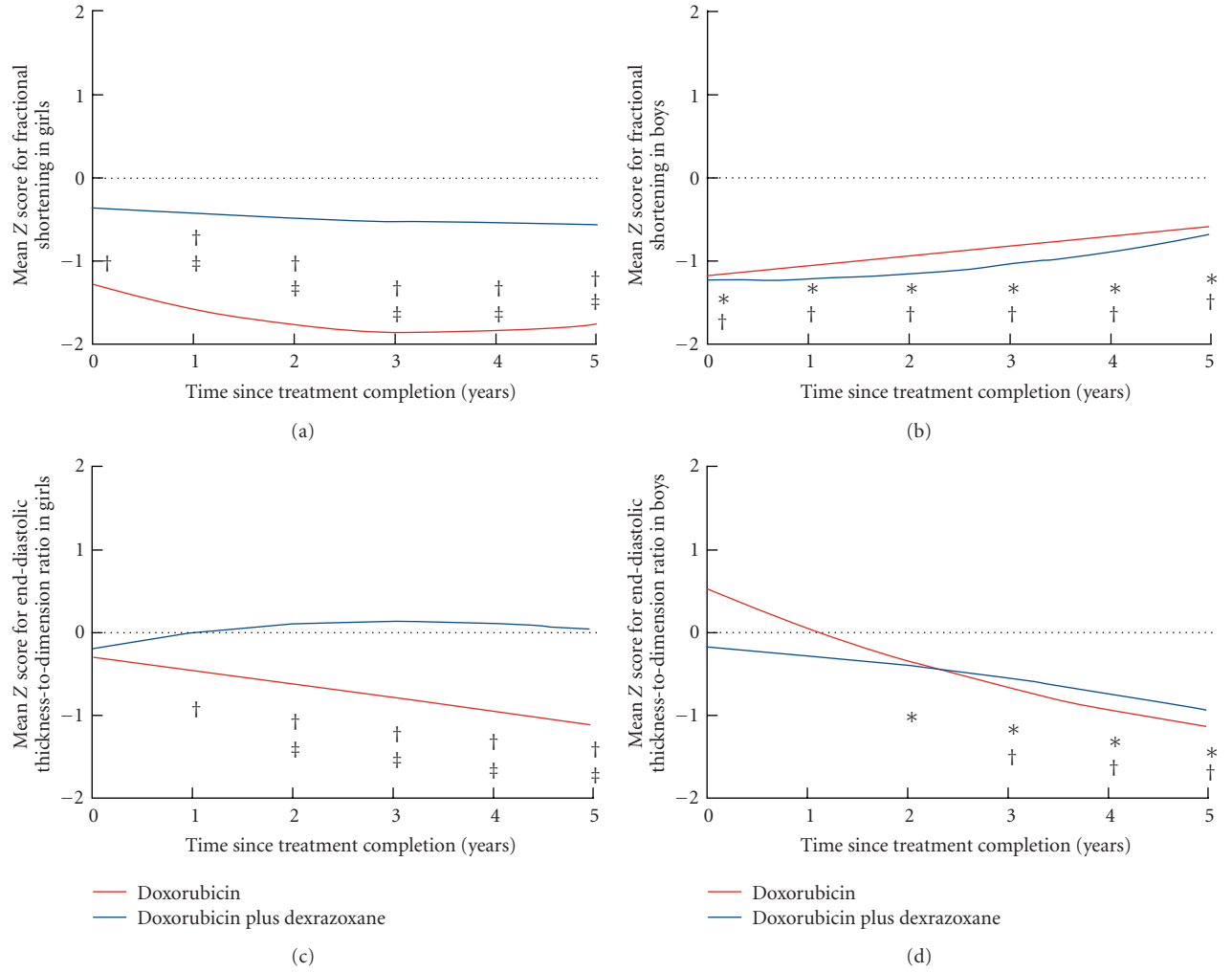

Figure 2: Mean left ventricular echocardiographic Z scores in boys and girls ($n = 134$). Plots are adjusted for age; $^{*}P \leq .05$ for comparison of the mean Z score of the doxorubicin plus dexrazoxane group with zero; $^{\dagger}P \leq .05$ for comparison of the mean Z score for the doxorubicin group with zero; $^{\ddagger}P \leq .05$ for comparisons of mean Z scores between the doxorubicin and doxorubicin plus dexrazoxane groups. From Lipshultz et al. [53]. Reprinted with permission from Elsevier.

pathologic ventricular remodeling. Additionally, a higher percentage of children had elevated levels of NT-proBNP than had elevated levels of cTnT before, during, and after treatment. This difference suggests that NT-proBNP may detect cardiac stress before any irreversible cell damage and death occurs, which may help identify children early in therapy who are at increased risk of eventual anthracycline-related cardiac abnormalities [59].

4.1.3. High-Sensitivity C-Reactive Protein. As a global inflammatory marker and a critical component of the immune system, high-sensitivity C-reactive protein (hsCRP) is widely used to assess patient health [64]. Systemic inflammation is associated with increased rates of cardiovascular disease in adults and may also be involved with the mechanisms underlying anthracycline-related cardiotoxicity and pediatric cardiomyopathy [65]. As such, elevations in hsCRP may be a strong indicator of cardiac stress [66].

Despite a small sample size, one study of 19 children with HF divided into three groups based on symptom severity found that serum hsCRP levels were associated with decreased LV function and discriminated between the different groups of symptom severity [65]. Another study of 156 survivors of childhood ALL showed that survivors had significantly elevated levels of hsCRP when compared to levels in sibling controls [67]. These findings have encouraged further research on the use of serum hsCRP measurements collected during therapy as potential predictors of late cardiac effects. Serum hsCRP may prove to be a valuable screening tool for identifying long-term survivors at increased risk of subsequent cardiac disease.

4.2. Nanoparticle-Capture Mass Spectrometry. The ability to identify heart-derived tissue proteins associated with myocardial injury that can be detected before marked elevations in cTnT could have profound implications on

earlier detection and clinical monitoring for doxorubicin cardiotoxicity. One pilot study using nanoparticle-mass spectrometry identified several candidate protein biomarkers previously implicated in cardiac dysfunction, remodeling, fibrosis, and hypertrophy [68]. Identification of these candidate biomarkers have the potential to increase the predictive value of more routinely used markers, such as cTnT, for earlier detection of cardiac damage, before irreparable damage and loss of cardiomyocytes occur. However, due to the small limited sample size, further studies evaluating the efficacy of nanoparticle-mass spectrometry may advance this novel diagnostic approach.

4.3. Echocardiography. Several detailed echocardiographic studies in 115 long-term childhood ALL survivors treated with doxorubicin have been conducted to better determine the long-term cardiac status of these patients [14, 69, 70]. These studies, ranging from 6 to 12 years of followup after treatment, have documented a persistent and progressive restrictive-like cardiomyopathy in long-term childhood cancer survivors treated with anthracyclines [14, 69, 70]. The restrictive cardiomyopathic-like nature of anthracycline cardiotoxicity may be of great clinical importance in that it suggests theories and treatments derived from studies of dilated cardiomyopathy may be of limited value in understanding anthracycline cardiotoxicity throughout life [71]. The findings of abnormal LV structure and function, as well as a restrictive-like cardiomyopathic pattern, are consistent with those of other long-term followup studies conducted in other groups of anthracycline-treated childhood cancer survivors [72–74].

5. Preventing Anthracycline-Induced Cardiotoxicity

5.1. Anthracycline Dosage. Treatment protocols using lower doses of anthracyclines have reduced the incidence of acute cardiac complications to less than 1% although chronic LV dysfunction is still a major clinical concern [50, 53]. In the 1970s, before the association between higher cumulative doses of anthracyclines and the greater risk of cardiotoxicity was known, clinical trials administered cumulative doxorubicin doses greater than 400 mg/m^2 to children with ALL. Lipshultz et al. found that patients who received such high cumulative doses experienced clinically important, progressive LV effects that continued even decades after the completion of doxorubicin treatment [14, 69, 70]. On the basis of this experience, cumulative doses of doxorubicin administered to children and adolescents with ALL were reduced in the 1980s such that high-risk children received a cumulative dose of no more than 360 mg/m^2, and standard-risk children received a relatively low cumulative dose of no more than 60 mg/m^2 [58, 75]. Followup of the high-risk patients suggested that some risk of delayed LV abnormalities remained, although the frequency of overt HF was much lower [14, 69, 70].

In the 1990s, analysis of the combined results of the Dana-Farber Cancer Institute's long-term survivors and those from patients treated in Denmark revealed that after a median followup of 8.1 years, the risk of LV abnormalities was lower in patients who received no more than 300 mg/m^2 than it was in those who received more than 300 mg/m^2 of doxorubicin [19]. On the basis of those results, the cumulative doxorubicin dose for high-risk ALL patients on the Dana-Farber Cancer Institute Protocol 95-001 were further reduced to 300 mg/m^2.

5.2. Liposomal Anthracyclines. Structural modifications of anthracyclines have been considered as possible cardioprotection strategies. Of the structural modifications of anthracyclines, liposome-encapsulated anthracyclines are possibly the most promising cardioprotectant. Liposome-encapsulated anthracyclines escape the leaky capillary system of tumor sites and as such remain concentrated there, in the interstitial fluid. They are also less likely to escape the tight capillary junctions of the heart. This ability to reduce the plasma levels of free doxorubicin is thought to be the source of the reduced cardiotoxicity provided by liposomal formulations of anthracyclines [76]. Although studies of liposomal-encapsulated anthracyclines are limited in children, biopsies have confirmed that these anthracyclines have a lower early cardiotoxicity than conventional anthracyclines [77], and studies by Marina et al. have helped to confirm their safety in children [78].

5.3. Treatment with Continuous Anthracycline Infusion. Because the cellular mechanisms underlying anthracycline cardiotoxicity are still not completely understood, it has been theorized that continuous infusion might provide some cardioprotective benefit by lowering peak serum levels of the drug [79]. This theory was supported by findings from observational studies in children that found higher dose rates to be associated with cardiotoxicity, independently of the effect of total dose [80]. In addition, in adults receiving anthracyclines, acute cardiotoxicity was diminished in protocols using continuous infusion [81]. On the basis of these findings, continuous infusion was incorporated into many pediatric protocols, despite a lack of evidence on its long-term cardioprotective efficacy [44, 82].

A randomized controlled trial of continuous (over 48 hours) doxorubicin infusion versus bolus doxorubicin infusion in 121 high-risk pediatric ALL cases found no cardiac-related benefit to using the continuous infusion after a median of 1.5 years after diagnosis [44]. Similar results were found after continued followup of this cohort at a median followup of 8 years [82]. In addition, several retrospective reviews reported no statistically significant differences in the echocardiographic characteristics of children with cancer 5 to 7 years after treatment with either continuous infusion (over 6 to 24 hours) or bolus infusion of anthracyclines [79, 80].

5.4. Treatment with Dexrazoxane. As mentioned above, anthracycline-related cardiotoxicity is likely related, at least in part, to the generation of ROS, which may be exacerbated by iron-dependent mechanisms [81]. This relationship has

led to the investigation of several iron-chelating agents, such as dexrazoxane, for preventing anthracycline cardiotoxicity [81]. Dexrazoxane is an iron-chelating agent that inhibits the formation of anthracycline-iron complexes that generate toxic and highly charged ROS. However, other mechanisms independent of oxidative stress have been proposed as mediators in the cardioprotective effect of iron chelation [23], such as the mitigation of DNA damage caused by dexrazoxane [76]. This proposal has led to great interest in the use of dexrazoxane in children [83]. Dexrazoxane is currently recommended by the American Society of Clinical Oncology for preventing cardiotoxicity in specific adult cancer treatment protocols [81].

Fearing that the protection dexrazoxane provides to cardiomyocytes might extend to cancer cells as well and perhaps lead to increased rates of second malignancies, some investigators have been reluctant to use dexrazoxane. Although such a relationship was previously reported [84], but questioned [85, 86], in a pediatric Hodgkin lymphoma trial, no association between dexrazoxane and second malignancies has been found [87].

A randomized controlled trial of dexrazoxane in children with ALL treated with doxorubicin used serial cTnT samples taken during therapy to measure cardiac damage [57]. Of the 82 children who received doxorubicin plus dexrazoxane, significantly fewer had cTnT elevations when compared with the 76 children who received doxorubicin alone. The difference between groups became even greater over the course of treatment. After 6 to 8 months, almost 50% of those treated with doxorubicin alone had an elevated cTnT level, as opposed to less than 10% of those treated with doxorubicin plus dexrazoxane. A recent followup report of this group at a median of 8.7 years found that event-free survival did not differ significantly between the two groups [53] and that there was no increased risk of recurrence or second malignant neoplasms [53, 87]. These findings show that dexrazoxane can provide long-term cardioprotection without hindering the efficacy of doxorubicin.

Serial echocardiographic measurements during the 4 years after this trial have also been reported [53]. Children treated with doxorubicin plus dexrazoxane had progressively less decreased LV fractional shortening and greater LV mass and LV wall thickness over time. Most recently, the protective effects of dexrazoxane reported in this trial appear to be sex related [53], which is consistent with recent findings from animal studies [88]. Females showed the greatest protective effect from dexrazoxane therapy, while males receive did not receive such benefit (Figure 2) [53]. These findings further highlight that there is still much to learn about the mechanisms underlying such differences [53, 89] although sex-related differences in the transport and clearance of doxorubicin have been reported [90, 91], as has dexrazoxane cardioprotection against the sex-related hormone, testosterone [92].

The protective effect of dexrazoxane against anthracycline cardiotoxicity is further supported by studies of childhood cancers other than leukemia [81, 83]. However, research is needed to fully understand the subtle risks associated with the use of dexrazoxane, what methods of dexrazoxane administration are most efficient, and what doses are necessary to achieve adequate protection.

5.5. Traditional Cardiovascular Disease Risk Factors. With more extended followup, the true incidence of chronic HF in long-term childhood cancer survivors treated with anthracyclines may exceed the reported 1% to 16% range [44, 93]. Chronic anthracycline cardiotoxicity is not only evident as symptomatic LV dysfunction, it also frequently manifests as subclinical abnormalities in LV structure and function. In some cases, these subclinical changes may progress to HF and cardiac death. Such effects may also leave long-term childhood cancer survivors more vulnerable to future non-anthracycline-related cardiovascular insults.

Long-term childhood cancer survivors, like the general population, may have one or more of the traditional risk factors for atherosclerosis, which could provide an additive risk of future cardiovascular complications beyond that directly related to cancer therapies. Obesity, physical inactivity, tobacco use, and diabetes mellitus are among the most commonly examined traditional modifiable atherosclerotic risk factors. An improved understanding of the lifetime cardiovascular risk associated with these factors in long-term childhood survivors may help guide treatment and predict any potential additional cardiovascular risk of specific cancer therapies, such as the use of anthracyclines [94].

5.5.1. Obesity. In the United States, childhood obesity rates have increased to where it has now become epidemic [95, 96]. Less than 5% of 12-to-19-year-olds were overweight in the late 1960s, while almost 17% were overweight by the year 2008 [96]. This report also shows that almost 32% of children and adolescents between 2 to 19 years old are at risk of overweight. One study showed that almost 80% of obese 10-to-14-year-olds who had an obese parent were obese as adults [97]. This relationship raises two main concerns: (1) childhood overweight and obesity are associated with poor health outcomes, such as coronary artery disease, hypertension, and diabetes [98] and (2) childhood obesity is strongly associated with adult obesity, which is associated with an increased risk of atherosclerotic disease and death. The American Heart Association's Childhood Obesity Research Summit concluded that: "Obesity contributes to a significant burden in terms of chronic diseases, rising healthcare costs, and, most importantly, disability and premature death. It appears that this burden will increase in the future [99]."

Studies of obesity in long-term survivors of childhood cancer have found similarly troubling trends suggesting that survivors may be at increased risk for obesity as a result of their cancer history. One study compared body fat between 170 pediatric cancer survivors and 71 sibling controls. This study found that more than one-third of survivors met the criteria for overweight or obese according to the body mass index (BMI), but this was no different than siblings. However, male survivors were found to have greater body fat and trunk fat compared to siblings, while no differences were found between female survivors and siblings [100].

Table 2: Areas for future research in anthracycline cardiotoxicity.[a]

Basic research	Clinical research
(1) Exploration beyond the oxidative stress hypothesis as a primary mechanism of anthracycline cardiotoxicity	(1) Reduction of anthracycline cardiotoxicity in clinical practice
(2) Implementation of long-term studies in animal models	(2) Identification of early signs of cardiac damage
(3) Identification of predictive markers of cardiac damage	(3) Educate clinicians: anthracycline-induced cardiotoxicity can initially respond to cardiac medications
(4) Determination of the relative impact of different mechanisms of myocardial damage	(4) Determination of the cardiotoxicity of targeted and combination therapies
(5) Exploration into the relationship between growth factors and anthracyclines	(5) Identification of a balance between cardiotoxicity with clinical benefit
(6) Understanding drug interactions in new combination therapies	(6) Definition of risks and benefits for subgroups of patients
(7) Assessment of the effects of anthracyclines on cardiac development	(7) Management of cardiac dysfunction in cancer survivors treated with anthracyclines
(8) Assessment of the effects of anthracyclines on non-myocyte cardiac cells	(8) Specifications of dietary and exercise recommendations for anthracycline-treated patients
(9) Assessment of risk-benefit factors in groups with compounding risk factors for cardiomyopathy	(9) Understanding the progression of anthracycline cardiomyopathy: systolic versus diastolic heart dysfunction
(10) Determination of genetic predispositions to anthracycline cardiotoxicity	(10) Expansion of the use of dexrazoxane and liposomal anthracyclines

[a] Data from Gianni et al. [23].

The largest report to date of nearly 8000 long-term survivors found that about 41% were either obese or overweight [100]. This study and others also found that despite a high prevalence of obesity, long-term survivors were not more likely to be obese than the general population although certain groups, such as survivors of ALL, were at increased risk of obesity [101, 102].

The idea that certain subgroups of long-term childhood survivors are at increased risk of obesity is supported by studies of those survivors exposed to cranial radiation. Many of these studies reveal treatment-related damage to the hypothalamic-pituitary axis, with subsequent growth hormone deficiency and eventual obesity. However, it should be noted that not all studies have found such a relationship and that other factors, such as obesity before diagnosis, may be more powerful predictors of obesity after treatment [103]. It is clear, though, that obesity is highly prevalent in survivors of all types of childhood cancer and may predispose this group to future health problems, especially atherosclerotic disease, which may be especially problematic for these patients who are less able to compensate for ischemic cardiac insults.

5.5.2. Physical Inactivity. Physical inactivity is associated with higher risk of cardiovascular disease as well as with other traditional atherosclerotic disease risk factors, such as insulin resistance and obesity. Physical activity is not only recommended by several medical associations, including the American Academy of Pediatrics, but guidelines have been created by several organizations, including the US Department of Health and Human Services [104, 105].

Physical inactivity appears to be more common in long-term childhood survivors than in the general population. Miller et al. [102] reported that male survivors watched significantly more hours of television compare to siblings. They also found that increased television viewing hours was associated with higher BMI and percent body fat in male and female survivors of childhood cancer. A survey of nearly 10,000 long-term survivors of childhood cancer and 3,000 of their siblings revealed that survivors were more likely than their healthy siblings and the general population to report being physically inactive and being less likely to meet recommended physical activity guidelines [106]. This survey and others have found that some long-term childhood survivors may be unable to comply with these guidelines as a result of the physical limitations incurred by their cancer-related surgery or treatment-related cardiac damage. Hopefully, interventions that lead to appropriate and safe increases in the physical activity of long-term survivors may decrease risk of atherosclerotic disease and its associated negative health outcomes [107].

5.5.3. Tobacco Use. Cigarette smoking is a well-known major preventable risk factor for cardiovascular disease and all-cause mortality among individuals in the general population. The increased rate of cardiovascular disease in smokers has been convincingly evident since the 1960s [108]. One systematic review of the health behaviors of long-term survivors found that most studies have reported lower rates of smoking in survivors relative to the general population although these rates are still high enough to be a concern and to warrant intervention [109].

Up to 17% of long-term childhood survivors in the United States are active smokers, compared to more than 20% of the general adult population [110, 111]. The increased cardiovascular disease risk associated with

smoking may be magnified in long-term survivors who may already have underlying cardiac abnormalities as a result of their malignancy and its treatment. Therefore, efforts aimed at smoking prevention and cessation in long-term childhood survivors are essential to improve long-term outcomes [112].

5.5.4. Insulin Resistance. The prevalence of insulin resistance and overt diabetes has risen steadily and parallels the rise in the prevalence of obesity and the decline in physical activity. In the United States today, almost 13% of adults aged 20 years or older have either diabetes or prediabetes, a prevalence that rose from 5.1% between 1988 and 1994 and to 7.7% between 2005 and 2006 [113].

Diabetes is a major risk factor for cardiovascular disease. Current recommendations for adults state that the added cardiovascular disease risk associated with diabetes is equivalent to that of a previous myocardial infarction. A recent report of more than 8000 long-term survivors found that these survivors are nearly twice as likely to report having diabetes as were their siblings [114].

Another longitudinal study of more than 200 long-term survivors found that 4% had diabetes, another 7% had impaired glucose tolerance, and another 4% had hyperinsulinemia [115]. These findings are especially worrisome given that the average age of adult long-term childhood survivors in the study was 25 years and that all were less than 40 years old, age cohorts that would otherwise would be considered at low-risk for impaired glucose metabolism. Cancer treatment-related cardiotoxicity may have left many childhood cancer survivors more vulnerable to cardiovascular disease [44]. Aggressive and early intervention is warranted to maximally reduce the risk in this population.

5.5.5. Hypertension. Hypertension is among the leading causes of cardiovascular disease. In 2008, 29% percent of US adults were hypertensive, an increase from almost 24% in 1988–1994 [116].

Survivors of childhood cancer have a higher risk of developing hypertension compared to the general population. A study of 5,599 childhood cancer survivors and 2,936 siblings reported that survivors were more likely to report taking medication for hypertension than their siblings (OR 1.9, 95% CI 1.6–202) [100].

In addition, a preexisting diagnosis of hypertension further increases the risk of clinically significant anthracycline cardiotoxicity [18]. Studies in older adults have shown that hypertension may work synergistically with doxorubicin increasing the risk of CHF [117]. Hershman et al. found that hypertension intensified the effect of doxorubicin on risk of CHF in older adults [118]. Further, studies in rats have shown a similar trend where hypertensive rats were more sensitive than normotensive rats to the cardiotoxic effects of doxorubicin [88, 118]. Therefore, monitoring cardiac status during and after anthracycline therapy is important, particularly in the long term, as risks for cardiovascular disease naturally increase with age.

6. Conclusions and Directions for Research

Effective anti-neoplastic therapies for childhood cancer are one of the great successes of modern medicine and have helped to create a large population of childhood cancer survivors. However, even years after successfully battling cancer, many survivors are burdened by the cardiotoxicity that can result from cancer therapy. There remains a growing need in both basic and clinical research to better understand the mechanisms of anthracycline cardiotoxicity, to develop effective and safe cardioprotection strategies, and to identify the risk factors for cardiac damage. Table 2 summarizes a number of the areas where further research could help to fill the current gaps in knowledge [23]. Most importantly, cardiologists and oncologists should collaborate to find a balance between the risks of cardiotoxicity and the benefits of oncologic therapy to maximize the quality of life and survival for long-term childhood cancer survivors.

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Review Article

Review of Cardiotoxicity in Pediatric Cancer Patients: During and after Therapy

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With the improvement in survival from childhood cancer, late effects of therapy are becoming more apparent. Cardiac disease, one of these late effects, has a significant impact on the life of survivors of childhood cancers. Most survivors are followed by primary care doctors and adult subspecialists after they have graduated from pediatric centers. Since much of the cardiac toxicity of therapy occurs years off of therapy, it is important for these physicians to be aware of how to monitor survivors for the development of cardiac toxicities. In this paper we will discuss the incidence of cardiac disease during treatment and in survivors, what treatment modalities contribute to its development and modalities utilized to screen for cardiac disease. Recommendations for posttherapy monitoring will be emphasized.

1. Introduction

Treatment for pediatric malignancies has greatly improved survival since the 1970s. According to SEER data, the mortality rate declined by almost 40 percent between 1975 and 1995 [1]. This decrease in mortality has been accompanied by an increase in the recognition of long-term side effects from the treatment of childhood cancers. The Childhood Cancer Survivor Study (CCSS) was established to monitor these side effects. The study has been following a cohort of patients, who were treated from 1970–1986 and had survived at least 5 years at enrollment in the study [2]. This cohort of survivors was found to have increased relative risk of a chronic health condition compared to their siblings of 3.3 (95% CI, 3.0–3.5) [3]. Chronic healthcare conditions attributed to cancer treatment include, but are not limited to, respiratory dysfunction, infertility, cognitive delays, cardiovascular disease, and renal failure [2, 3]. In a subanalysis of the CCSS population, 14,358 patients returned a survey regarding cardiovascular health [4]. Congestive heart failure had a prevalence of 1.7% versus 0.2% in siblings, valvular abnormities of 1.6% in survivors versus 0.5% in siblings, and pericardial disease of 1.3% in survivors versus 0.3% among siblings. This increase risk highlights the need for survivors of childhood cancers to be monitored for the development of cardiovascular disease long term after treatment.

Please note that this is not a systematic review, but an attempt to educate caregivers whose focus does not lie primarily in the fields of hematology-oncology regarding the pediatric cancer treatments which may place survivors at risk for developing cardiac dysfunction. It also includes recommendations for monitoring for the development of cardiac dysfunction. This paper is comprised of published data written in English which was compiled through Medline, with a focus on studies that included patients that were under the age of 18 at time of their cancer treatment. Due to the inclusion criteria, the reader should be aware of a potential bias regarding negative study results which are less likely to be published.

2. Risk Factors

The treatment of children with cancer includes chemotherapy, radiation, and surgery. Both chemotherapy and radiation therapy can contribute to the increased risk for cardiovascular disease that survivors of childhood cancer experience (see Table 1).

Table 1: Cancer therapies utilized in pediatric population associated with cardiotoxicity.

Type of therapy	Dose that places at highest risk	Time of usual presentation	Cardiac manifestations
Radiation therapy [65]	>30 gray to heart	Up to decades after treatment has ended	Pericarditis, coronary artery disease, valvular disease, arrythmias
Anthracyclines [5, 7]	>300 mg/m^2 doxorubicin isotoxic cumulative dose	Acute: during therapy Chronic: months to years posttherapy (longer follow higher the incidence)	Acute-arrythmias, hypotension Chronic-CHF
Cyclophosphamide [33, 34]	>150 mg/kg or >1.55 g/m^2 given as one dose or per one course	ECG changes: 1–3 days after therapy CHF: up to 2 weeks after therapy	CHF, Myocarditis
Cytarabine [33, 34]	High doses	3–28 days after initiation of therapy	Pericarditis, ventricular, and atrial arrythmias
Cisplatin [33, 34]	Usually when receiving with other chemotherapy	Arrythmias/hypotension: acute within hours Vascular toxicities: usually days after infusion but reports 4 and 18 mths post therapy	Arrythmias Vascular toxicities (CVA, AMI)
Ifosfamide [34, 41]	Higher doses	6–23 days after first dose	CHF, arrythmias

CHF: Congestive Heart Failure, ECG: Electrocardiogram.

2.1. Anthracycline Therapy. Anthracyclines are the class of chemotherapeutic agents that are most frequently linked to cardiac dysfunction in children. The traditionally used anthracyclines, doxorubicin, and daunorubicin were developed in the 1960s from the bacterial strain *Streptomyces peucetius* [5]. After or during administration of an anthracycline, patients can experience acute cardiac toxicity which manifests as acute hypotension or transient rhythm disturbances. This is usually transient and resolves without intervention [6]. Early chronic and late onset chronic cardiotoxicity manifests as a decrease in cardiac function which can lead to congestive heart failure (CHF). This is thought to be due to a decrease in left ventricular wall thickness, indicating a decrease in cardiac tissue [7–10].

The incidence of cardiac dysfunction postanthracycline therapy varies depending upon how cardiac dysfunction is defined and the length of time between the end of therapy and evaluation [11, 12]. In a retrospective cohort study of 6,493 patients who had received therapy on pediatric oncology trials with an anthracycline, Krischer et al. confirmed early cardiotoxicity (defined as congestive heart failure, abnormal measurements of cardiac function that prompted therapy to be disrupted, or sudden death from a presumed cardiac event) in 106 (1.6%) of the patients [13]. Van Dalen et al. followed a cohort of 830 patients for a mean of 8.5 years after anthracycline therapy and found that the risk of clinical heart failure was 2.5% [14]. Some studies evaluate patients for subclinical cardiac disease, patients that are not symptomatic from their cardiac dysfunction. In a systematic review including 25 different studies which each included >50 pediatric patients treated with an anthracycline, the reported frequency of subclinical cardiotoxicity varied from 0% to 57%. Recently De Caro et al. published a cross-sectional study evaluating the presence of subclinical cardiotoxicity in pediatric patients treated with anthracyclines. Seventeen of the 55 patients (30%) were identified as having subclinical heart disease, but this did not correlate with alterations in the response of the cardiovascular system to dynamic exercise evaluated by cardiopulmonary exercise testing [15].

It has been well established that the development of congestive heart failure can occur at any anthracycline dose, but the risk for development increases with increased cumulative dose of anthracycline, especially doses $\geq$300 mg/m^2 [8, 13, 16–28]. It has also been noted that the longer it has been since a patient has received anthracycline treatment the higher their risk is for developing changes in cardiac function [10, 28, 29].

Earlier age at diagnosis and start of treatment with anthracycline-based therapy has correlated with an increase risk of cardiac disease in many studies that evaluated cardiac function after completion of therapy [8, 19, 25, 29, 30]. However, not every study demonstrates this correlation as noted in the systematic review by Kremer et al. [11] and other studies [24, 29, 31]. These studies involve small number of patients from 80–265. A larger study that evaluated 6,493 patients during therapy found that age at time of diagnosis was not a statistically significant predictor of cardiotoxicity, though children less than 9 had an increase risk of sudden death or CHF [13]. In general expert panels have recommend that patients who receive anthracycline therapy at an earlier age are monitored more closely for development of cardiac disease.

Female gender has also been associated with increased risk for cardiac disease in several studies [9, 13, 16, 32]. The reason female gender has been correlated with this increased risk is unknown. Lipshultz et al. hypothesized that it may be due to "differences in oxidative stress, differential expression of the multidrug-resistance gene, and body composition" [9]. As with age, there are some studies that do not echo this correlation [19, 29, 31]. The largest study that found

female sex as predictive factor for CHF was the study by Kirscher et al. As stated above this study evaluated the occurrence of cardiotoxicity during therapy. 585 out of the 6,493 patients received radiation to the heart which may have influenced some of their results [13]. Green et al. also found the correlation between female sex and development of cardiotoxicity in their case control study of 2,710 treated for Wilms tumor. In this study "the risk for girls was estimated to be approximately four times that for boys with the same level of cumulative doxorubicin exposure and radiation to the lung and the left abdomen (P, .005)" [16]. This leaves the question of whether radiation may be contributing to the increase rate of cardiotoxicity in females in these studies.

2.2. Other Chemotherapeutic Agents. Other chemotherapy agents that have cardiotoxic side effects include cyclophosphamide, ifosfamide, cytarabine, and cisplatin. Paclitaxel, fluorouracil, and amsacrine also have cardiotoxic side effects, but are rarely used in the first-line treatment of pediatric tumors [33, 34]. Newer agents, such as tyrosine kinase inhibitors, have also been found to be cardiotoxic [35–37]. For extensive review of cardiotoxic chemotherapeutic agents please refer to the review by Pai and Nahata [34].

Cyclophosphamide, an alkylating agent, can produce CHF or myocarditis. These symptoms are usually present by 14 days after therapy [34]. Cyclophosphamide is rarely cardiotoxic at low/standard doses but can cause severe cardiotoxicity when administered at high doses, such as when used for myeloablation in stem cell transplant [38, 39]. When Goldberg et al. recalculated the normal dose in mg/kg that is given during transplant as dose per m^2, patients with higher dose per m^2 have an increased risk for cardiotoxicity. It was also noted that patients less than age 12 had far less cardiotoxicity compared to older patients, though younger patients tended to receive a lower dose/m^2 than older patients [38]. The advantage to Goldberg study, though it had a small sample size of 84, is that the patients had not received other cardiotoxic therapy such as anthracycline therapy or radiation. The incidence of CHF in Golderbergs study was 0/32 in patients receiving $\leq 1.55\,g/m^2$ and 6/52 in patients receiving $>1.55\,g/m^2$. Van der Pal et al. evaluated a cohort of 601 patients of which 514 had evaluable echocardiograms. 164 of these patients received $<10\,g/m^2$ of cyclophosphamide and 60 received $>10\,g/m^2$. Their analysis did not find a correlation between high doses of cyclophosphamide and decrease in left ventricular shortening fraction, but this could be due to the fact that all but 10 of the patients also received other cardiotoxic therapy.

Ifosfamide, also an alkylating agent, can illicit congestive heart failure or arrhythmias [34, 40–42]. CHF usually occurs within 6–23 days after initiation of ifosfamide and the risk of CHF is generally thought to increase with higher dose delivery of the medication [41, 42], though, as with cyclophosphamide, study by van der Pal et al. did not support this correlation.

After administration of cytarabine, an antimetabolite, patients are also at risk for cardiac complications. Review of the literature also reveals case reports of pericarditis associated with the administration of cytarabine [43–45]. It is also associated with atrial and ventricular arrhythmias along with CHF [33, 46–48]. These complications are rare and associated with administration of high doses.

Cisplatin has been reported to be associated with arrhythmias in several case reports [49–52]. Most of these reports were in patients receiving cisplatin in combination with other chemotherapeutic drugs. Cisplatin decreases levels of calcium and magnesium, both of which can increase the risk for arrhythmias if not corrected [33]. There have been case reports of vascular toxicity and acute myocardial infarctions/cerebral vascular accidents with the administration of cisplatin, specifically as part of the treatment of germ cell tumors [53–57]. The rare occurrence of vascular accidents should not deter clinicians from using this efficacious drug, but even in young patients one needs to consider vascular toxicities in a differential diagnosis of a patient presenting with consistent symptoms following cisplatin therapy [54].

Tyrosine kinase inhibitors include drugs such as imatinib and sunitinib. Imatinib (Gleevec) is the most well-known tyrosine kinase inhibitor and is used mainly for the treatment of chronic myelogenous leukemia, but more recently has also been used in phase I and II studies treating relapsed solid tumors [58–61]. Tyrosine kinase inhibitors as a drug class have been linked with development of left ventricular dysfunction, heart failure, and arrhythmias [35, 37, 62]. These events have been rarely reported with imatinib [63, 64], but the incidence of symptomatic events in patients treated with sunitinib or sorafenib was 18% in an observational study of 74 patients [62]. This emphasizes the importance of closely monitoring patients for the development of cardiotoxicity when treating them with a tyrosine kinase inhibitor, especially if they have previous cardiac disease, risk factors for the development of cardiac dysfunction, or if one is employing a newer, less studied tyrosine kinase inhibitor.

There are no specific guidelines for monitoring patients treated with chemotherapy drugs besides, anthracyclines, likely due to the relatively low frequency of these events. Providers should be aware that cyclophosphamide, ifosfamide, cytarabine, cisplatin, and tyrosine kinase inhibitors may induce cardiotoxicity so that they can watch for signs and symptoms of these events during and after treatment.

2.3. Radiation Therapy. Radiation therapy that is directed at the mediastinum increases the risk for cardiovascular damage and sequela postcancer therapy. Radiation to the mediastinum is most often utilized for the treatment of Hodgkin's lymphoma and breast cancer. Presentations of radiation damage include pericarditis, cardiomyopathy, coronary artery disease (which may lead to acute myocardial infarction), valvular disease, and conduction system arrythmias [65, 66]. Pericarditis clinically presents either as sudden onset of pleuritic chest pain, dyspnea, fever, and friction rub or can be clinically silent. On ECG (electrocardiogram), ST segment elevation and/or T wave inversion can be seen. Patients exposed to thoracic radiation can develop systolic and/or diastolic dysfunction (with diastolic being more common) and go on to develop dilated, hypertrophic, and restrictive

cardiomyopathies [67]. Radiation primarily affects the mitral and aortic valves [65, 68, 69] and presents with fibrosis with or without calcifications [67]. Conduction system arrhythmias can be early, which are usually transient or late, occurring months to years after treatment. Late conduction abnormalities include atrioventricular nodal bradycardia, intranodal blocks, and all other types of heart block [65, 67].

Incidence of radiation-induced cardiovascular damage varies depending upon several variables including the end point measured, time postcompletion of therapy, radiation techniques, and dosing. Pericarditis prior to newer radiation techniques was seen in up to 40% of the patients, but with new techniques and attempt at lowering doses this incidence has been greatly reduced [65]. In study by Carmel and Kaplan the incidence of pericarditis in patients treated for Hodgkins was reduced from 20% with whole pericardial irradiation to 2.5% when subcarinal blocking was utilized along with thin lung block technique [70]. Adams et al. screened asymptomatic patients who were diagnosed with Hodgkin's disease prior to age 25 that were $\geq$5 years out from therapy with ECG, echocardiograms, and exercise stress tests. The majority (41/47) of the patients received 36–44 gray of radiation. 42.6 percent of these patients had a significant valvular defect, 5/43 had findings suggestive of systolic dysfunction, and 16/43 had findings suggestive of diastolic dysfunction. 35/43 had conduction abnormalities including sinus tachycardia and bradycardia [71]. In pediatric studies evaluating patients that had received doses of radiation $\leq$25 gray the incidence of cardiac dysfunction seen on echocardiograms or nuclear imaging were much lower ranging from 0–2.5% [22, 72, 73]. In a study evaluating patients for death from cardiac dysfunction in patients who were treated for Hodgkin's disease 4/544 patients treated at age <19 died from valvular heart disease, CHF, pericarditis or cardiomegaly, 6/544 died from an acute myocardial infarction. All of the patients that died had received a radiation dose of >30 gray. There were no deaths in the group of patients treated at age <19 that had received <30 gray [22, 72–74].

The factors that increase the risk of developing postradiation cardiotoxicity are the volume of the heart exposed to the radiation beam, higher total dose of radiation [66, 74], the length of followup time from radiation (the farther out from therapy the more likely you will develop cardiotoxicity), younger age at exposure and higher fractionated dose [65, 75]. The majority of the trials involving pediatric patients that evaluate for cardiac radiation toxicity focus on Hodgkin's disease survivors, have small sample sizes, recruit patients postcompletion of therapy and include patients treated with chemotherapy. Patient's treated with lung irradiation for solid tumors such as Ewing's sarcoma or Wilm's tumor can experience an increased risk for cardiac disease, though there are limited studies evaluating cardiotoxicity in these subgroups [16, 31].

3. Monitoring

Patients receiving therapy that has potential cardiotoxicity require close monitoring during and after therapy. The goal of monitoring during therapy is to identify early signs of cardiotoxicity in order to modify a patient's therapeutic plan so that the risks of further development of cardiac disease are decreased. These modifications of therapy have to be balanced with risk of decreasing antitumor effect of the therapy. Posttherapy patients may require life-long monitoring for late cardiotoxic effects, especially if they have received mediastinal radiation or higher doses of anthracyclines. The following is an analysis of several different modalities available for the monitoring of cardiotoxicity.

3.1. Echocardiogram. Echocardiograms are the most frequently used modality in the screening for cardiac disease during or after therapy. Echocardiograms are noninvasive and readily available. They provide means to evaluate the left ventricular ejection fraction (LVEF) along with systolic and diastolic cardiac function. As per Altena et al., "diastolic measurements are probably the most sensitive to early changes in cardiac function [76]." Many studies also use the measurement of fractional shortening (FS). In the only published guidelines for monitoring therapy during anthracycline treatment in pediatric population [77] Steinherz et al. recommended that a drop in FS by an absolute value of $\geq$10 percentile units or FS $\leq$ 29% be considered a significant deterioration of function [78]. The disadvantage of echocardiograms is that they are preload dependent for several of the parameters and are dependent on the expertise and interpretation of echocardiographist [76]. The question of whether decline in cardiac function during therapy correlates with long-term development of cardiac impairment still remains [79]. In the evaluation of pericarditis echocardiograms provide information regarding long-term sequela of this disorder such as development of a pericardial effusion, but may be normal in the setting of acute pericarditis [80]. Echocardiograms also provide useful information after radiation therapy by evaluating for valvular defects.

3.2. Radionuclide Angiocardiography (RNA) (Includes MUGA and Radionuclide Ventriculography). RNA is considered the gold standard for estimating LVEF. Unlike echocardiograms, there is low intraindividual and intraobserver variation when obtaining and analyzing results, but only limited information regarding diastolic function is obtained. RNA's also expose patients to radiation [76]. Another concern with using LVEF as a screening tool lies in its ability to accurately predict which patients will go on to develop cardiac impairment [76, 81]. Steinherz et al. included RNA testing along with an echocardiogram as part of their recommendations for monitoring for deterioration of function during anthracycline therapy [78]. Despite these recommendations, RNAs are not widely utilized in protocols enrolling pediatric cancer patients for monitoring for cardiotoxicity of the therapy [77]. In order to minimize confounding variables, it is recommended that RNAS or echocardiograms are obtained

at least 3 weeks after anthracycline therapy, when patients are normothermic and have a hemoglobin greater than 9 g/dL [77].

3.3. Electrocardiograms (ECG). ECGs are a noninvasive, inexpensive tool in the evaluation of conduction abnormalities that may develop after radiation and during the administration of certain chemotherapeutic agents. In addition ECGs can demonstrate signs of cardiomyopathies. They do not provide any information regarding LVEF and interpretation of the study varies between observers [76]. There is some evidence to suggest that prolonged corrected QT intervals may predict cardiac disease [82]. For the above reasons, obtaining an ECG is recommended as part of monitoring for cardiac dysfunction in some protocols and as part of long-term followup.

3.4. Biomarkers. Due to the concern regarding the ability of echocardiograms and RNAs to predict which patients will go on to develop cardiac impairment during treatment [76, 79, 81] and lack of sensitivity to detect early stages of cardiomyopathy [83–85], there has been much recent interest in the use of biomarkers. Biomarkers include B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP), cardiac troponin T (cTnT), and cardiac troponin I (cTnI). Mavinkurve-Groothuis wrote a review regarding biomarkers in the detection of pediatric anthracycline cardiotoxicity. The review included a total of 14 studies with patient numbers ranging from 15–63 per study and time from last dose of anthracycline until the evaluation point varying from immediately until 17.5 years after therapy. These variations made it difficult for the authors to make recommendations regarding the most sensitive method to use to detect cardiomyopathy, and when the best timing for obtaining echocardiograms and biomarkers is. Ultimately, it was concluded that there was a significant relation between elevated biomarkers and cardiac dysfunction in 6 of the 14 studies [83]. Mavinkurve-Groothuis et al. recently published a study on a cohort of 122 asymptomatic survivors, a large number compared to previous studies of this type. None of the patients had an elevated cTnT and 16 had elevated NT-pro-BNP levels [86]. The elevated NT-pro-BNP levels correlated with increased dose of anthracycline received, but not with changes in ejection fraction.

It appears that biomarkers for cardiomyopathy may provide some clinical utility, but studies with larger number of patients need to be performed. It will also be necessary to serially follow children with elevated levels long term in order to monitor the future development of cardiomyopathy and to determine best timing of biomarkers.

4. Monitoring during Therapy

The only published guidelines for monitoring for cardiotoxicity during therapy in pediatrics was published by Steinherz et al. in 1992 [78]. These guidelines pertain specifically to monitoring when anthracyclines are being administered or a patient receives mediastinal radiation. Prior to the beginning of therapy, ECG, echocardiogram, plus/minus RNA should be collected. When the total anthracycline dose given is $<300\,mg/m^2$, an echocardiogram should be obtained before every other course of anthracycline administration. Once a patient has received greater than $299\,mg/m^2$, an echocardiogram should be performed before every cycle of anthracycline administration. The recommendation that is currently not frequently followed [77] is the addition of RNA once anthracycline dose is $>399\,mg/m^2$ or $>299\,mg/m^2$ and patient has received radiation therapy >1000 cGY to mediastinum.

5. Late Effect Monitoring Recommendations

The Children's Oncology Group (COG) published the most recent recommendations for long-term followup of childhood cancer survivors on line at http://www.survivorshipguidelines.org/ [87]. These recommendations give detailed guidelines regarding frequency of monitoring based on the age of exposure to anthracycline, total dose of anthracycline received, and administration of potentially cardiotoxic radiation therapy. Page 34 and 35 of the guidelines pertain particularly to the cardiac monitoring after anthracycline dosage. In order to calculate total dose of anthracycline a patient received, one must convert the dose to doxorubicin isotoxic doses. Recommended conversions are doxorubicin multiply the dose by 1; daunorubicin multiply the dose by 0.833; epirubicin multiply the dose by 0.67; idarubicin multiply the dose by 5; mitoxantrone multiply the dose by 4. These dose conversions are per the COG long-term followup guidelines, but there is "a paucity of literature" to support the conversions. They are solely intended to be used to base monitoring on. Pages 91 and 92 pertain specifically to monitoring for cardiotoxicity after radiation therapy. Modalities of monitoring include scheduled echocardiograms's (ECG), detailed history and physical exam. For timing of echocardiograms or MUGA scan, please refer to Table 2. The Scottish Intercollegiate Guidelines Network (SIGN) has also developed long-term followup of survivors of childhood cancer guidelines that were published online in 2004. They recommend that echocardiograms are obtained at regular intervals during treatment with anthracyclines and every three years thereafter in patients who have received a modest dose $<250\,mg/m^2$. A detailed cardiac assessment should be performed for survivors of childhood cancer who are pregnant or planning a pregnancy or who wish to take part in competitive sports. As far as radiation they state that "healthcare professionals should be aware that mediastinal irradiation over 30 Gy is a risk factor for cardiac disease later in life and monitoring is necessary." Details of this monitoring are not specifically given [88].

Another key component to long-term followup of patients is to screen for cardiovascular risk factors. This screen includes a fasting lipid profile, smoking history, family history of early coronary artery disease in expanded first degree pedigree (Male $\leq$ 55 y; Female $\leq$ 65 y), blood pressure (BP) on 3 separate occasions interpreted for age/sex/height, body mass index (BMI), fasting glucose (FG), and physical

Table 2: Timing of echocardiograms or MUGA scan postcancer therapy as per children's oncology group long-term followup guidelines for survivors of childhood, adolescent, and young adult cancers version 3.0 [87].

Age at treatment	Radiation with potential impact to the heart	Anthracycline dose converted to doxorubicin isotoxic dose	Recommended frequency
<1 year old	Yes	Any	Every year
		<200 mg/m^2	Every 2 years
	No	≥200 mg/m^2	Every year
1–4 years old	Yes	Any	Every year
	No	<100 mg/m^2	Every 5 years
		≥100 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
≥5 years old	Yes	<300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
	No	<200 mg/m^2	Every 5 years
		≥200 mg/m^2 to <300 mg/m^2	Every 2 years
		≥300 mg/m^2	Every year
Any age with decrease in serial function			Every year

activity history [89]. Kavey et al. separates patients into three stratifications high, moderate, and at risk. In general cancer survivors are considered to be at risk for cardiovascular disease, but if they have 2 or more risk factors, as per above, they are considered to be at moderate risk. When a patient is considered to be at moderate risk from at risk the goal for LDL (low density lipoprotein) changes from ≤160 mg/dl to <130 mg/dl, BMI goal from ≤95% to ≤90% and BP goal from ≤95% + 5 mm Hg to just <95%. Goal for FG is <100 mg/L and Hemoglobin A1c < 7% regardless of risk stratification. In general lifestyle modifications are recommended if patients do not meet these goals with close followup and then possible medications in the future to treat hyperlipidemia and hypertension. In the case of FG > 125 an endocrine referral needs to be made to initiate treatment for diabetes mellitus. These recommendations were published by the American Heart Association and endorsed by the American Academy of Pediatrics.

6. Conclusion

Currently, there is ongoing research into developing methods to deliver treatment for childhood cancers that reduce the risk of developing long-term sequela from treatment. Different formulations of anthracyclines have been and continue to be developed that are hoped to be less cardiotoxic. There is clinical trial literature to support that liposomal doxorubicin is less cardiotoxic than doxorubicin. Also, pretreatment with dexrazoxane has been found to decrease the risk of anthracycline-induced CHF, but most of these studies have been performed in adults [90, 91]. Pediatric clinical trials continue to be developed to evaluate if we can decrease doses of cardiotoxic chemotherapeutic agents or reduce radiation therapy doses in order to prevent long-term side effects from the therapy without decreasing survival. Hodgkin's lymphoma is a good example of this. Doses of radiation administered in modern trials have been greatly reduced. The most recently closed COG trial for intermediate risk Hodgkin's lymphoma evaluated whether or not radiation can be eliminated based on response to multiagent chemotherapy.

Until we can eliminate the cardiotoxic side effects of treatment for pediatric cancers it is important that clinicians providing care to survivors are aware of the potentially cardiotoxic treatments their patients have received and to be well versed in the methods used in the detection of cardiotoxic developments. This is to try and initiate early treatment and hopefully reduce worsening of symptoms. Well-designed prospective studies that evaluate monitoring modalities and the frequency at which monitoring should occur have yet to be published. There are online guidelines available that are based on review of the current literature and expert opinion. The COG and SIGN have published guidelines that are accessible to clinicians and families for reference online at http://www.survivorshipguidelines.org/ and http://www.sign.ac.uk/guidelines/fulltext/76/index.html [88]. These are not to take place of clinical judgment, but to serve as a good starting point for designing a monitoring plan [87]. Patients need also to be made aware of their risk so that they can implement lifestyle modifications that will decrease their risk of development of cardiac disease.

Conflict of Interests

I, Joy M. Fulbright, as the author of the paper, do not have any direct financial relations with any commercial identity mentioned in this paper that might lead to a conflict of interests.

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Review Article

Arterial and Venous Thrombosis in Cancer Patients

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The most frequent ultimate cause of death is myocardial arrest. In many cases this is due to myocardial hypoxia, generally arising from failure of the coronary macro- and microcirculation to deliver enough oxygenated red cells to the cardiomyocytes. The principle reason for this is occlusive thrombosis, either by isolated circulating thrombi, or by rupture of upstream plaque. However, an additionally serious pathology causing potentially fatal stress to the heart is extra-cardiac disease, such as pulmonary hypertension. A primary cause of the latter is pulmonary embolus, considered to be a venous thromboembolism. Whilst the thrombotic scenario has for decades been the dominating paradigm in cardiovascular disease, these issues have, until recently, been infrequently considered in cancer. However, there is now a developing view that cancer is also a thrombotic disease, and notably a disease predominantly of the venous circulation, manifesting as deep vein thrombosis and pulmonary embolism. Indeed, for many, a venous thromboembolism is one of the first symptoms of a developing cancer. Furthermore, many of the standard chemotherapies in cancer are prothrombotic. Accordingly, thromboprophylaxis in cancer with heparins or oral anticoagulation (such as Warfarin), especially in high risk groups (such as those who are immobile and on high dose chemotherapy), may be an important therapy. The objective of this communication is to summarise current views on the epidemiology and pathophysiology of arterial and venous thrombosis in cancer.

1. Introduction

The greater part of human mortality and morbidity (certainly in the developed world) focuses on cardiovascular disease and its risk factors, cancer, and connective tissue disease [1]. The pathophysiology of cardiovascular disease (endothelial damage leading to hypertension and thrombosis) is established [2], whilst those subjects with connective tissue disease (generally inflammatory) are also at risk of possible life-terminating atherothrombosis [3]. A relationship between cancer and thrombosis has been recognised for almost 150 years, and each year brings additional data that confirms this association [4, 5]. Furthermore, the large proportion of terminal events in neoplastic diseases are thrombotic, leading to the hypothesis that cancer is a prothrombotic disease [6–9]. However, such thromboses may occur in arteries and/or veins, and many authorities fail to differentiate between these two circulations, generally focusing on venous thromboembolism (VTE). Nevertheless, of PubMed citations of works on arterial and venous thrombosis, approximately 25% are to arterial thrombosis.

An additional aspect of thrombosis and cancer is the inevitably adverse effect of chemotherapy (often anti-neoplastic and cytotoxic) in promoting thrombosis [8, 9]. Although there are isolated reports where hypercoagulability and thrombosis closely follows chemotherapy [10, 11], guidelines advocating prophylactic anticoagulation therapy in the para-antineoplastic drug setting are becoming available. Indeed, one study named thromboembolism and infection as leading precise causes of death in cancer patients on chemotherapy [12].

The objective of this paper is to summarise potential pathophysiological mechanisms to explain this relationship, and to update facets of both arterial and venous thrombosis in various cancers. To achieve this aim, on-line search engines such as PubMed and Medline were probed using key

words cancer, arterial thrombosis, venous thrombosis, and anticoagulation. Whilst acknowledging advances brought by tissue culture and animal models, the paper will focus on human disease.

2. The Pathophysiology of Thrombosis

Perhaps the oldest and most dominant theory of the pathophysiology of thrombosis is that of Virchow, which has three separate but overlapping parts: the contents of the blood, the blood vessel wall, and blood flow [13]. We currently interpret this triad in terms of, respectively, platelets and coagulation factors (with minor roles for red and white blood cells), the endothelium, and blood turbulence (as may be present at valves and at bifurcations) and venostasis [14]. Certainly, however, these principles are as equally applicable to arterial thromboses and to venous thromboses, and also to cancer (Table 1). Indeed, patients with various cancers frequently demonstrate abnormalities in each component of Virchow's triad, leading to a prothrombotic or hypercoagulable state. The mechanisms are likely to be multiple and, probably, synergistic. For example, tumour cells may be directly prothrombotic, inducing thrombin generation, whilst normal host tissues may stimulate (or be stimulated to) prothrombotic activity as a secondary response to the cancer. However, dissecting the exact mechanisms is frustrated by comorbidity and treatment effects, such as bed rest, infection, surgery, and drugs. Nevertheless, Virchow's triad also gives us the opportunity to dissect and identify different aspects of the causes of thrombosis.

Table 1: Virchow's triad in cancer.

Abnormal blood flow
(i) Increased plasma viscosity [114, 115]
(ii) Increased stasis due to immobility (e.g., being bed-bound, in a wheelchair)
Abnormal blood constituents
(i) Increased platelet activation and aggregability, for example, increased soluble P selectin, beta thromboglobulin [15–51]
(ii) Loss of haemostasis with increase in procoagulants for example, increased fibrinogen, cancer procoagulant, PAI-1 [66–89]
Abnormal blood vessel wall
(i) Damaged or dysfunctional endothelium (e.g., increased soluble E selectin, increased soluble thrombomodulin, possibly also related to chemotherapy) [95–97]
(ii) Loss of anticoagulant nature and therefore acquisition of a procoagulant nature (e.g., increased von Willebrand factor, tissue factor, reduced tPA, possibly also related to chemotherapy) [83, 93, 94]
(iii) Angiogenesis (altered release of, and response to, growth factors) [101–107]

2.1. The Contents of the Blood: Cells. Pathologists focus on cells and on plasma molecules. The former clearly centre on the platelet, although there are potential roles (if only minor) for white blood cells and red blood cells, the latter as ADP donors [15, 16]. Examples of platelet (hyper)activity in cancer include reduced life span in myeloma, reduced sensitivity to prostacyclin in endometrial, and cervical cancer [17, 18], with increased aggregability and higher levels of platelet specific products soluble P-selectin, platelet factor 4, thrombospondin and beta-thromboglobulin in lung, breast, prostate, ovarian, and other cancers [19–26]. These and other findings support the general hypothesis of altered platelet activity in cancer, especially in metastatic disease [27–29]. Furthermore, it has been suggested that inappropriate platelet activity promotes metastases [30, 31].

There are several plausible theories as to the causes of this excess platelet activity. Cancer cells may activate platelets *in vitro* by contact, by releasing platelet stimulators such as ADP and thromboxane A2, and by generating thrombin through the activity of the tumour-associated procoagulants. Increased von Willebrand factor, ristocetin cofactor, and enhanced ADP-induced platelet aggregation have all been demonstrated [32–36], and all these mechanism may promote thrombosis. However, in at least one clinical setting, the true value of this has been questioned, as Canobbio et al. [37] found that hypercoagulability was more likely to be related to coagulation than to the expected increase in platelet aggregability. Nevertheless, there are several calls for antiplatelet therapy in cancer [38–40], although concerns have been aired [41].

A rapidly expanding area is that of microparticles [42, 43]. Increased numbers of platelet microparticles have been described in gastric, colon, and breast cancer [44–46]. Interest in platelet microparticles follows a number of themes; in the promotion of angiogenesis and metastases [46–48], in the promotion of thrombosis (such as by bearing tissue factor and phospholipids, thus providing a platform for thrombosis) [45, 49, 50], and in the promotion of invasiveness [51]. The tumour itself may also shed microparticles, and these too may be prothrombotic [52–54].

Monocytes may also be involved in cancer [55]. Early work suggested a role in an immunological response to neoplasia [56, 57], and although this persists, a more recent view linking monocytes to coagulation has been introduced, based on their ability to express tissue factor [58–61]. However, other mechanisms may also be important, such as the delivery of cytokines and a role in angiogenesis [62, 63] and there are also reports of the procoagulant activity of monocyte microparticles [64], and also of cross-talk between the monocyte and the platelet [65], all of which have the potential to promote thrombosis.

2.2. The Contents of the Blood: Soluble Plasma Molecules. There is also considerable evidence which implicates soluble coagulation factors in cancer-related thrombosis [66]. The normal clotting-fibrinolytic system of haemostasis involves a fine balance between the activation and inhibition of platelets, procoagulant factors, anticoagulant factors, and fibrinolytic factors [67]. This can easily be disrupted as tumour cells can, for example, activate the coagulation

system directly through interactions with the clotting and fibrinolytic systems to generate thrombin [68]. The delicate balance between the coagulation and fibrinolytic systems can easily shift to induce a prothrombotic state, perhaps via an excess of procoagulant proteins such as tissue factor, fibrinogen and plasminogen activator inhibitor (PAI-1), and/or deficiencies in other molecules, such as anti-thrombin, Proteins C and S, and tissue plasminogen activator (tPA) [67, 69]. However, perhaps the greater part of the literature in this area considers tissue factor and cancer procoagulant.

Tissue factor is primary initiator of coagulation. Forming a complex with factor VII to activate factors X and IX, it is produced by monocytes and the endothelium [59] and is functional both at the surface of the cell and as a soluble component of plasma [70, 71]. Thus i*n vivo* expression of tissue factor, either by tumour and/or "normal" cells, and soluble tissue factor has been implicated in intratumoral and systemic activation of blood coagulation via the extrinsic pathway, as well as in tumour growth and dissemination [72–75].

Cancer procoagulant is a cysteine proteinase growth factor that is a calcium-dependent, Mn^{2+} stimulated enzyme [76]. Unlike tissue factor, cancer procoagulant is a direct activator of factor X without the need for factor VII and is found in malignant and fetal tissue, but not in normally differentiated tissue [77]. Concerns that at least some part of cancer procoagulant activity could be accounted for by contaminating tissue factors seem to have been dispelled [78]. In the presence of factor V, cancer procoagulant may further enhance thrombin generation by up to 3-fold. Increased cancer procoagulant levels have been reported in patients with acute promyelocytic leukemia, malignant melanoma, and cancers of the colon, breast, lung, and kidney, and there is *in vitro* evidence that it may also be involved in metastatic potential [79–82]

Numerous other proteins within the coagulation cascade have been shown to be abnormally elevated, often in association with a fall in the activity of "anticoagulant" factors. For example, reduced levels of t-PA activity have been described in patients with gastrointestinal cancer [83], whilst that of PAI-1 and other inhibitory factors of the fibrinolytic pathway can be elevated [84]. Both of these factors are likely to lead to a prothrombotic or hypercoagulable state. In addition, there are decreases in other anticoagulant factors, including anti-thrombin and resistance to activated protein C. The evidence of this on-going underlying state of heightened coagulation in cancer is clear from the numerous studies looking at levels of fibrinogen and other indices of fibrin turnover including D-dimers [71, 85–89]. Increased levels of the latter reflect increased clot turnover (thrombolysis) which in turn implies increased thrombotic load, as is present in actual venothromboembolic disease, and levels of D-dimers are part of the clinical assessment of subjects with suspected venothromboembolism [90]. However, there is evidence of very high D-dimer levels in patients with cancer who do not have VTE. This suggests that elevated D-dimer levels in patients with VTE and malignancy are not solely due to presence of thrombus. Knowlson et al. suggest that high D-dimer levels in malignancy are likely to reflect the biology of the underlying tumour, with higher levels observed in breast, prostate, and bowel cancers [91].

2.3. Abnormalities of Vessel Wall. The role of endothelium in mediating the prothrombotic or hypercoagulable state is well-known, and disturbances in vascular function may be assessed by changes in plasma levels of certain molecules such as von Willebrand factor (vWf), soluble thrombomodulin, and soluble E-selectin [92]. Increased vWf has long been described in cancer [93, 94], and this may not only indicate endothelial damage but also seem likely to contribute to thrombosis by promoting platelet-platelet and platelet-subendothelium adhesion, as may increased fibrinogen [92–94]. Similarly, increased soluble (i.e., plasma) thrombomodulin (as in present in cancer [95]) may account for the loss of anticoagulant membrane thrombomodulin at the endothelial surface [96]. Thus changes in vWf and thrombomodulin are likely to promote coagulopathy and thus provide a paradigm for thrombosis in cancer. Increased soluble E selectin in cancer may simply be a marker of endothelial disturbance with no direct implications for hameostasis [97]

Endothelial cells may become prothrombotic under the influence of inflammatory cytokines such as tumour necrosis factor (TNF) and interleukin (IL)-1. Such cytokines suppress endothelial fibrinolytic activity, increase endothelial cell production of IL-1 and vWf, and downregulate thrombomodulin expression that diminishes the activation of the anticoagulant protein C [98]. Cytokines such as TNF and IL-1, often increased in cancer [99], also increase the endothelial expression of E selectin, platelet activating factors, and tissue factor [98, 100]. Thus hypoxia and/or cytokine-mediated endothelial cell damage or dysfunction has the potential to further contribute to hypercoagulable state. A damaged endothelium may also present less of a challenge to a metastatic tumour cell seeking to penetrate the vessel wall. Solid tumours growing outside of the blood vasculature may also increase the permeability of the microvasculature, allowing fibrinogen and other plasma-clotting proteins to leak into the extravascular space where procoagulants associated with tumour cells or with benign stromal cells can initiate clotting and subsequent fibrin deposition [100].

Several findings suggest a link between angiogenesis and thrombosis. One of the oldest provides a rationale for a role for platelet derived growth factor (PDGF), and platelet derived endothelial growth factor, possibly shed from para-neoplastic thrombus, in neovascularisation [101, 102]. Others have localised tissue factor expression in the vascular endothelium of breast cancer tissue, which strongly correlate with the initiation of angiogenesis, hence suggesting a further possible link between the prothrombotic states and angiogenesis in these patients [103, 104]. Tissue factor expression has also been shown to correlate positively with microvessel density and the expression of the angiogenic modulator, vascular endothelial growth factor (VEGF) [105]. Interestingly, VEGF induces hyperpermeability by a direct action on the endothelium [106] and (unlike basic fibroblast growth factor) promotes platelet activation and adhesion [107]

although both *in vitro*. An additional factor is the possibility that platelet-derived VEGF and other angiogenic molecules may be important in malignancy [108–110].

2.4. Abnormalities of Blood Flow. There seems to little firm *in vivo* data directly implicating this third aspect of Virchow's triad in the pathogenesis of human cancer, although imaging studies of blood flow may be a useful investigation [111]. What would seem to be a likely mechanism in cardiovascular disease [112] may not be the case in neoplasia, although there are *in vitro* data [113]. Nevertheless, blood viscosity at both high and low rates of shear [114], and a yield stress index measured preoperatively in cancer patients, has been correlated with the incidence of post-operative DVT [115]. The possibility arises that abnormal blood vessel formation (perhaps related to cancer angiogenesis and factors promoting this) may cause flow disturbance.

3. The Effects of Therapy and Staging on the Risk of Thrombosis

Apart from what may be described as the "natural" pathophysiology, as exemplified by Virchow's triad, many interventions to treat cancer are prothrombotic. There is ample evidence that numerous chemotherapeutic agents, including methotrexate, cisplatin and etoposide, as well as hormonal therapies used in cancer, such as medroxyprogesterone acetate and thalidomide, have all been implicated as risk factors for thromboembolism [116–121]. Other interventions such as central venous catheter placements, surgery, sepsis, and venous stasis from immobility also contribute to risk of thromboembolism [122], although some of this extra risk may be due to local inflammation and/or infection [123]. Furthermore, the general principle that chemotherapy induces thrombosis extends to nonmalignant diseases such as lupus [124]. An exact position for a role of radiotherapy in promoting thrombosis is marred in many studies by combination chemotherapy. Nevertheless, there are instances where radiotherapy does indeed increase the risk of thrombosis but may also damage the endothelium, and collectively, these issues prompt the need for pro-active anticoagulant therapy in high risk groups [121, 125–128].

Levels of plasma markers of thrombin and plasmin generation have been related to staging, prognosis and intervention in patients with various cancers, including those of the cervix, lung, ovary, prostate, and breast. For example, in the study by Gadducci et al. [128], levels of prothrombotic indices were significantly raised in patients with cervical cancer, and related to surgical-pathological stage and tumour size, but not to histologic type. Similarly, several studies have shown an association between activation of blood coagulation and fibrinolysis with distant metastasis, histologic type of tumour and response to chemotherapy; indeed, gross abnormalities of prothrombotic indices might even be a sign of unfavourable prognosis in certain patients [129–131]. However, others failed to note any changes in preoperative or sequential measurements up to 9 months postoperatively of fibrinopeptide A, fibrin fragment B beta 15–42, fibrinogen and serum fibrin degradation products that correlated with early recurrent breast cancer, although some markers were higher in patients with oestrogen receptor positive tumours, or increased postoperatively, largely because of an increase in patients with oestrogen receptor negative tumours [132].

4. Arterial Thrombosis in Cancer

As discussed, there is considerably more data on venous thrombosis than for arterial thrombosis in cancer. Nevertheless, thrombosis in arteries has long been recognised, although the exact mechanisms, in many cases, remain obscure [133–135]. However, increased levels of coagulation molecules, concurrent disease (such as endocarditis), use of growth factors, and cytotoxic chemotherapy may all precipitate thrombosis [136–140]. A potential mechanism for the latter may be endothelial damage with the loss of its natural anticoagulant nature and acquisition of a procoagulant profile [141]. However, the fact that a large proportion of these studies are case reports underlines the rarity of arterial thrombosis in cancer [138–141]. Ross et al. provided additional possible pathogenic mechanisms related to atherosclerosis whilst Lowe summarised common risk factors for arterial and venous thrombosis [142, 143].

5. Prophylaxis and Treatment

A detailed discussion of the prevention and treatment of thromboembolism in cancer is beyond the scope of this paper, although at least one commentator refers to treatment of arterial cancer with anticoagulants [134]. Nevertheless, primary prevention of VTE, possibly by vitamin K antagonists (VKAs) should be considered for "high-risk" cancer patients during and immediately after chemotherapy, when long-term indwelling central venous catheters are placed, during prolonged immobilization from any cause, and following surgical interventions [118, 127]. For example, in cancer patients going for general surgery without prophylaxis, the incidence of deep vein thrombosis is approximately 29% as compared to 19% of patients without cancer [144]. Thus a possible route for the prevention of VTE in high-risk cancer patients undergoing surgery or adjuvant chemotherapy may be the use of long-term low-intensity anticoagulation [145]. However, there are concerns of the safety of VKA anticoagulants in cancer as these may cause an increase in all bleeding, major bleeding, and minor bleeding compared to patients free of cancer [146]. A meta-analysis found no evidence that warrants treatment with VKAs with the aim of improving survival [147].

These and other data suggest that, for many, low molecular weight heparins (LMWHs) will be the therapy of choice [155], not merely because of a reduced rate of complications such as haemorrhage [127], but also because it improves overall survival [156]. Lee et al. reported a rate of recurrent VTE of 17% in patients on VKA anticoagulants compared to 9% in those on an LMWH [157], and later noted that the use of a LMWH relative to coumarin derivatives was associated with improved survival in patients with solid tumours who

Table 2: Potential treatments of patients with cancer.

Patient group	Role of VTE prophylaxis
Hospitalised	Consider UFH, LMWH, or fondaparinux (strongly consider if bedridden and active cancer)
Ambulatory patients free of VTE but receiving systemic chemotherapy	Routine prophylaxis not recommended (conflicting data, risk of haemorrhage, low risk of VTE)
Patients with myeloma free of VTE on thalidomide or lenalidomide plus chemotherapy or dexamethasone	LMWH or low dose warfarin (target INR 1.5)
About to undergo surgery	Consider UFH, LMWH, or fondaparinux for 7–10 days. Consider extended (4 week) prophylaxis with LMWH after major surgery, obesity, and a history of VTE.
Those with established VTE to prevent recurrence	LMWH 5–10 days in the initial phase, then long-term treatment (6 months) with LMWH preferred to oral anticoagulation.
Active cancer (metastatic disease, continuing chemotherapy).	Indefinite anticoagulation should be considered

Table amended from [148]. See also [149, 150]. UFH: unfractionated heparin. LMWH: low molecular weight heparin. VTE: venous thromboembolism.

Table 3: Evidence that not all cancers are associated with the same risk of VTE.

Rank	Reference [151]	Reference [152]	Reference [153]	Reference [154]
1	Ovary	Pancreas	Kidney	Bone
2	Pancreas	Head/neck	Pancreas	Ovary
3	Liver	CNS	Gastric	Brain
4	Blood	Upper GI	Brain	Pancreas
5	Brain	Endocrine		Lymph nodes
6	Kidney	Lung		Cervix
7	Lung	Colorectal		Stomach

See particular references for fine details. CNS: central nervous system; GI: gastrointestinal. A model for predicting chemotherapy-associated VTE places more emphasis on cancers of the stomach and pancreas than on cancers of the lung, bladder, testes, lymph nodes, and female reproductive system [12].

did not have metastatic disease at the time of an acute VTE [158]. Indeed, a recent international guideline on the use of anticoagulants in cancer for prophylaxis and treatment is dominated by LMWHs [148] (Table 2). Although use of LMWH compared to unfractionated heparin confers a survival advantage, the precise role of LMWHs in survival in those free of VTE is unclear but demands careful prospective analysis [159]. But whatever treatment mode is adopted, its use is likely to be long-term in high risk groups [148, 149, 160].

6. Conclusion

It has been long been recognised that cancer confers a prothrombotic or hypercoagulable state, most likely through an altered balance between the coagulation and fibrinolytic systems [161]. More recently it is clear that this risk can be related to long-term prognosis and treatment [162–164], and hospitalisation for a VTE is a risk factor for a second cancer [165]. Whilst most thromboses in cancer are venous, arterial thrombosis is common, possible because the two share many risk factors [140]. Indeed, patients with an unprovoked VTE are at increased risk of an arterial thrombosis [166]. Procoagulants such as tissue factor are expressed by many tumours [73, 75, 104], and although platelet turnover and activity are also increased, it is unclear whether or not platelets themselves and/or their products actively promote thrombosis [167, 168], although a high platelet count is a risk factor for chemotherapy-associated thrombosis [169]. Risk factors for VTE whilst on chemotherapy include presence of metastases, high leukocyte count and platin-based chemotherapy [170]. There is also a growing view that some cancers are more prothrombotic than others (Table 3). Although a flawed analysis, a crude summation of this table suggests that pancreatic cancer and ovarian cancer are most likely to provoke a VTE.

Although guidelines and a consensus statement for anticoagulant treatment are available [148–150, 171], further work is needed to elucidate the mechanism (s) leading to the prothrombotic state in cancer, the potential prognostic and treatment implications, and the possible value of quantifying indices of hypercoagulability in routine clinical practice. Carefully designed studies with the appropriate methodology to establish the predictive value of various abnormalities of the prothrombotic or hypercoagulable state are needed. In this respect the development of a risk factor score, which includes leukocyte count, platelet count, and levels of tissue factor, soluble P-selectin and D-dimer, points a possible way

forward in identifying those at greatest risk of thrombosis, possibly due to chemotherapy, and who therefore warrant treatment [172–174]. In support of this hypothesis is data showed the value of adding soluble P-selectin and D-dimer to a risk calculator [175].

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Review Article

Multimodality Imaging in the Evaluation of Cardiovascular Manifestations of Malignancy

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Up to one third of the population will die as a direct result of cancer. Accurate and timely diagnosis of disease often requires multiple different approaches including the use of modern imaging techniques. Prompt recognition of adverse consequences of some anti-cancer therapies also requires a knowledge of the optimum imaging strategy for the problem at hand. The purpose of this article is to review not only some of the commoner cardiovascular manifestations of malignancy but also to discuss the strengths, weaknesses and appropriate use of cardiovascular imaging modalities.

1. Introduction

The heart is sometimes overlooked when considering the myriad systemic effects of cancer. However, cardiovascular manifestations of malignant disease (or its treatment) are not rare, are often significant, and have historically been diagnosed late in the natural history of disease—or even remained undetected until postmortem. In the past, clinicians relied upon echocardiography to confirm cardiac involvement in malignant disease. However, contemporaneous noninvasive cardiac imaging with computed tomography (CT) and cardiovascular magnetic resonance (CMR) offers unparalleled opportunities for early diagnosis and surveillance in this patient population.

This paper will focus on the specific (and often complementary) roles of the four principal noninvasive imaging modalities (echocardiography, multidetector computed tomography (MDCT), cardiac magnetic resonance (CMR), and nuclear medicine) in patients with cancer [1, 2]. Because there is considerable overlap between the techniques in regard to their clinical indications, our goal is to familiarize the clinician with the strengths and limitations of each modality to facilitate rational investigation for each specific clinical scenario.

2. Noninvasive Imaging Modalities for Evaluation of Cardiac Masses and Malignant Cardiovascular Disease

2.1. Echocardiography. Echocardiography remains the primary mode of initial investigation in suspected cardiovascular involvement by malignant disease [3]. This is by virtue not only of its availability, portability, and low cost but also because of its uniquely high temporal resolution, which offers a "real-time" assessment of cardiac structures that is currently unmatchable by CT or CMR at a comparable spatial resolution [4]. Fast-moving structures like the mitral or aortic valves can be accurately displayed over time [5]. Therefore, valvular involvement by disease, both malignant and infective (as a possible consequence of neutropenia), requires a very high temporal resolution in anemic, septic,

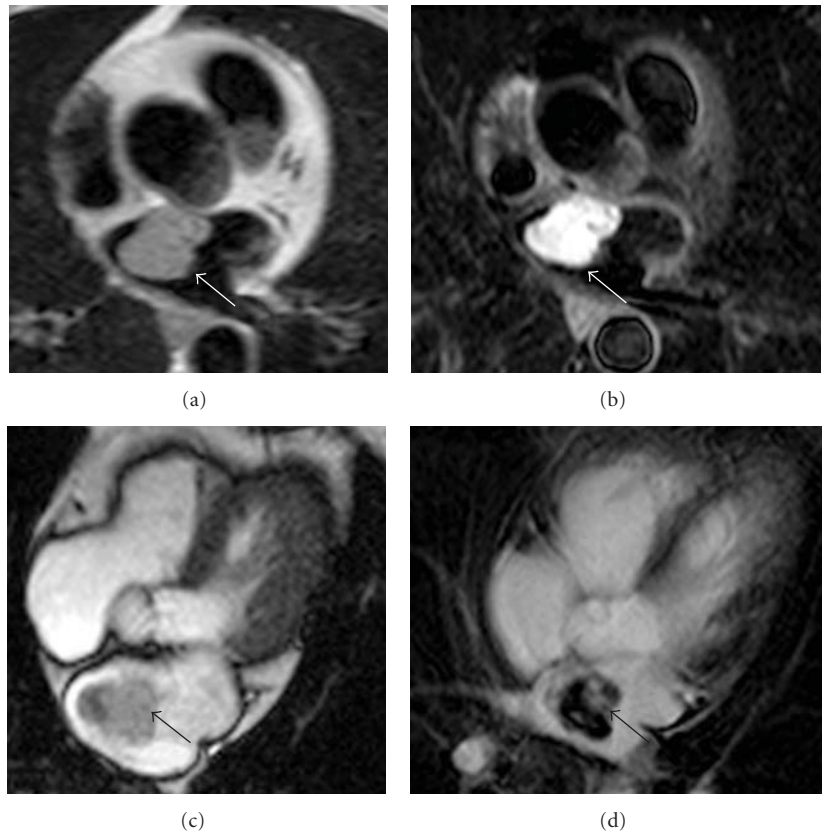


Figure 1: Left atrial myxoma. A lobulated mass is situated in the left atrium adjacent to the interatrial septum (a). On T2-weighted images, the mass appears uniformly high signal ((b), white arrow). Note that the mass is less well appreciated on bright blood cine imaging ((c), black arrow) and could be overlooked if it were smaller. Late gadolinium enhancement images (d) demonstrate patchy uptake of contrast within the mass (black arrow). The location and imaging characteristics are fairly typical for myxoma.

and tachycardic patients. Transesophageal echo (TEE) offers the advantage of a rapid and very high resolution survey of the valves and cardiac chambers in patients who may be too sick to undergo any other form of imaging [6].

A further advantage of echocardiography is its relative robustness in the face of sustained arrhythmia or frequent premature atrial or ventricular contractions. Image quality can be maintained in the face of significant rhythm disturbance unlike CT and CMR which usually "construct" an image based on an average of data derived from multiple sequential heart beats using a process known as "segmentation." Thus the varying cardiac cycle lengths introduced by arrhythmia cause considerable image perturbation frequently rendering the study nondiagnostic. Echocardiography is not subject to these constraints since multiple frames are acquired real-time in a single cardiac cycle, avoiding the need for segmentation [7].

Newer techniques in echocardiography have been less well studied in malignancy. Interrogation of myocardial strain using tissue Doppler or speckle tracking may provide earlier warning of chemotherapy-induced dysfunction than standard 2D echo techniques [8]. Three-dimensional echocardiography is in its infancy, and its clinical utility in the diagnostic evaluation of malignancy has not yet been well characterized [9].

2.2. Multidetector Computed Tomography (MDCT). CT is a versatile technique that has evolved rapidly in the last decade. Multidetector computed tomography (MDCT) was revolutionized by the invention of the 4 slice scanner in 2001 and has progressed through iterations that have involved 16, 32, 64, 256, and currently 320 detector rows. This has reduced the time required to scan an entire thorax from 40 seconds to a minimum of only 1 or 2 seconds. This is especially valuable for sick, intubated, or claustrophobic patients. The utility of MDCT has been further increased with the development of software for the scanner that permits cardiac gating. Images may be acquired at a relatively quiescent point towards end diastole, effectively "freezing" all cardiac motion. This, combined with the exquisite spatial resolution of MDCT, offers major advantages for assessment of the cardiac chambers, pericardium and surrounding vascular structures [10].

Not only does cardiac MDCT have high spatial resolution (0.5–0.65 mm in most cases) but this resolution is isotropic, that is, the lengths of the imaging element—the voxel—are equal in x, y, and z axes. This permits reconstruction of the raw data set (acquired in the axial plane) along any axis desired without any discernible loss of image quality. Interrogation of an abnormality in any plane desired makes MDCT an extremely powerful tool. This reformatting

Table 1: Relative strengths and weaknesses of non-invasive imaging modalities.

	ECHO	MDCT	CMR	RNA
Availability	++++	+++	+	++
Temporal resolution	++++	++	+++	+
Spatial resolution	++	++++	+++	+
Contrast resolution	++	+++	++++	+
Cost	Low	Medium	High	Low
Thoracic vessels	+	++++	++++	−
Cardiac function	+++	++	++++	+++
Speed of acquisition	+++	++++	+	++
Radiation	None	Moderate	None	Moderate
Tissue characterization	+	++	+++	−
Suitability for sick or claustrophobic patients	++++	++++	+/−	+/−

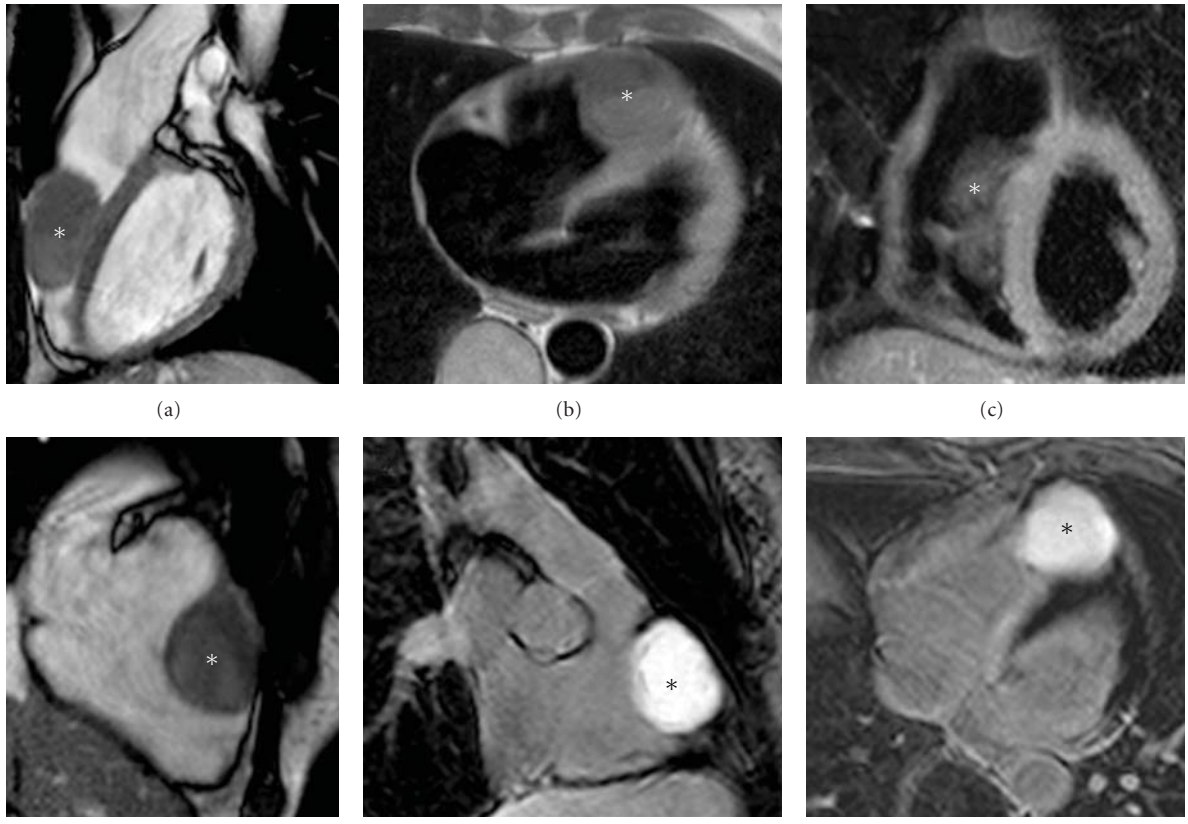


Figure 2: Fibroma. An ovoid mass partially obstructs the right ventricular outflow tract ((a)–(f), asterisk). The mass is of intermediate intensity on T1-weighted imaging ((a) and (b)) and low signal on T2-weighted imaging (c). This combination of findings would make malignancy relatively unlikely since many neoplasms have a relatively high water content and thus are high signal on T2 sequences. Dramatic contrast uptake is, however, evident on the postgadolinium images ((e) and (f)). Dense fibrous tumors may behave in this way, and the diagnosis of fibroma was later confirmed.

occurs after the patient has left, which allows flexibility in postprocessing workflow. This is an important distinguishing feature from the common bright-blood gradient echo or steady-state sequences used to evaluate cardiac anatomy and function in CMR, which are not isotropic and require accurate planning of cardiac planes prospectively.

Noncontrast MDCT is of limited value for soft tissue assessment other than lung parenchyma. It is, however, very sensitive for calcium and is the technique of choice to confirm pericardial calcification in the context of possible constriction. For assessment of the cardiac chambers and thoracic vasculature, administration of iodinated contrast

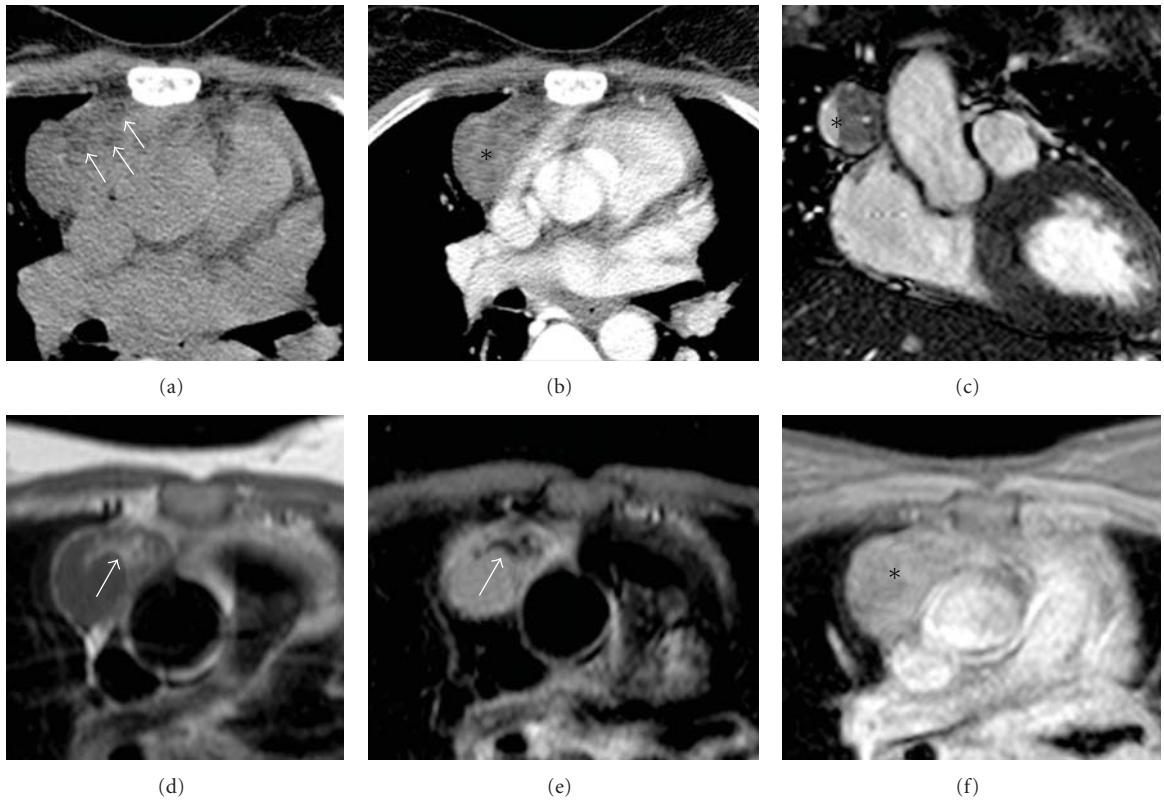


Figure 3: Teratoma. A well-circumscribed solid mass is present adjacent to the right atrial appendage ((b), (c), (f) asterisk). Foci of low attenuation are identified within it on noncontrast axial MDCT ((a), white arrows). Similar areas can be seen on the T1-weighted image ((d), white arrow) and show signal "dropout" with a fat-suppressed sequence ((e), white arrow). The presence of fat in a mixed density mediastinal lesion raised the possibility of teratoma, and this diagnosis was confirmed at pathology.

medium is required. This poses a problem in patients with chronic kidney disease, especially in the presence of diabetes. This may in some cases constitute a contraindication to the study because of the risk of contrast-induced nephropathy (CIN). Patients with GFR lower than threshold (often defined as <30 mL/min/kg) may receive contrast after careful consideration of risk/benefit ratio but the possibility of worsening nephropathy and potential dialysis has to be discussed [11, 12].

The principal disadvantage of MDCT is patient radiation exposure. However, this needs to be considered in the context of the patient's pre-existing malignancy and the overall likelihood of benefit from the scan [13]. Thoracic MDCT doses vary widely according to the scan parameters used. The mean effective dose can be anywhere between 5 and 25 mSv for a single examination (the minimum and maximum doses quoted are roughly the same as for conventional coronary angiography and technetium MIBI nuclear study, resp.). Of particular concern is the radiation dose to the female breasts, lungs, and esophagus/thymus because these organs are sensitive to radiation-induced carcinogenesis [14].

2.3. Cardiovascular Magnetic Resonance (CMR). CMR is generally underutilized in the assessment of cardiovascular malignancy. This is primarily because of a lack of availability and expertise in this field outside of large centers.

CMR combines good spatial and acceptable (segmented) temporal resolution with unsurpassed soft tissue contrast resolution over a much wider dynamic range than MDCT. Not only is it excellent for anatomical assessment, it also provides hemodynamic information regarding flow velocity, biventricular volume and systolic function, and tissue characterization. The latter is a major strength; T2-weighted sequences may demonstrate that a mass has a high water content (raising suspicion of neoplasia in the appropriate context) or may, for example, demonstrate pericardial inflammation after radiotherapy as a cause for a patient's atypical chest pain. Administration of gadolinium-based contrast agents (GBCAs) can be combined with imaging sequences that are particularly sensitive to the uptake of gadolinium. The rate of uptake and pattern of enhancement may offer further insights into the underlying pathology and frequently enable a distinction between tumor and thrombus to be made with confidence [15]. Nonetheless CMR does not allow precise histopathological diagnosis in the majority of cases.

Measurement of LV volumes and function is highly reproducible by CMR, much more so than for any other modality [16]. Screening for small decrements in ventricular

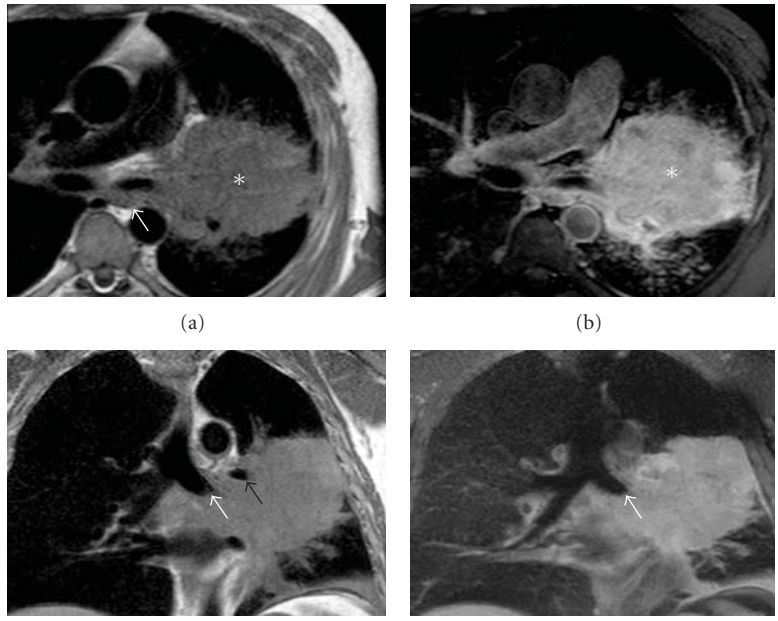


Figure 4: Bronchogenic carcinoma. A large mass (asterisk) is shown in axial ((a) and (b)) and coronal ((c) and (d)) planes. On T1-weighted images the mass demonstrates significant near-uniform enhancement after gadolinium contrast ((a) and (c) before contrast; (b) and (d) after contrast). The mass infiltrates posterior to the carina ((a), white arrow) and occludes the left main bronchus ((c) and (d), white arrow). The left main pulmonary artery is severely attenuated ((c), black arrow).

Table 2: Chemotherapeutic agents associated with left ventricular dysfunction.

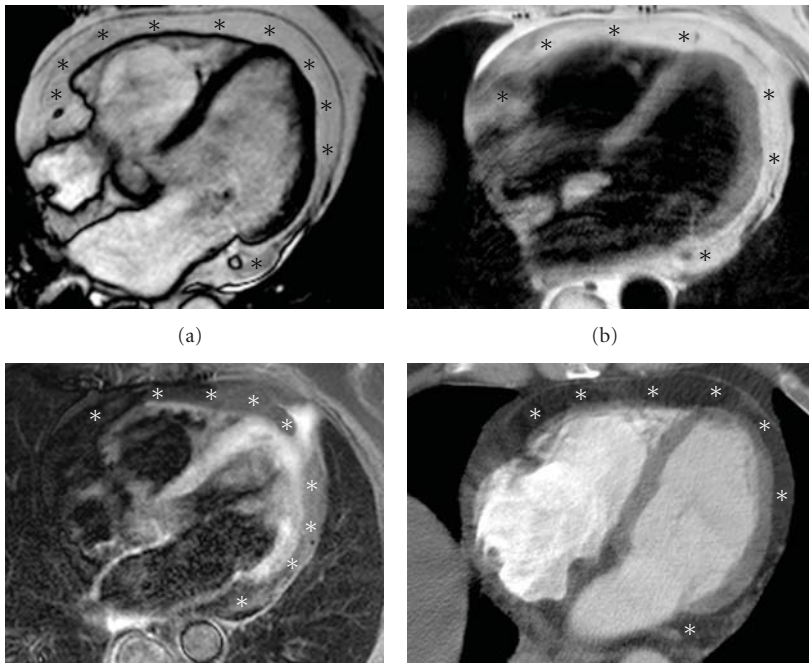
Chemotherapy agents
Anthracyclines
Doxorubicin
Epirubicin
Idarubicin
Alkylating agents
Cyclophosphamide
Ifosfamide
Antimetabolites
Docetaxel
Monoclonal antibody-based tyrosine kinase inhibitors
Bevacizumab
Trastuzumab
Proteasome inhibitor
Bortezomib
Small molecule tyrosine kinase inhibitors
Dasatinib
Imatinib mesylate
Lapatinib
Sunitinib

function in patients receiving cardiotoxic chemotherapy is a function that has been historically performed by radionuclide angiography. In the future it seems probable that CMR will take on at least a portion of this work perhaps targeting the younger patients who have most to gain from sequential followup with a technique that involves no ionizing radiation.

Angiographic delineation of the major vascular structures in the chest is readily achieved by CMR using both static "snapshot" imaging and time-resolved magnetic resonance angiography which delineates the passage of contrast through the vascular tree providing differential enhancement of arterial and venous structures. This may be useful in establishing degree of obstruction in, for example, SVC syndrome as well as facilitating interventional planning.

A certain amount of subjective information may also be gained about relative lung perfusion in cases of unilateral tumor involvement of the pulmonary arteries or veins, with delayed parenchymal blush often occurring on the obstructed side. Formal measurements of relative flow may be made using phase velocity mapping which is a flow sensitive technique akin to echo Doppler. The ability to interrogate a vessel in any plane renders CMR far more flexible than its sister modality.

CMR has both limitations and definite exclusions. Amongst the former, a number lack availability and expertise both to perform and interpret the studies. CMR is also rarely a rapid method of gathering data and so is poorly tolerated by the claustrophobic and very unwell for whom the challenge of remaining still and breath holding repetitively on command is often insurmountable. Symptomatic claustrophobia is very common occurring in up to 25% of patients although only 5-6% of all patients fail to complete an exam for this reason [17].



(a) (b) (c) (d)

Figure 5: Epicardial fat. Echocardiography raised concerns about excessive soft tissue anterior to the right ventricle in this patient on long-term steroids. Bright blood cine (a) and T1-weighted images (b) show circumferential high signal around the heart (asterisks). The appearances suggest an unusual amount of pericardial fat, and this was confirmed on fat-suppressed CMR (c) where there is evidence of signal drop out from the fatty region (asterisks—compare with (b)). MDCT is also very sensitive for fat which it displays as low-density regions of negative Hounsfield attenuation ((d), asterisks). Excessive mediastinal lipomatosis is not uncommon in patients taking steroid preparations.

Critically ill patients may be unable to enter the scan room if attached to standard infusion pumps because of possible magnetic interference. Similarly the presence of a pacemaker or defibrillator currently remains a near-absolute contraindication to CMR in most institutions worldwide.

Pregnancy is not an absolute contraindication of itself; attempts are generally made to keep the radiofrequency power deposition levels as low as possible primarily because of theoretical concerns about heating of the fetus. Similarly gadolinium contrast is generally not given although there are no data to suggest harm to the fetus at standard clinical doses.

In many of the situations where CMR is difficult or contraindicated, the patient may be equally well served by a timely MDCT study plus echo where function or flow data is vital.

2.4. Nuclear Medicine: Radionuclide Angiography (RNA). The main goal of RNA is the visualization of the cardiac chambers and great vessels. This requires the temporary labeling of the blood with a suitable radioactive tracer. It provides an accurate evaluation of the structure and function of the heart, including ejection fraction, regional wall motion variability, and diastolic function [18].

RNA is widely used for the assessment of the cardiac function after chemotherapy, principally because of its ready availability [19]. However, although its reproducibility is very high, the main disadvantages of RNA are its limited temporal resolution and the use of ionizing radiation (approx. 3–6 mSv), which makes CMR a more attractive and highly reproducible method of evaluating cardiac function without a radiation penalty [20].

The relative merits and demerits of each of the 4 principal modalities discussed above are summarized in Table 1.

3. Multi-Modality Imaging in Specific Clinical Scenarios

3.1. Characterisation of Cardiac Tumors. Cardiac tumors may be categorised as either primary or secondary. Primary tumors are rare, ranging from 0.001% to 0.030% [21] and three quarters of these tumors are benign. The most common primary tumor is myxoma (Figure 1) (about 50%); the remainder includes lipoma, papillary fibroelastoma, cavernous hemangioma, fibroma (Figure 2), rhabdomyoma, paraganglioma, mediastinal teratoma (Figure 3), and lymphangioma. Of the malignant primary tumours, about 95% are sarcomas and 5% are primary lymphomas and primary cardiac carcinoid.

Secondary tumors, however, are much more common than primary tumors, with an incidence of metastasis to heart of 10% [22, 23]. The most frequent underlying malignant origin is the lung (Figure 4). Secondary involvement may be the result of direct invasion, lymphatic or

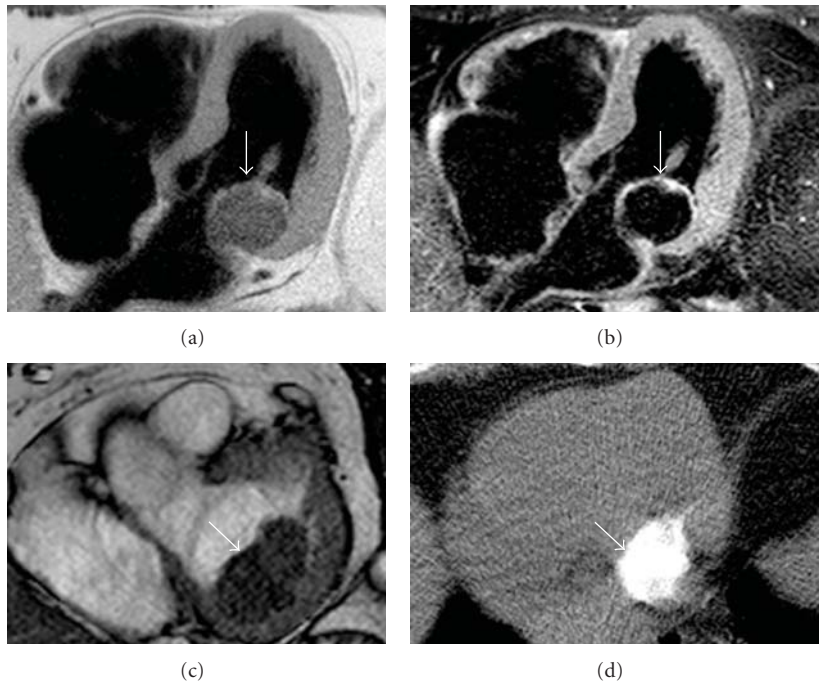


Figure 6: Mitral annular calcification (MAC). A classic "pseudotumour" MAC is seen in older patients, often with a history of diabetes or hypertension. It presents as focal mass-like lesions most frequently adjacent to the lateral mitral annulus ((a) and (b), white arrow). In this example the signal characteristics on CMR are typically being low signal on T1-weighted images (a) and T2-weighted images (b). Its relation to the posterior mitral annulus is well appreciated on the short axis bright-blood cine view ((c), white arrow). Noncontrast MDCT excludes any residual diagnosis about the diagnosis—the mass is of very high attenuation consistent with calcium ((d), white arrow).

hematogenous spread. In rare cases, direct transvascular extension may occur (e.g., renal cell carcinoma extending into the right heart via the inferior vena cava). The detection of a cardiac mass should therefore always lead to a screen for primary malignancy elsewhere in the body.

There is a group of nonneoplastic conditions of the heart and pericardium that can mimic cardiac tumors. These include pericardial cysts, lymphadenopathy, lipomatous hypertrophy of the atrial septum, pericardial fat (Figure 5), caseous calcification of mitral valve [24], coronary artery aneurysm, and thrombus. Despite the lack of malignant potential of these lesions, they can be associated with considerable morbidity and even mortality due to inappropriate treatment. For this reason, their recognition and differentiation from malignant tumors is crucial [25]. The most frequent pseudotumor is thrombus, which is discussed separately below.

For diagnosis of cardiac tumors, TTE and TEE are widely used as they can localize the tumor and give information about size, shape, attachment, and mobility. Contrast echocardiography is also used for assessment of intracardiac masses [26]. However, for complex tumors and large or infiltrating tumors, the combination of echocardiography with either MRI or MDCT provides better definition and more precise preoperative planning [27].

Tumor breach of tissue planes is often depicted with greater certainty by MDCT than CMR due to better spatial resolution. Detection of small amounts of tumor may be better by CMR because of its superior contrast resolution for soft tissue. The presence of calcium, however, is recognised with greater ease using MDCT than CMR which can be helpful when assessing mitral valve masses (Figure 6).

3.2. Thrombus. Thrombus is the most common intracardiac mass involving the left ventricle or left atrium [28]. Its identification and proper characterization is very important so that anticoagulant therapy is not delayed (Figure 7). Although TTE can detect the presence of thrombus and is usually the primary screening tool, it has limited sensitivity for this purpose [29]. Laminated mural thrombi may be difficult to distinguish from myocardium and slow blood flow within aneurysms. Late gadolinium enhancement CMR is very sensitive for the presence of thrombus [30]. Several distinguishing CT imaging features have been described to differentiate thrombus from other tumors including size, origin, shape, and prolapse [31]. However, the accuracy of MDCT in this regard has not been established in any large studies.

3.3. Pericardial Disease. Pericardial disease related to cancer encompasses both the direct effects of tumor invasion as well as the indirect consequences of thoracic surgery and/or radiotherapy.

The initial evaluation for pericardial effusion is usually by transthoracic echo. Echocardiography is useful in evaluating the physiological changes in pericardial diseases [32]. Malignant pericardial effusion is not uncommon, and TTE is generally the most sensitive method for detecting

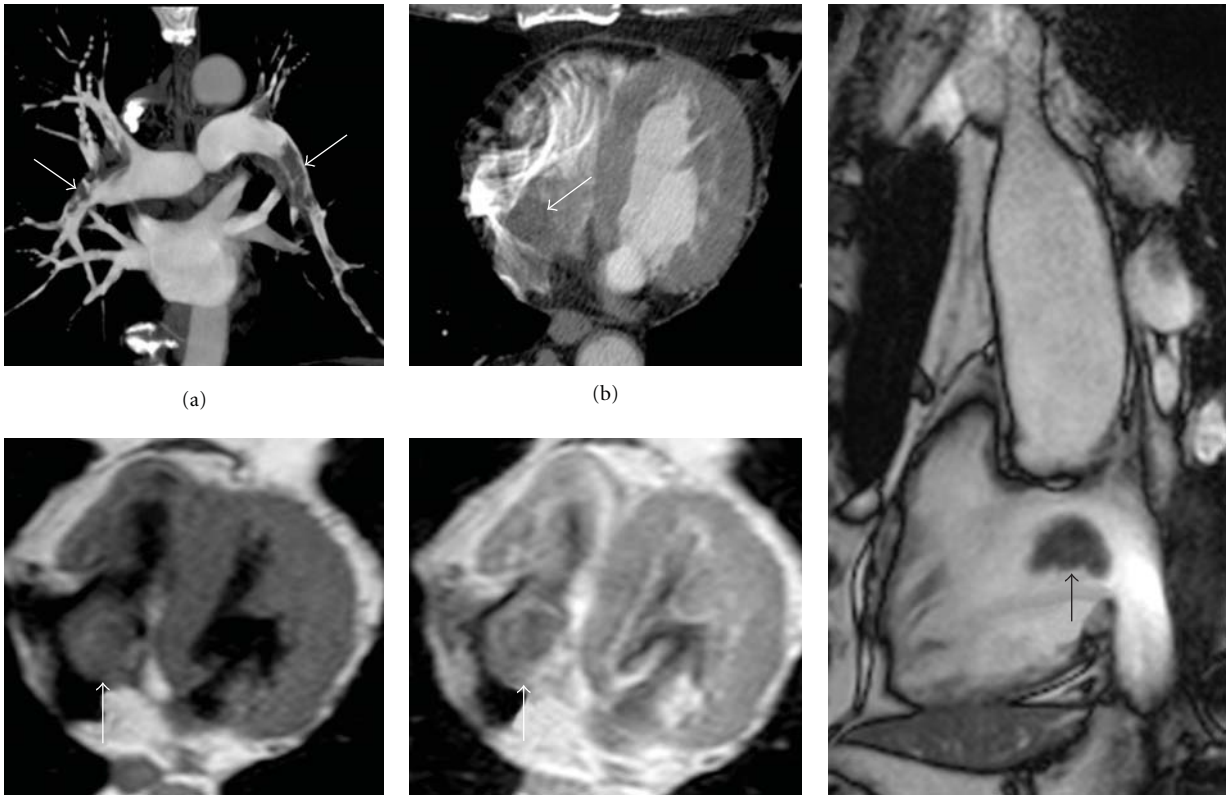


Figure 7: Thrombus. A coronal maximum intensity projection image from a contrast MDCT study demonstrates multiple pulmonary emboli ((a), white arrows). On the same study the possibility of a right atrial mass was raised ((b), white arrow), although it was uncertain whether this was real or simply an appearance due to incomplete mixing of opacified SVC blood with unopacified IVC blood. Cine CMR demonstrates that the mass is clearly real ((c), black arrow). Further characterization by CMR demonstrates that the mass is low signal on T1 weighted images ((d), white arrow) and remains low signal following gadolinium administration ((e), white arrow). The appearances and clinical presentation were entirely consistent with right atrial thrombus. The mass disappeared with subsequent anticoagulation.

both incipient and frank tamponade (Figure 8). However, it is limited in the assessment of pericardial extension, pericardial thickening, and inflammation, whereas CMR and MDCT excel in this regard. MDCT is the best technique for depiction of pericardial calcification. In addition, the composition of pericardial collections (simple or complex) may be inferred from measurements of Hounsfield density. This may guide subsequent management since complex collections are unlikely to respond well to percutaneous drainage and often require surgical intervention.

CMR is better at differentiating small pericardial effusions from pericardial thickening and provides a functional and structural assessment of the pericardium. CMR can also evaluate physiological consequences of pericardial constriction. Specific imaging techniques for pericardial constriction include cine-tagged imaging which can demonstrate tethering of the myocardium during systole. Real-time cine imaging may be used to demonstrate septal bounce seen in constriction [33].

CMR may show pericardial inflammation (e.g., acutely after radiotherapy) with T2-weighted or late gadolinium enhancement imaging.

4. Cardiovascular Complications of Cancer Therapy

The therapeutic options for patients with cancer include complex combinations of medications, radiation therapy, and surgery. Many of these treatments have important potential adverse cardiovascular effects. Indeed, cardiovascular events represent the second most common cause of mortality after cancer recurrence [34]. Although there is no unified consensus for the assessment and monitoring of the cardiovascular complications of cancer treatment, noninvasive imaging is increasingly used [35].

4.1. Radiation. Mediastinal irradiation is not uncommon for solid and lymphomatous malignancies involving the chest [36]. The potential adverse effects include arteritis, pericarditis, cardiomyopathy, valvular disease, and conduction anomalies.

Radiation-induced valvular disease is limited, affecting approximately 6–15% of patients exposed to mediastinal radiation [37]. Valvular regurgitation is more common [38]. The typical findings include valvular thickening, fibrosis, and

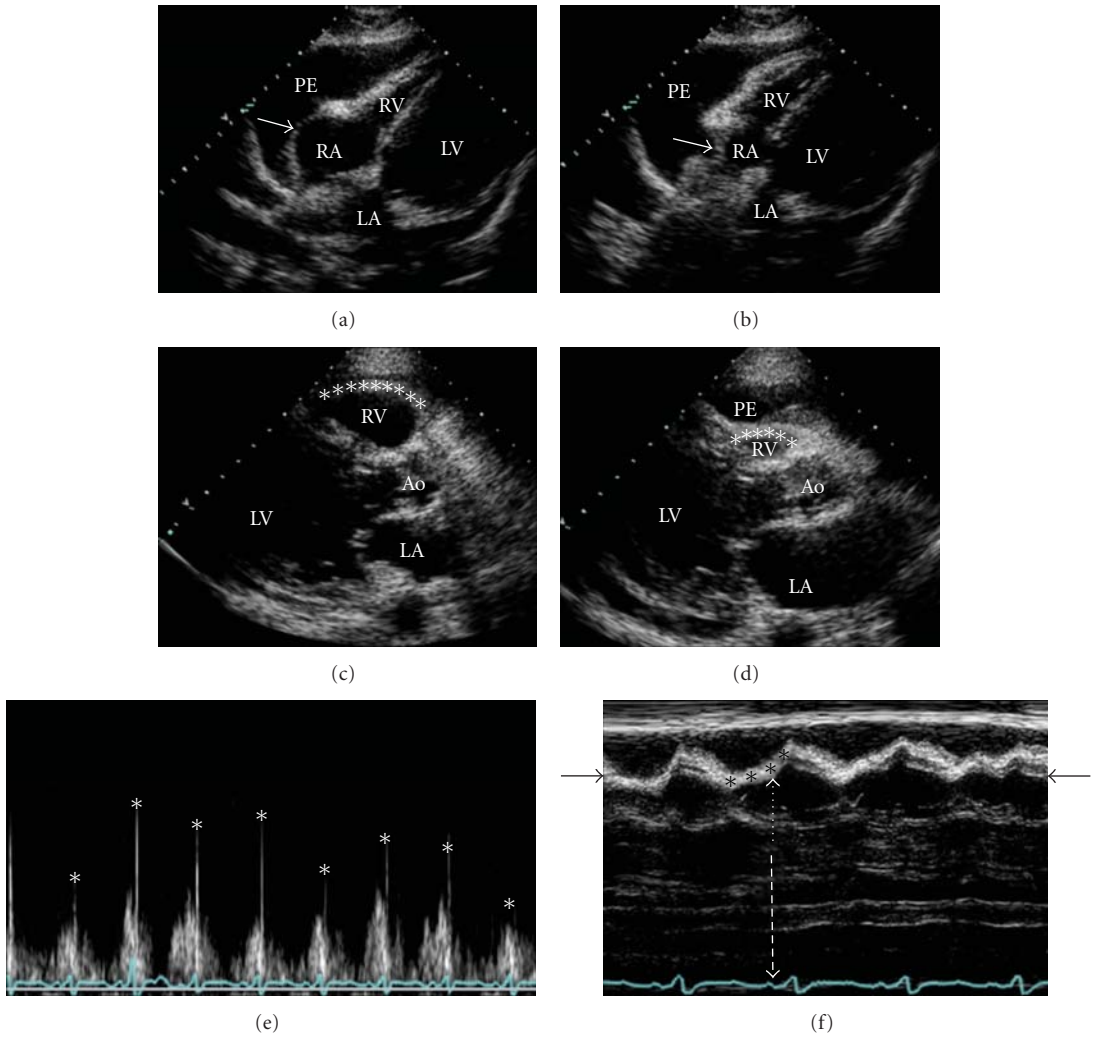


Figure 8: Echo signs of tamponade. Diastolic inversion of the right atrial (RA) free wall is an early sign of raised intrapericardial pressure ((a) and (b)), white arrow—note collapse/inversion of the RA free wall in early diastole (b) as the intrapericardial pressure exceeds the RA pressure. Right ventricular diastolic inversion is a later but more specific sign of tamponade ((c) and (d)) asterisks outline the RV free wall—the RV shows diastolic collapse (d) due to the adjacent effusion (PE). Note also the relative enlargement of the left ventricle (LV) in this case; a result of chemotherapy-related cardiomyopathy. Doppler techniques are often very helpful in establishing the diagnosis of tamponade—transtricuspid flow variability of greater than 33% on a beat-to-beat basis ((e), asterisks represent peak transtricuspid flow for each recorded beat) is suggestive of tamponade. M-mode Doppler has a very high sampling (frame) rate compared to standard B-mode Doppler and is therefore useful for timing the motion of the RV free wall with respect to the cardiac cycle ((f), horizontal white arrows indicate the RV free wall; as would be expected this moves in normally during systole but is slow to move outwards in early-to-mid diastole (black asterisks)—in fact full outward excursion only occurs late in diastole (dotted short arrow) aided by the filling from atrial contraction (dotted long arrow indicates *P* wave on ECG, i.e., atrial systole)).

calcifications. TEE is the best imaging modality to evaluate valvular function.

Pericardial disease induced by radiation is typically a long-term complication and may develop years after treatment, manifesting as silent pericardial effusions or with constrictive pericarditis, with or without pericardial fluid. Echo together with CMR may both be required to support a clinical diagnosis of constriction. Cardiomyopathy after radiation is predominantly due to diastolic dysfunction with a restrictive pattern—these features may be most evident on echo which is best suited to evaluate abnormalities of diastolic function. This is primarily because of its very high temporal resolution which permits beat-to-beat (real-time) measurement of the transmitral flow abnormalities which characterize diastolic impairment.

4.2. Chemotherapy. Many chemotherapy drugs have the potential to cause cardiotoxicity. The chemotherapy agents associated with LV dysfunction are shown in Table 2. Different expert working groups have developed practice guidelines for cardiac monitoring requirements in patients

undergoing chemotherapy. For example, the recommendations of the Canadian Trastuzumab working group include LVEF assessment before trastuzumab treatment is started and repeated every 3 months until completion of therapy. Several authors have also described development of myocardial fibrosis in conjunction with certain chemotherapeutic agents demonstrated by late gadolinium enhancement on CMR [39].

4.3. Others. The use of devices for chemotherapy, such as indwelling venous catheters, predisposes to thrombus formation typically at the tip of the catheter. This is often well depicted by CMR. MDCT can be confusing since incomplete mixing in the right atrium during the first pass of contrast often simulates filling defects—definite CT confirmation of a real mass is best achieved by performing a delayed acquisition 1-2 minutes after contrast injection.

5. Conclusion

The extent of potential cardiovascular involvement by malignancy is broad. Four main non-invasive imaging methods are available for evaluation of suspected cardiovascular complications of malignancy. They are useful for the exclusion of other diseases and to guide proper management of these patients. Non-invasive imagers are well educated in the strengths and weaknesses of the various imaging techniques; optimum use of this expensive technology is most efficient when proper dialogue occurs between cancer and imaging specialists.

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Review Article

Management of Concomitant Cancer and Abdominal Aortic Aneurysm

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Background. The coexistence of neoplasm and abdominal aortic aneurysm (AAA) presents a real management challenge. This paper reviews the literature on the prevalence, diagnosis, and management dilemmas of concurrent visceral malignancy and abdominal aortic aneurysm. *Method*. The MEDLINE and HIGHWIRE databases (1966-present) were searched. Papers detailing relevant data were assessed for quality and validity. All case series, review articles, and references of such articles were searched for additional relevant papers. *Results*. Current challenges in decision making, the effect of major body-cavity surgery on an untreated aneurysm, the effects of major vascular surgery on the treatment of malignancy, the use of EVAR (endovascular aortic aneurysm repair) as a fairly low-risk procedure and its role in the management of malignancy, and the effect of other challenging issues such as the use of adjuvant therapy, and patients informed decision-making were reviewed and discussed. *Conclusion*. In synchronous malignancy and abdominal aortic aneurysm, the most life-threatening lesion should be addressed first. Endovascular aneurysm repair where possible, followed by malignancy resection, is becoming the preferred initial treatment choice in most centres.

1. Background

Malignancy and aortic aneurysms are common diseases, particularly among aging population. Nearly three quarters of malignant cases are diagnosed in people aged 60 years and over [1]. Abdominal aortic aneurysms occur in about 7-8% of male population over the age of 65 years and is rare under the age of 55 years [2]. The coexistence of malignant disease and aortic aneurysm presents a real management challenge, especially in establishing the therapeutic priorities and the ideal treatment approach. This study aims at reviewing the diagnosis modalities and treatment options and the changes that have taken place with the advances in the management of both cancer and aortic aneurysms, particularly with the development of minimally invasive procedures.

2. Design and Methods

The MEDLINE and HIGHWIRE databases were searched using the terms ("neoplasms"[MeSH Terms] or "neoplasms"[All Fields] or "cancer"[All Fields]) and ("aortic aneurysm"[MeSH Terms] or "aortic"[All Fields]) and ("aneurysm"[All Fields] or "aortic aneurysm"[All Fields]). All abstracts from the English language articles and foreign language articles were examined by a single reviewer. Papers detailing relevant data were assessed for quality and relevance independently by two separate reviewers. All case series, review articles, and references of such articles were searched for additional relevant papers. Papers that outlined their relevant experience and outcome of their approach sufficiently to allow comparison were included; articles that failed to detail the effect of treatment approach on outcome were excluded. A total of 139 articles were identified. Of these 139 papers, 75 were case series, 57 were case reports, and 5 were discussion papers on various aspects of aortic aneurysm and cancer and all were included in this paper.

3. Incidence

Although the true incidence of concomitant malignancy and aortic aneurysm is difficult to establish, most centers

report a low incidence of intra-abdominal malignancy in patients with abdominal aortic aneurysm. Malignancies were found in 4% of AAA cases in one of the earlier reviews covering a period of 22 years (Table 1). Some authors report a much higher incidence rate, with up to 14% of AAA cases associated with malignancy in one series published in Japan (Table 1). Based on the natural history of AAA simulated to match the age-specific prevalence rate for male subjects, AAA was estimated to coincidentally occur in 8.3% of patients with intra-abdominal malignancy. This includes colorectal cancers detected using virtual colonoscopy [3].

4. Aetiology

Aortic aneurysms are due to degenerative changes in the aortic wall. Some reports have found an association between the presence of cancer and mycotic aortic aneurysm. For instance, Mycobacterium bovis was found in the wall of a ruptured abdominal aortic and femoral artery aneurysm following intravesical bacillus Calmette-Guérin (BCG) therapy for bladder cancer [14, 15]. Listeria monocytogenes infection was also found in the wall of a resected thoracic aneurysm two months before advanced rectal cancer was diagnosed. The authors believed that the rectal cancer predisposed the patient to the development of an arterial infection associated with L. monocytogenes [16]. Clostridium septicum mycotic aortic aneurysm has been reported simultaneously with colon cancer [17]. The presence of infection influences the natural history and management. These findings do not establish a causal association but do raise the possibility of an infective aetiology in a very small number of aneurysms.

5. Clinical Presentation

Most synchronous abdominal aortic aneurysms and cancers are found incidentally during the investigation or treatment stages. Nevertheless, suspicion of the presence of cancer has been occasionally raised during the workup for aortic aneurysm and vice verse. Table 2 details some examples of such cases.

6. Investigations

Computerised tomography (CT) scan is the most common investigation reported to detect the presence of abdominal aortic aneurysms concomitantly with visceral malignancies and vice verse. Occasionally, malignancies are detected incidentally during laparotomy [22] or following an endoscopic procedure such as bronchoscopy [20], upper gastrointestinal [21], or lower gastrointestinal [23] endoscopy. Virtual colonography [3, 24, 25] or whole-body CT scanning [26] was recommended by some as a more cost-effective strategy to use in population-based screening programmes but not widely accepted.

7. Management

There is no consensus on the best management approach for patients with simultaneous aortic aneurysm and malignancy. Several strategies have been considered, namely, to repair the aneurysm first and treat the malignancy later, to resect the malignancy first and repair the aneurysm later, to undertake both procedures simultaneously, and in some cases to treat the malignancy and manage the aneurysm conservatively.

Aortic aneurysm repair is a prophylactic procedure and is worthwhile where the lifetime risk of rupture exceeds the risk from treatment. The prognosis of cancer is therefore central to the decision making process.

The perceived increase risk of aortic aneurysm rupture following cancer surgery, the significant delay in the treatment of cancer if aneurysm is treated first, and the risk of graft infection are the other important considerations in the management of concomitant aortic aneurysm and cancer.

Table 3 summarizes the different approaches used in the treatment of different patient groups in case series and their outcome.

8. Discussion

The treatment of AAA with coexisting malignancy represents a challenging issue to the cancer and vascular specialists in terms of priority, timing, and expected outcome. Most published papers consist of fairly small case series. Prospective randomized controlled trials with adequate statistical power have understandably not been done in this area. In the absence of such level of evidence, one has to combine the best available evidence with a sound clinical judgment applied on each individual case within a multidisciplinary setting.

The management challenge was reflected on a survey of 46 general and vascular professors in the USA in 1985 who gave their responses as to which condition should receive priority of treatment [39]. Excision of the carcinoma first was favored by about a third of them, repair of the aneurysm first was favored by another third, and the remaining third stated that they would withhold a decision until laparotomy was performed. The survey was undertaken in the mid-eighties and a similar survey in the current era would probably show different opinions, especially with the introduction of endovascular and laparoscopic approaches and the availability of advanced preoperative staging techniques and adjuvant therapy.

There is some evidence that abdominal surgery increases the risk of aneurysm rupture, especially when the AAA diameter is over 5 cm. Baxter et al. [11] from the Mayo Clinic reported two AAA ruptures in the immediate postoperative period following 20 CRC (colorectal cancer) excisions (10% incidence rate). A similar phenomenon was noted by Lin et al. from the Michael E. DeBakey Departement of Surgery, with AAA rupture incidence rate of 6% following CRC resection [33]. Swanson et al. [40] noted this complication in ten previously asymptomatic patients with aneurysms within 36 days of a prior laparotomy, with a mean AAA diameter of 9.1 cm. On the other hand, Durham et al. [41] prospectively studied 33 patients (29 men, 4 women) with a known abdominal aortic aneurysm who underwent 45 operations. The estimated risk of rupture was 3% of all patients undergoing major operation in this study. It was hypothesized that a reduction in the collagen contents of

Table 1: Prevalence of aortic aneurysm and concomitant malignancy.

Source	AAA	Malignant disease	Colorectal cancer	Observation period, yr
Szilagyi et al.,1967 [4]*	803	31 (3.9)	9 (1.2)	22
Nora et al., 1989 [5]	3500	NA (the emphasis is on CRC)	17 (0.5) (those underwent operations for Ca and AAA)	12
Morris and Colquitt, 1988 [6]	158 (looking at all but with histologically proven ca)	20 (12.7)	6 (3.8)	12
Tennant 1990 [7]	247	4 (1.6)	0	5
Oshodi et al., 2000 [8]	676	8 (1.2)	4 (0.6)	20
Tsuji et al., 1999 [9]	162	4 (2.5)	1 (0.6)	10
Matsumoto et al., 2002 [10]	260	29 (11.2)	16 (6.2)	14
Baxter et al., 2002 [11]	10 872	NA	83 (0.8)	15
Yamamoto et al. [12]	408 (using FOB to detect CRC)	—	6 (1.5%) with cancer and 16 (3.9) with polyps	—
Onohara et al. [13]	112	16 (14%)	—	—

* This study was performed in the pre CT/Duplex era and therefore unlikely to detect cancer. AAA: abdominal aortic aneurysm. CRC: colorectal cancer. NA: not applicable. FOB: faecal occult blood.

Table 2: Examples of clinical presentation of aortic aneurysm and/or associated malignancy.

Source	Setting	No. of cases	Mode of presentation*
Upchurch and Clair [18]	Cancer in aortic aneurysm case	1 case	Ruptured AAA associated with aortocaval fistula was complicated by C. Septicum sepsis. CRC was suspected and found on investigations.
Tsui, et al. [19]	Cancer in aortic aneurysm case	1 case	Haemoptysis in TAA was initially related to the aneurysm. Lung cancer was suspected thereafter and found.
Van Doorn et al. [20]	Aortic aneurysm in cancer case	1 case	Sepsis and widened mediastinum developed after CRC operation. Thoracic aneurysm was suspected and found.
Mohamed et al. [17]	Aortic aneurysm in cancer case	1 case	CT scan in a patient with sepsis and abdominal pain revealed ruptured aorta with pseudoaneurysm. Repeated CT scan in another centre found CRC in pelvis.
Sebastian et al. [21]	Cancer in Aortic aneurysm case	1 case	Unsettled dysphagia in TAA was investigated further. Oesophageal cancer was found.

* AAA: abdominal aortic aneurysm. CRC: colorectal cancer.

aortic wall following trauma may predispose the aortic aneurysm to rupture, through a mechanism mediated by collagenase and protease activation [40, 42].

The effect of delayed cancer treatment on the long-term outcome remains unclear. Ideally, any delay in cancer management should be avoided. A few months delay before initiating treatment of oesophageal cancer, for example, would have an impact on the stage of the cancer, and thereby on the patients' prognosis [43]. Nevertheless, disease stage at the time of diagnosis is probably the most important influence on survival, and some delay in treatment may not strongly be associated with variation in survival [44]. Delays occurring due to poor organization or the magnitude of the first operation requiring prolonged recovery before the second operation took place, need to be tackled as modern practice allows.

Authors from many large centers (the Mayo Clinic, USA [23], The Cleveland Clinic Foundation, USA [30], the University of Naples Federico II and University of Turin, Italy [36, 37], the Michael E. DeBakey Department of Surgery, USA [8], the Keio University School of Medicine, Japan [13], the Imperial College London, UK [46], the Concord Repatriation General Hospital, Australia [31], and others [16, 45]) agree that the most life-threatening (or symptomatic) lesion should be addressed first. Large abdominal aortic aneurysms, obstructing colonic cancers, or bleeding gastric cancers, for example, should be treated first where possible. The treatment modality may be a minimally invasive procedure (e.g. stenting for obstructing CRC) that can allow optimization and a better planned therapy [36].

A one-stage operation to repair the aortic aneurysm and resect the malignancy has the advantage of avoiding a

Table 3

Reference (first author)	Type of cancer	No. of cases	Group	Approach	AAA rupture rate (period)	Interval between AA repair and cancer treatment	Delay in cancer treatment	Cancer outcome	Graft complication rate	% mortality rate (mode)
Baxter et al. [11]	CRC	83 (of 435 AAA pts over 8 yrs)	One: 44pts	CRC treated first. AAA average size 3.8 cm	1/44 ruptured (7yrs later) 1/44 died of sepsis following repair of AAA (1 yr later)		4 days	13% recurrence		4.5% (30 d)
			Two: 20pts	CRC treated first. AAA average size 5.4 cm	2/20 (10%) had rAAA postoperatively. 1 died		8 days	33% recurrence		10% (30 d)
			Three: 12pts	AAA and CRC treated simultaneously. AAA average size 6.4 cm	0%		15 days	17% recurrence		14% (30 d)
			Four: 7pts	AAA treated first. AAA average size 6 cm	0%		122 days	9% recurrence		8% (30 d)
Porcellini et al. [27]	Different types (urinary tract, GI, and lung)	25	One: 11	EVAR performed first. AAA average size 5.9 cm		6.5 days (average)			2/11 graft occlusion—0/11 infection	0% (periop)
			Two: 7	Open surgery performed first. AAA average size 6.8 cm	0	34 days		3 died of mets (11, 15, and 39 mo)	1/14 graft infection	3/14 died after AAA repair
			Three: 6	One-stage operation	0	0		1 died of mets (15 mo)		0%
			Four: 1	Cancer first	1	82 d		alive (55 mo)	0	0%
Herald et al. [28]	CRC	7	Open: 5	AAA and CRC treated simultaneously. AAA average size?	0		NS	NS	0%	
			EVAR: 1	AAA and CRC treated simultaneously. AAA average size NS	0	0	NS	Alive (12 months)	0%	
			EVAR: 1	AAA before the CRC. AAA average size NS	0	14	NS	Alive (6 months)	0%	

Table 3: Continued.

Reference (first author)	Type of cancer	No. of cases	Group	Approach	AAA rupture rate (period)	Interval between AA repair and cancer treatment	Delay in cancer treatment	Cancer outcome	Graft complication rate	% mortality rate (mode)
Chai et al. [29]	CRC	2		EVAR followed by CRC resection	0	7	NS	Alive (12 months)	100% (graft occlusion). Case report type	
Sheen et al. [30]	Pancreas	1		EVAR followed by pancreatectomy	0	9	NS	Alive (1 month)	0%	
Hafez et al. [31]	Renal	27	11	One stage	0	0		80% survival	0 (57months)	
			13	AAA first	0	?		35% survival	0 (57months)	
			3	Renal malignancy first	0	?		80% survival	0 (57months)	
				different grouping						
Matsumoto et al. [10, 32]	Gastric and colorectal cancer	25 (out of 186 AAA repairs) - high risk pts only included	Group 1: 14	One-stage operation	0		NA	2 died of renal failure (10 mo) or mets (2yrs)	NA	0 (Periop)
			Group 2: 11	Two-stage operation	0		NA	1 died of Mi (3 mo)	NA	0 (Periop)
Lin et al. [33]	CRC	108	Group 1: 46	CRC treated first. AAA second: group A: 35 open/group B: 11 EVAR		A: 42 d/B: 35			2/11 (Group B) had sigmoid ischaemia	
			Group 2: 38	AAA first: Group C: 26 open/ Group D: 12 EVAR			C: 115/ D: 12	Significant periop morbidity/mortality in Group C		
			Group 3: 8	Combined						

Table 3: Continued.

Reference (first author)	Type of cancer	No. of cases	Group	Approach	AAA rupture rate (period)	Interval between AA repair and cancer treatment	Delay in cancer treatment	Cancer outcome	Graft complication rate	% mortality rate (mode)
Suffat et al. [34]	All (mostly CRC)	7 (127 AAAs)	Group 1: 3	One stage					0%	
			Group 2: 1	Two stage (?)					0%	
			Group 3: 3	EVAR			Few days		0%	
Komori et al. [35]	gastric	6 (222 AAAs)	Group 1: 3	CRC first (advanced cancer)				71% alive at 4 yrs		
			Grorp 2: 1	AAA first (>6 cm)						
			Group 3: 2	One stage						
Shalhoub et al. [36]	CRC	13	Group 1: 10	CRC first; Open AAA (3) or EVAR (7) second	0				0	
			Group 2: 2	AAA first (diameter 7&8 cm)	0				0	
			Group 3: 1		0				0	
Oshodi et al. [8]	All	56 (676)		One-stage open surgery	3 deaths/ 7 early reoperation	0			0	0 (Periop)
Galt et al. [37]	renal	10		One stage	0	0	NS	1 died from mets	0	
Veraldi et al. [38]	CRC	14	Group 1: 9	One stage	0	0		NA	0 (up to 5yrs)	0 (Periop)
			Group 2: 7	Two stage	0	31 d		NA		

* AAA: abdominal aortic aneurysm. CRC: colorectal cancer. GI: Gastrointestinal. NS: not specified. NA: not applicable/not provided. EVAR: endovascular aneurysm repair.

second major abdominal operation, avoiding the potential risk of ruptured aneurysm following the cancer resection stage, avoiding the potential delay in cancer treatment if the aortic aneurysm was addressed first, and avoiding the potential difficulty in dealing with adhesions resulting from an earlier laparotomy [31–33]. Most studies have not shown any significant increase in the risk of graft infection following a one-staged operation (see Table 3, [8, 13, 27, 28, 30, 31, 33–37, 45]). Nevertheless, few reports have documented a possible correlation between graft infection and simultaneous open abdominal surgery [27, 46, 47]. The cumulative morbidity and mortality were significantly higher in one-staged operations when compared to two-staged operations in some reports (Lin et al. [33]), and the one-staged option as a primary approach was unfavorable by some authors accordingly (Lin et al. [33] and Hafez et al. [31]). Combined operation in cases where both lesions pose a life-threatening condition (e.g. large aneurysm with advanced obstructing malignancy) is supported by most authors, providing a very high attention to details in place (thoughtful antibiotic coverage and possible irrigation of operative field with antibiotics [32], usage of antibiotic-bound grafts [23], good-risk patient selection, verified good colonic blood supply to avoid necrosis, possible use of omental wrap around the vascular graft [11, 32, 45], possible spray of fibrin glue around anastomosis [32], using extra-anatomic bypass instead of a grafted aorta [32], etc.) (Baxter et al. [11], Lin et al. [33], Robinson et al. [23], Suffat et al. [34], and Shalhoub et al. [36]). Some authors, however, remain in favor of a combined operation as a primary management approach to synchronous lesions [8, 13, 31, 32, 34], especially for fairly clean operations such as gastric [13, 34] or urological cancers [31, 37].

Staged operation (repair of aortic aneurysm first or resection of malignancy first) has the theoretical advantage of avoiding major longer operation and avoiding the risk of cross-contamination and consequent devastating graft infection. Nevertheless, many reports have shown a significant time delay before the second operation (especially when malignancy is treated first) [8, 11, 33, 35, 38, 48], a high incidence of catastrophic sequelae (ruptured aortic aneurysm in the case of treating the malignancy first) [11, 23, 27, 33], or a significant decrease in the long-term survival, especially when one pathology was treated eventually [31, 38, 45]. Despite these unfavourable 'side effects' of staged operations, this option (malignancy-first or aorta-first approach) remains the preference for some authors [6, 35, 36]. Few questions such as the impact of aneurysm repair in staged procedure on the timing of adjuvant therapy and the effect of radiotherapy on the EVAR stent need further well-controlled studies in the future.

Endovascular aortic repair (EVAR) in the treatment of concomitant malignancy has attracted much attention more recently [27, 31, 33, 34, 36, 38]. As EVAR does not involve a laparotomy, patients recover quickly and in most cases would be able to undergo the cancer surgery within a couple of weeks if required. Drury and colleagues [49] performed a systematic review and meta-analysis of randomized controlled trials on EVAR and showed a persistent reduction in 30-day mortality (1.6 versus 4.7%) and lower incidence of major complications (including cardiac, respiratory, and renal) after EVAR procedures when compared to open procedures [49]. In line with these results, most authors dealing with synchronous AAA and malignancy have found a persistent decrease of the interval period between repairing the aortic aneurysm using EVAR and performing the malignancy operation in the two-staged approach [27, 33, 36], a persistent reduction in operative morbidity and mortality [27, 33] that was sustained up to 3-4 years of followup [27, 33], and a significant reduction in length of hospital stay (unless endoleak has to be ruled out [36, 38]), and in the intraoperative blood loss [27, 33, 36, 50]. Colonic ischaemia is rare after an EVAR procedure. However, recent prior colonic surgery may predispose patients to such a complication as reported in 2 patients who had right hemicolectomy (with confirmed patent IMA) followed by a staged EVAR (18% incidence rate) in one report [33]. Lin and colleagues recommended using additional preoperative imaging to confirm the presence of SMA/IMA collateral flow before embarking on such staged operations [33, 38]. Endovascular aneurysm repair, where possible, followed by malignancy operation has become the initial preferred treatment choice in some centers [31, 33, 34, 38]. The risk of vascular graft infection is also likely to be less with an EVAR procedure, as there is no risk of direct contamination during the resection of abdominal malignancy.

Patients with advanced/end-stage malignancy and large aortic aneurysm require sound ethical consideration and balanced clinical judgment [6, 8, 35, 45]. A good understanding of the expected outcome in each specific cancer type, as well as the presence of other comorbidities (age, physiologic well-being, etc.) is essential for a proper decision making within a multidisciplinary team approach. Aneurysm repair would be considered inappropriate if curative resection is not feasible, even if the EVAR procedure can be carried out with minimum morbidity. The EVAR II trial is particularly helpful in this context. Patients who were deemed unfit for open aortic aneurysm repair were randomly allocated to best medical therapy alone or EVAR and best medical therapy. The trial was weakened by a significant number of patients that crossed over to undergo aneurysm repair. Nevertheless, the trial showed that patients with significant comorbidity do not show any survival benefits with AAA repair [51]. These data can be relevant to cancer patients with poor prognosis who are, on a similar basis, unlikely to benefit from AAA repair.

The need for adjuvant therapy for cancer treatment is another factor to consider when planning for a staged or simultaneous operation [36]. Lauro et al. have raised concerns regarding chemotherapy treatment (associated with aggressive hydration and corticosteroids) in patients known to have AAA > 6 cm. Such treatment may result in enlargement of major arteries and may increase the risk of rupture [42]. There are no documented reports of chemotherapy-related aneurysm rupture so far. Chemotherapy administered to patients before or after EVAR had no consequences in some reports [36]. Data on the risk of aneurysm rupture due to chemotherapy is limited and should not be an

important consideration in management decision. It would be entirely reasonable to await the response of chemotherapy and get a better estimate of prognosis before undertaking the repair of aneurysm.

The extent of nodal dissection has significant effect on the overall cancer prognosis, including the need for adjuvant therapy. No technical difficulties or specific limitation have been reported in this respect, including performing a D2 lymphadenectomy in gastric cancer [13] or total mesorectal excision and full node dissection in rectal cancer [38]. However, a one-staged operation appears to be correlated with more D2 dissection and less total gastrectomy rate when compared to staged operations in some series [45]. The effect of paraaortic tissue dissection during open aortic aneurysm repair on the cancer staging or outcome (in terms of cancer dissemination or effect on chemoradiotherapy) or the effect of finding metastatic malignancy following the first stage of treatment (malignancy-first approach) on the cost-effectiveness of aortic-repair stage [36] remains to be investigated further.

Treatment priorities and patients' best interest should be considered when one of the two lesions is found incidentally intraoperatively [38]. Treating the most immediate life-threatening condition and a two-staged operation might be a sensible option in such circumstances. It should be possible to diagnose aneurysms on CT in most patients preoperatively but malignancy may be occasionally overlooked on the preoperative CT scan for aneurysms. The increasing use of EVAR techniques means that most of these lesions will be detected on preoperative or postoperative surveillance scans and can be treated in the stages.

The management decision for concomitant malignancy and aortic aneurysm needs to be made for each individual case based upon the best estimates of risks of aneurysm rupture, operative risks, prognosis of malignancy, and patient preference. There are multiple variables and it will be difficult to obtain high-level evidence for these patients. It is therefore essential to discuss such cases in a multidisciplinary setting to achieve a consensus opinion before gaining approval from the patient on one option or another.

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Review Article

Saddle Pulmonary Embolism in a Cancer Patient with Thrombocytopenia: A Treatment Dilemma

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The association between cancer and venous thromboembolism (VTE) is well established. Saddle pulmonary embolism is not uncommon in hospitalized cancer patients and confers a higher mortality. We report a case of saddle pulmonary embolism in a cancer patient with thrombocytopenia, discuss the bleeding risks, complexity of managing such patients and review current guidelines.

1. Introduction

Pulmonary embolism (PE) is common in hospitalized patients. Overall mortality for major pulmonary embolism is 22% and as high as 65% in those who require cardiopulmonary resuscitation [1]. Saddle pulmonary embolism in cancer patients carries a very poor prognosis, with mortality of >80% at one year [2]. A number of patients with cancer and pulmonary embolism have concomitant thrombocytopenia, posing a great therapeutic challenge.

We report a case of saddle pulmonary embolism in a cancer patient with thrombocytopenia and discuss the bleeding risks, complexity of managing such patients and review current guidelines.

2. Case Report

A 73-year-old female with history of hepatocellular carcinoma due to long-standing hepatitis C, presented to the emergency center with a sudden syncopal episode at home. Her past medical history was significant for portal hypertension, and variceal bleeding requiring blood transfusions. She was receiving sorafenib, which required dose reduction due to thrombocytopenia. Her platelets fluctuated between 46,000–113×10^9 during the treatment.

On examination she was stable with a blood pressure of 128/72 mmHg; heart rate of 80 beats per minute; respiratory rate of 22/minute; temperature 36.7°C; and O_2 saturation of 96% on 2-3 liters oxygen via nasal cannula. Heart sounds were normal with no signs of heart failure.

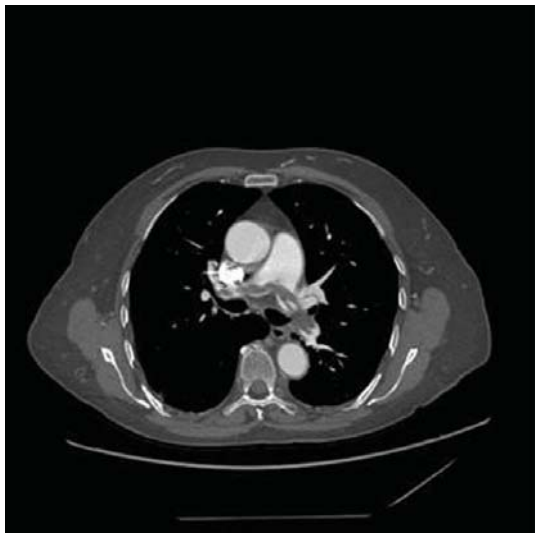

Figure 1: CT scan showing a saddle pulmonary embolus, extending into the right and left pulmonary arteries.

Relevant investigations included a 12 lead electrocardiogram (ECG), which showed sinus rhythm with left axis deviation, and no evidence of ischemia.

Serum troponin was marginally elevated at 0.12 ng/mL (Normal values: 0.00–0.03 ng/mL). Computerized (CT) scan of the lungs showed saddle PE with extension into the lobular braches (Figure 1). Chest X-ray was normal and venous Doppler study of the legs showed a partially attached right femoral thrombus. Platelet count was 60×10^9/L (Normal values: $>150{,}000 \times 10^9$/L) and D-dimer was >20.00 mcg/mL (Normal values: 0.00–0.4 mcg/mL). Hemoglobin, international normalized ratio (INR), activated partial thromboplastin time (aPTT), renal and liver function tests were within normal limits. Echocardiogram showed normal left and right ventricular (RV) systolic function with no pericardial effusion. Right ventricular systolic pressure was 29 mmHg.

She was treated with LMWH (Enoxaparin in a dose of 1 mg/kg subcutaneously twice daily) and inferior vena cava (IVC) filter was placed to prevent migration of the lower extremity thrombus. In view of her thrombocytopenia, hemodynamic stability and no evidence of RV dysfunction, she was not given thrombolytics. The patient's hemoglobin and platelets remained stable throughout the hospitalization and she was discharged home on LMWH.

3. Discussion

Venous thromboembolism (VTE) is common in cancer patients; with significant in hospital mortality [1, 3]. In a large retrospective cohort study of hospitalized cancer patients, overall incidence of VTE was 4.1% [4]. Cancer patients with VTE have higher in-hospital mortality compared to those who did not have VTE (16.3% versus 6.3%; $P < .001$) [4]. In patients with PE, comorbidities like older age (>70 years), congestive heart failure, RV dysfunction and cancer increase the likelihood of mortality by at least 2-3-fold [3].

Cancer induces a prothrombotic state [5, 6]. Malignant neoplasm alone is associated with a 4-fold increased risk of VTE without chemotherapy, and cytotoxic immunosuppressive therapy increases the risk to more than 6-fold [7]. The most common chemotherapy agents associated with VTE are: thalidomide, lenalidomide with or without dexamethasone, L-asparginase, bevacizumab, tamoxifen, estramustine, capecitabine, erlotinib, sunitinib, vinorelbine, trastuzumab, paclitaxel-albumin-bound, letrozole, and bortezomib [8]. In addition to chemotherapy agents, central venous catheters (CVC) also act as predisposing factors. The incidence of venographic CVC-related DVT in cancer patients varies from 27% to 66% [9]. Risk of VTE also increases significantly in patients undergoing major surgical procedures for cancer [10].

Saddle pulmonary embolism in cancer patients carries a very poor prognosis, with mortality of >80% at one year [2]. The treatment of saddle pulmonary embolism, particularly in the setting of concomitant thrombocytopenia, remains unclear and creates a great therapeutic challenge. The issue of treating thrombotic disease in cancer patients with thrombocytopenia secondary to myelosuppressive therapy has not been studied in large randomized clinical trials and therapy in these cases should be individualized based on risk benefit ratio.

3.1. Examining Guidelines for Treatment of PE. Treatment of saddle PE includes anticoagulants, thrombolytics and catheter based or surgical embolectomy [2]. In the absence of any large scale data, treatment should be individualized according to clinical status, evidence of RV dysfunction, cancer staging and risk of bleeding. Anticoagulants (heparin and warfarin) remain an integral part of all treatment plans.

3.2. Anticoagulants. National and international guidelines recommend LMWH as the first-line agent and Vitamin K antagonist (VKA) warfarin as a second line agent for the initial and long-term treatment of VTE in cancer patients [11–15] (Table 1). These recommendations are based on 4 clinical trials of VTE in cancer patients, comparing LMWH with warfarin from 3–6 months duration. Data beyond 6 months treatment with either LMWH or warfarin do not exist.

In a study of 146 cancer patients with VTE, in which enoxaparin 1.5 mg/kg was compared to warfarin (INR goal of 2-3), there were no significant differences at 3 months between the two treatment groups based on combined outcomes of recurrent VTE or major bleeding episodes (warfarin 21.1%; (95% confidence interval (CI), 12.3%–32.4%) versus enoxaparin 10.5%; (95% CI, 4.3%–20.3%); ($P = .09$)). This study enrolled only 47% cancer patient with DVT and PE without hemodynamic instability [16].

In another randomized trial of 676 cancer patients with VTE in which dalteparin in a dose adjusted protocol (200 IU/Kg daily for the first month and then 150 IU/Kg daily for the next 5 months) was compared to warfarin, there was

Table 1: Summary of guidelines for treatment of VTE in cancer [11–15].

Condition	ASCO	NCCN	AIOM/ESMO	ACCP
Initial treatment (acute phase)	- 5–10 days = LMWH preferred	- LMWH, UFH (IV), FXa-I according to clinical situation	- LMWH, UFH (IV) For CrCl less than 25–30 mL/min, either LMWH, UFH with antiXa monitoring	- LMWH or VKA for minimum of 90 days
Long-term treatment (chronic phase)	- LMWH for 180 days - If LMWH not available then VKA - indefinite in active disease	- LMWH preferred - Indefinite in patients with active and persistent RF - DVT for 3–6 months - PE for 6–12 months	- LMWH for 90–180 days - Long-term for patients with active cancer	- LMWH or VKA for as long as cancer active
Thrombolytic for initial treatment	Only in limb-threatening thrombosis	Massive DVT or PE with hemodynamic instability	NA	NA
IVCF	- Presence of CI - Recurrent VTE despite AC	- Presence of CI - New PE that might be life-threatening of PHTN	- Presence of CI - Recurrent PE despite treatment	- In patients with acute PE, if anticoagulant is not possible due to high-risk of bleeding - As soon as risk of bleeding is minimal, AC should be started

VTE: venous thromboembolism; ASCO: American Society of Clinical Oncology; NCCN: National Comprehensive Cancer Network; AIOM: Italian Association of Medical Oncology; ESMO: European Society of Medical Oncology; ACCP: American College of Chest Physician; LMWH: low-molecular-weight-heparin; UFH: unfractionated heparin; FXa-I: factor- Xa inhibitor; VKA: vitamin K antagonist; RF: risk factors; DVT: deep-vein thrombosis; PE: pulmonary embolism; IVCF: inferior vena-caval filter; CI: contraindication; PHTN: pulmonary hypertension; AC: anticoagulation; IV: intravenous; NA: not addressed. CrCl: creatinine clearance.

a significant decrease in the cumulative risk of recurrent VTE in patients receiving dalteparin compared to warfarin (8.3% versus 15.8%; hazard ratio, 0.48; $P = .002$). PE with or without DVT comprised only 30% of total enrolled patients [17].

In another trial of 91 cancer patients with VTE, in which 3 different regimens were compared: (1) enoxaparin 1.0 mg/Kg twice daily for 5 days followed by once daily 1.0 mg/Kg for 175 days; (2) enoxaparin 1.0 mg/Kg twice daily for 5 days then enoxaparin 1.5 mg/Kg once daily for 175 days; (3) enoxaparin 1.0 mg/Kg twice daily with warfarin for minimum of 5 days with an INR goal of 2-3; there were no significant differences between enoxaparin and warfarin in safety profile and recurrent VTE. In this study 45% of cancer patient with VTE had PE [18].

In a recent study of 200 cancer patients with VTE, in which tinzaparin in a dose of 175 International Factor Xa Inhibitory Units/Kg was compared to warfarin for an INR goal of 2-3, there was a significant decrease in cumulative risk of recurrent VTE at 10 months in patients assigned to tinzaparin ($P = .044$) [19]. In this trial, only 21% of patient had PE [19]. A recent meta-analysis showed superiority of LMWH over VKA in lowering rates of recurrent VTE in cancer patients [20]. Low-molecular-weight heparins (LMWHs) have become anticoagulants of choice due to their predictable pharmacokinetic and pharmacodynamic profiles. These agents are not therapeutically interchangeable due to their different molecular weight, half-life, and antiXa to IIa ratio [21]. LMWHs are considered intermediate acting anticoagulants with predictable kinetics. Specific pharmacokinetics of different anticoagulants, platelet monitoring, and recommendation for reversal in cases of bleeding are reviewed in Table 2. Monitoring of antiXa is recommended in obese patients, underweight patients, and patients with renal insufficiency, due to accumulation of LMWHs [22–27].

Warfarin is considered an alternative agent to LMWH. Due to major drug interactions between warfarin and chemotherapy, nutritional deficiency, and use of nonchemotherapy agents in cancer patients, frequent dose monitoring and modifications for warfarin is needed.

The difficulty in maintaining the narrow therapeutic index of warfarin also was shown in a major cancer trial where a therapeutic range INR (2-3) was achieved in only 46% of the patients [17]. Risk of VTE recurrence increases with subtherapeutic INR [30].

Direct factor-Xa inhibitor, fondaparinux, can also be considered for the initial (acute phase) treatment of PE. Fondaparinux was studied in a randomized clinical trial that showed noninferiority to unfractionated heparin in the acute treatment of PE; however, only 20% of patients enrolled in each arm had cancer. The incidence of VTE recurrence was 3.8% in the fondaparinux group and 5.0% in the unfractionated-heparin group, for an absolute difference in favor of fondaparinux of 1.2% (95% confidence interval, −3.0 to 0.5). The reported incidence of major bleeding was 2% in the fondaparinux group and 2.4% in the unfractionated heparin [33]. Due to lack of extended treatment trials, the role of fondaparinux for long-term treatment of VTE in cancer patients in unknown [13–15, 28].

Recently fixed-dose subcutaneous weight-adjusted unfractionated heparin (UFH) has also been recommended for the acute treatment of VTE [15]. The strength of this recommendation is weak and is based only on 2 studies,

Table 2: Pharmacokinetics of different anticoagulants [22–29].

Anticoagulant	Molecular weight	$T^{1/2}$ (h)	Elimination route	Antidote	Platelet monitoring	AntiXa monitoring
Enoxaparin (lovenox)	3,500–5,500	4.5–7	Renal		- Thrombocytopenia of any degree should be monitored closely - Discontinue for platelet count falls below 100,000/mm^3	- 1 mg/kg Q12 = 0.6–1.1 IU/mL - 1.5 mg/kg daily = 1.0–1.5 IU/mL
Dalteparin (fragmin)	5,600–6,400	3–5	Renal	Protamine sulfate 1 mg per 100 U of heparin or less than 100 mg over 2 hours to lower risk of reaction. Protamine partially reverses the effect of LMWH	- For platelet counts between 50,000 and 100,000/mm^3, reduce dose of dalteparin by 2,500 IU until the platelet count recovers to $\geq$100,000/mm^3 - Discontinue for platelet counts <50,000/mm^3	- 100 IU/kg Q12 = 0.4–1.1 IU/mL - 200 IU/kg daily = 1.0-2.0 IU/mL
Tinzaparin (innohep)	5,600–7,500	3-4	Renal		- Thrombocytopenia of any degree should be monitored - Discontinue for platelet count below 100,000/mm^3	175 IU/kg = 0.85–1.0 IU/mL
Unfractionated heparin	5,000–30,000	1-2	Renal/endothelial	Protamine sulfate 1 mg per 100 U of heparin or less than 100 mg over 2 hours to lower risk of reaction.	- Thrombocytopenia of any degree should be monitored - Discontinue for platelet count below 100,000/mm^3 or if recurrent thrombosis develops (sign and symptoms of HIT)	aPTT monitoring
Fondaparinux (arixtra)	<2,500	17–21	Renal	Recombinant factor VIIa 90 mcg/kg	- Thrombocytopenia of any degree should be monitored - Discontinue for platelet count falls below 100,000/mm^3	- 2.5 mg = peak at steady state 0.39–0.5 mg/L; trough at steady state 0.14–0.19 mg/L - 5 mg, 7.5 mg, 10 mg = peak at steady state 1.20–1.26 mg/L; trough at steady state 0.46–0.62 mg/L

IV: intravenous; SC: subcutaneous; U: unit; UFH: unfractionated heparin; LMWH: low-molecular-weight heparin; $T^{1/2}$: half-life elimination; HIT: heparin-induced thrombocytopenia; aPTT: activated partial thromboplastin time.

each including only 22% patients with cancer with less than 20% patients with PE. Patients with hemodynamic compromise were excluded from these trials; therefore, PE patients with cardiovascular compromise should not receive UFH subcutaneously [15].

Recommended treatment duration of VTE in cancer patients is 6–12 months and indefinite in cases of metastatic or active cancer [11–15].

3.3. Thrombolytics. In the absence of contraindications, systemic thrombolytics should be considered in patients with massive PE and hemodynamic instability [11, 15]. The recommended dose of r-tPA is 100 mg intravenously over 2 hours via peripheral vein [15].

However, cancer patients have been excluded from thrombolytic trials; hence evidence-based guidelines for the use of thrombolytics in this subset of population is lacking.

Except for a case report where streptokinase was used for the treatment of PE associated with heparin-induced thrombocytopenia [35], no other data exists on the use of thrombolytics in patients with PE and thrombocytopenia. Clinical judgment should be used and therapy individualized in each case.

3.4. Thrombectomy. Catheter and surgical thrombectomy are an option in selected patients. In a pregnant patient with PE and thromobcytopenia (due to myelodyplastic syndrome), successful emergency pulmonary embolectomy has been reported [36]. However, large-scale data in cancer patients is lacking [15].

3.5. IVC filter. Placement of IVC filter is recommended in patients with contraindication to anticoagulation, failure of

Table 3: Multivariate analysis of the risk of developing fatal and major bleeding in cancer patients with venous thromboembolism (VTE) [31, 32].

	Fatal bleeding			Major bleeding	
Variables	Odds ratio (95% CI)	*P*-value	Variables	Odds ratio (95% CI)	*P*-value
Body weight <60 kg	2.5 (1.1–5.3)	.021	Recent major bleeding	2.4 (1.1–5.1)	.003
Recent major bleeding	3.0 (0.96–9.1)	.058	CrCl < 30 ml/min	2.2 (1.5–3.4)	<.001
Serum creatinine >1.2 mg/dL	2.8 (1.3–5.8)	.008	Immobility for ≥4 days	1.8 (1.2–2.7)	.005
Immobility for ≥4 days	4.1 (1.9–8.7)	.001	Metastatic cancer	1.6 (1.1–2.3)	.03
Metastatic cancer	3.1 (1.4–7.1)	.006			

Confidence interval: CI; creatinine clearance: CrCl.

Table 4: Multivariate analysis for major bleeding and bleeding risk index classification [34].

Risk factors	Odds ratio (95%CI)	*P*	Points
Recent major bleed	2.7 (1.6–4.6)	<.001	2
Serum creatinine >1.2 mg/dL	2.1 (1.7–2.8)	<.001	1.5
Anemia	2.1 (1.7–2.7)	<.001	1.5
Cancer	1.7 (1.4–2.2)	<.001	1
Clinically overt pulmonary embolism	1.7 (1.4–2.2)	<.001	1
Age >75 y	1.7 (1.3–2.1)	<.001	1
0 point: low risk 0.1% (95% CI: 0.0–0.2)	1–4 points: intermediate risk 2.8% (95% CI: 2.4–3.3)	>4 points: high risk7.3 % (95% CI: 4.0–9.1)	

anticoagulation, massive pulmonary embolism, severe cardiopulmonary disease with deep vein thrombosis, and free floating iliofemoral or inferior vena cava thrombus [11–15, 37].

To date, there are no randomized clinical trials available in the cancer literature to assess the long-term safety and efficacy of filters. IVC filters carry short-term and long-term complications such as hematoma; misplacement, migration, thrombosis, recurrent PE, filter fracture, IVC occlusion and vena caval syndrome [38]. The insertion of an IVC filter does not obviate the need for long-term anticoagulation [15].

3.6. Assessing and Addressing Bleeding Risks. Prior to initiation of anticoagulation risk of bleeding should be assessed. Reported bleedings (major and minor combined) in cancer trials associated with VKA and LMWH are 3%–16% and 6%–11%, respectively [8, 23]. The Prospective registry, Registro Informatizado de La Enfermedad Thromboembólicà (RIETE), showed that patients with VTE and evidence of recent major bleed (<30 days prior to diagnosis of VTE) had significantly higher rates of fatal bleeding (4.1% versus 0.6%; $P < .001$) and mortality (9.5% versus 7.7%; $P < .005$) compared to those without [39]. Multivariate analyses of RIETE showed that patients with a body weight of less than 60 kilograms, serum creatinine of >1.2 mg/dL, recent major bleeding, immobility for >4 days, clinically overt PE, and metastatic cancer had higher odds of developing fatal or major bleeding (Table 3) [31, 32] When RIETE investigators cross-validated the predictive model into a validated group, after determination of point scores, the incidence of major bleeding was 0.1% (95% CI: 0.0–0.2) in low-risk patients; 2.8% (95% CI: 2.4–3.3) in those at intermediate risk, and 6.2% (95% CI: 4.0–9.1) in high-risk patients. The incidence of major bleeding in the three groups was statistically different ($P < .001$) (Table 4) [34]. These prospective data have not measured the effect of thrombocytopenia into the bleeding risk scores. Advanced age, renal insufficiency, metastatic cancer, anemia, immobility, recent major bleeding, and clinically overt PE should prompt healthcare providers to closely monitor these patients for bleeding complications while receiving anticoagulation.

Transient thrombocytopenia due to myelosuppressive chemotherapy needs to be taken into consideration prior to initiation of anticoagulation as bleeding risks double from 10% at a platelet count of 20,000/mm^3 to 20% when the platelet count drops to below 10,000/mm^3 in solid tumor patients [40]. The timing and kinetics of platelet nadir is dependent on the mode of action, dose, and addition of multiple cytotoxic agents. Cytotoxic agents such as ifosfamide, carboplatin, etoposide, mesna, doxorubicin, and dacarbazine are associated with an early nadir. Delayed nadir can be seen in regimens containing nitrosoureas and melphalan. Novel agents such as lenalidomide and bortezomib can contribute to thrombocytopenia when added to other cytotoxic agents [40]. Enrolling cancer patients in VTE trials has been limited due to strict inclusion criteria; mainly to prevent bleeding complications. Cancer trials for VTE have excluded patients with platelet count as low as 30,000/mm^3 to as high as 150,000/mm^3 [16–19]. National Comprehensive Cancer Network (NCCN) considers platelet counts of less than 50,000/mm^3 as a contraindication to prophylactic or therapeutic anticoagulation therapy [14]. American Society of Clinical Oncology (ASCO) recommends using therapeutic

anticoagulation in cancer patients with preexisting thrombocytopenia with caution; therefore, close monitoring of platelets and hemoglobin is required in cancer patients [13]. Choosing an anticoagulant should be based upon the half-life, reversibility, tolerability, patient's preference, and cost [13]. Pharmacokinetic, pharmacodynamic, and monitoring parameters specific to each anticoagulants are discussed in Table 2. Briefly, unfractionated heparin provides a short half-life with complete reversibility by protamine sulfate; therefore, it is considered ideal agent for patients that may require rapid surgical interventions such as thrombectomy. LMWHs are considered intermediate to long-acting agents. Partial reversal of LMWHs in bleeding can be achieved by use of protamine sulfate. The half-life of fondaparinux is longer than LMWHs and partial reversibility can be achieved by administration of Recombinant factor VIIa (rVIIa) in bleeding episodes [15, 23]. Vitamin K can be administered for reversal of bleeding associated with VKA. Fresh frozen plasma and cryoprecipitate can be administered in cases of life-threatening bleeding associated with anticoagulants [15]. In patients taking warfarin, Food and Drug Administration (FDA) has made recommendations regarding the potential benefits of genotype testing, to help reduce the bleeding risks in individual patients.

Risk of intracranial hemorrhage with thrombolytics in PE is about 3% [3]. In a study of 104 patients with acute PE who received fibrinolytic therapy, 19% of patients experienced major bleeding. In this study, cancer, diabetes, and an elevated INR before initiation of fibrinolytic therapy were found to be an independent predictors of major bleeding [41].

The exact risk of bleeding in thrombocytopenic patients with PE is unknown. Platelet count less than 150,000/mm^3 has been a predictor of short-term composite event such as mortality [42]. In clinical practice, platelet count of less than $50{,}000 \times 10^9$ is a contraindication to thrombolytic therapy [43].

No recommendations can be made regarding the use of thrombolytics in patients with thrombocytopenia and acute PE, until large-scale data is available. Use of thrombolytic agents in cancer patients requires close attention to bleeding risks and overall prognosis.

4. Conclusion

There are several published guidelines for the treatment of VTE in cancer patients.

However, data on the management of saddle PE and particularly in patients with thrombocytopenia is lacking. Large-scale prospectively collected data and future studies are needed to address the best possible treatment option in these patients.

Conflict of Interests

The authors do not report any conflict of interests regarding this work.

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Case Report

Spontaneous Hemopericardium Leading to Cardiac Tamponade in a Patient with Essential Thrombocythemia

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Acute cardiac tamponade requires urgent diagnosis and treatment. Spontaneous hemopericardium leading to cardiac tamponade as an initial manifestation of essential thrombocythemia (ET) has never been reported in the literature. We report a case of a 72-year-old Caucasian female who presented with spontaneous hemopericardium and tamponade requiring emergent pericardiocentesis. The patient was subsequently diagnosed to have ET. ET is characterized by elevated platelet counts that can lead to thrombosis but paradoxically it can also lead to a bleeding diathesis. Physicians should be aware of this complication so that timely life-saving measures can be taken if this complication arises.

1. Introduction

Pericardial diseases principally manifest as pericarditis or pericardial effusion. Pericardial effusions resulting in cardiac tamponade can occur from a number of causes, including pericarditis, malignancy, acute myocardial infarction, end-stage renal disease, congestive heart failure, collagen vascular disease, and viral and bacterial infections. Hemopericardium and resulting tamponade can result from any form of chest trauma, free wall rupture following myocardial infarction, retrograde bleeding into the pericardial sac following aortic root (type A aortic) dissection, as a complication of any invasive cardiac procedure, anticoagulation, and acute leukemias. In this paper, we describe a case of cardiac tamponade resulting from hemopericardium as an initial manifestation of essential thrombocythemia (ET).

2. Case Presentation

A 72-year-old Caucasian female presented to her primary care physician for ear pain. She was prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) for her pain. A week later, she presented to the emergency department (ED) with episodes of chest pressure, worsening shortness of breath, and orthopnea. The patient had no known chronic medical illnesses in the past and was not on any other prescription medications. She had a 50-pack year history of smoking.

On physical examination, her heart rate was 115 beats/minute and blood pressure was 123/44 mm of Hg. Other vital signs were within normal limits. She had jugular venous distension on neck examination. Cardiovascular examination revealed tachycardia and positive pulsus paradoxus. Chest examination was unremarkable.

Laboratory data showed normal electrolytes and renal functions. Her white count was elevated at 12,900 cells/microliter, hemoglobin was marginally low at 11.2 g/dl, and platelet count was elevated at 745,000 cells/microliter. Cell differential was within normal limits. Cardiac biomarkers were within normal limits. TSH level was 3.57 mIU/L. Electrocardiogram (ECG) showed normal sinus rhythm and left atrial enlargement. There were no electrical alternans or changes of pericarditis on the ECG.

Chest X-ray showed cardiomegaly and small left sided pleural effusion. Computed tomography (CT) scan of the chest in the ED showed a moderate-sized pericardial effusion and a small left pleural effusion. Cardiology consultation was obtained due to the presence of pericardial effusion.

A transthoracic echocardiogram confirmed pericardial effusion with evidence of tamponade physiology (Figure 1). The patient was taken to cardiac catheterization laboratory and pericardiocentesis was done. A total of 300 mL of hemorrhagic fluid was drained during the initial procedure. Drainage of pericardial fluid resulted in immediate improvement of patient's symptoms. A pigtail catheter was left in place and the patient was transferred to coronary care unit. Over next two days, additional 310 mL of hemorrhagic fluid was drained and subsequently pigtail catheter was removed.

Pericardial fluid examination was unremarkable for any evidence of malignancy or infection. The etiology of hemorrhagic pericardial effusion was unclear even after extensive evaluation for malignancy, infection, autoimmune disease, or any other obvious systemic disease.

The patient continued to have elevated platelet count throughout the hospital stay with the highest platelet count being 855,000 cells/microliter. She denied any history of prior thrombotic or bleeding episodes. The elevation in platelet count was thought to be due to reactive thrombocytosis. The patient was discharged on fourth hospital day. She was instructed to followup with her primary care physician in two weeks with complete blood count to ensure resolution of thromobycytosis.

At followup, the patient continued to have elevated platelet counts. She was referred for hematology evaluation. A peripheral blood smear, bone marrow aspiration, and core biopsy were done for further evaluation of thrombocytosis. Peripheral blood smear showed occasional giant platelets with no platelet aggregates. There were no immature myeloid forms. Bone marrow aspirate showed prominent megaloblastoid change and increased number of megakaryocytes. Core biopsy also showed increased number of megakaryocytes. The megakaryocytes exhibited large hypersegmented nuclei with occasional megakaryocytic mitoses. Flow Cytometry was negative for any immunophenotypic abnormalities. Fluorescence in situ hybridization (FISH) for BCR-ABL translocation was negative arguing strongly against chronic myeloid leukemia. JAK 2 real-time PCR assay was negative for JAK2 V617 mutation. Thus, bone marrow biopsy showed megakaryocytic hyperplasia with dysmegakaryopoiesis consistent with ET.

3. Discussion

Pericardial effusions can be serous or hemorrhagic. The etiology of pericardial effusion is often influenced by the geographical region and patient-related factors. Hemorrhagic pericardial effusions often have different etiologies than serous effusions. In a retrospective study done by Atar et al., the most common cause of hemorrhagic effusions was found to be iatrogenic (31%) namely, secondary to invasive cardiac procedures followed by malignancies [1].

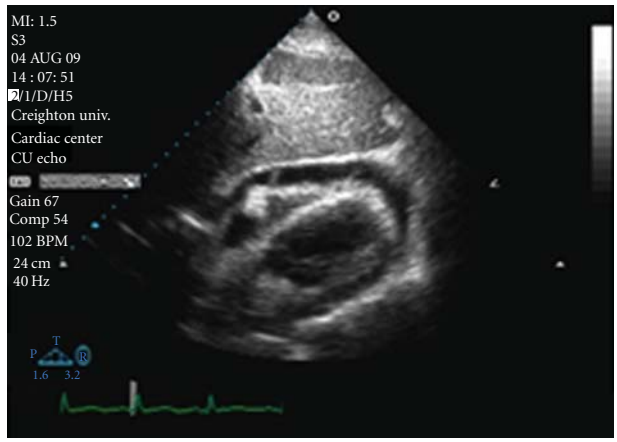

Figure 1: Subcostal view of hemorrhagic pericardial effusion. (There is a collapse of the right ventricular free wall during diastole.)

Bleeding diathesis leading to spontaneous hemopericardium secondary to congenital coagulation defect has been sparsely reported in the literature [2–4].

ET is currently classified among the *bcr/abl* negative, "Classic" myeloproliferative disorders (MPDs), which also include polycythemia vera (PV) and primary myelofibrosis (PMF) [5, 6]. Each of these MPDs represents a stem cell derived clonal myeloproliferation. ET is characterized by megakaryocyte expansion leading to increased platelets. ET is an uncommon disease with prevalence of 2-3 cases per million. Median age at diagnosis is usually between 65–75 years with female preponderance. The life expectancy of ET patients is generally long and similar to that of an age-matched normal population [7]. Many patients with ET are asymptomatic, but a large number of them manifest symptoms or signs of bleeding, usually as ecchymoses or mucosal hemorrhage, or microvascular thrombosis, usually as erythromelalgia, digital ischemia, or transient ischemic attack [8, 9]. The risk of thrombohemorrhagic complications remains unpredictable in individuals. The initial presentation in our patient was spontaneous hemopericardium that required emergency pericardiocentesis. Bleeding in ET is thought to be secondary to Acquired Von Willebrand disease (AVWD) and due to qualitative platelet defects. The main sites affected are skin, mucous membranes, and gastrointestinal tract. Severe bleeding is rare but fatal intracranial bleeding has been reported. AVWD in ET patients is characterized by the loss of large von Willebrand factor (VWF) multimers that results in a functional defect of the VWF, with increasing platelet counts (usually >1.5 million). Normalization of the platelet count results in normal plasma VWF multimeric distribution and regression of the hemorrhagic tendency [10]. Serious hemorrhages may be triggered by simultaneous antithrombotic therapy with anticoagulants, antiplatelet therapy, and NSAIDs. We believe that hemorrhagic conversion of pericardial effusion in our patient was triggered by NSAID therapy. However, we cannot exclude the possibility of viral syndrome resulting in pericarditis with subsequent conversion to hemorrhagic

pericardial effusion from bleeding complications related to ET. Kayrak et al. reported a similar case of a patient with essential thrombocythemia treated with acetylsalicylic acid, which resulted in hemorrhagic pericardial effusion [11]. The patient was successfully treated with clopidogrel therapy without any hemorrhagic or thrombotic event. Averback and Moinuddin describe a case of pericardial effusion secondary to essential thrombocythemia [12]. However, the patient had trilineage hyperplasia and authors describe autopsy features consistent with agnogenic myeloid metaplasia with predominant megakaryocytic proliferation. The diagnosis of ET on the basis of current WHO criteria is questionable in this case. Thus, we believe that our case is the first one of ET manifesting with spontaneous hemopericardium as the initial manifestation. Also, the diagnosis of ET in our patient was made based on WHO criteria [13]. In ET, bone marrow findings are remarkable for the presence of large, but mature-appearing, megakaryocytes with deeply lobulated and hyperlobulated nuclei that are most often dispersed throughout the biopsy sections [14]. Our patient did have morphological megakaryocyte abnormality consistent with diagnosis of ET.

Pericardial effusion related to ET should be treated based on current standards of care. Patients with cardiac tamponade require urgent pericardiocentesis. Bleeding complications may be prevented by avoiding use of high-dose aspirin and NSAIDs. In patients with bleeding complications related to ET and AVWD, treatment of thrombocytosis may be considered [15]. Patients with ET requiring antiplatelet therapy can be treated with clopidogrel therapy [11].

To summarize, spontaneous hemopericardium is infrequently encountered among patients with ET, and its clinical recognition may be difficult. Therefore, in patients with ET who manifest acute dyspnea or clinical signs of hemodynamic embarrassment, hemopericardium and tamponade should be ruled out. Pericardiocentesis is life saving in these patients since their clinical course is otherwise relatively benign.

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Case Report

Myocardial Infarction due to Endocarditis

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We present a case of a 43-year-old man who sustained a myocardial infarction due to infective endocarditis.

1. Introduction

Myocardial infarction (MI) is usually due to underlying atherosclerosis, but can also occur uncommonly due to embolic phenomenon associated with endocarditis.

2. Case Report

A 43-year-old male with a history of acute myeloid leukemia and multiple episodes of bacteremia presented to the hospital with syncope. A computerized tomographic (CT) scan of the head showed multiple cerebral infarcts. One week later he developed chest pain. On examination his blood pressure was 118/65 mm Hg with no signs of heart failure. A 12-lead electrocardiogram showed ST elevation in inferior leads, V5 and V6 (Figure 1). Laboratory tests showed an elevated Troponin I with a peak value of 6.9 ng/mL (normal value <0.4 ng/mL) and normal blood cultures. A diagnosis of ST elevation myocardial infarction (MI) was made, and the patient was treated with aspirin, beta-blockers, and nitrates. The diagnosis of MI due to endocarditis in our case was made on clinical grounds, and coronary angiogram was not done. Heparin was not given due to a history of severe thrombocytopenia. A transesophageal echocardiogram showed vegetations on mitral and aortic valves, mitral regurgitation, with normal left ventricular systolic function (Figure 2). CT scan showed multiple infarcts in lungs, spleen, and kidneys. He died one week later due to new cerebral infarcts. Postmortem examination was not carried out.

3. Discussion

Systemic and pulmonary embolization is the most common presentation of nonbacterial thrombotic endocarditis (NBTE) [1]. Stroke is the commonest embolic event, frequently affecting the middle cerebral artery territory [2]. MI is not uncommon in NBTE patients with an incidence of 7.5% [3]. The management of MI in patients with endocarditis is similar to general population, but the use of thrombolytics can lead to bleeding complications [4]. Although heparin is traditionally used in cases of NBTE to prevent recurrent thromboemboli, there are no large scale trials of anticoagulants in patients with MI associated with NBTE. There are only few case reports of MI due to endocarditis, and both inferior and anterior wall MI has been documented in these cases [5, 6]. In cases where angiogram has been done, no specific pattern of coronary involvement has been documented [6].

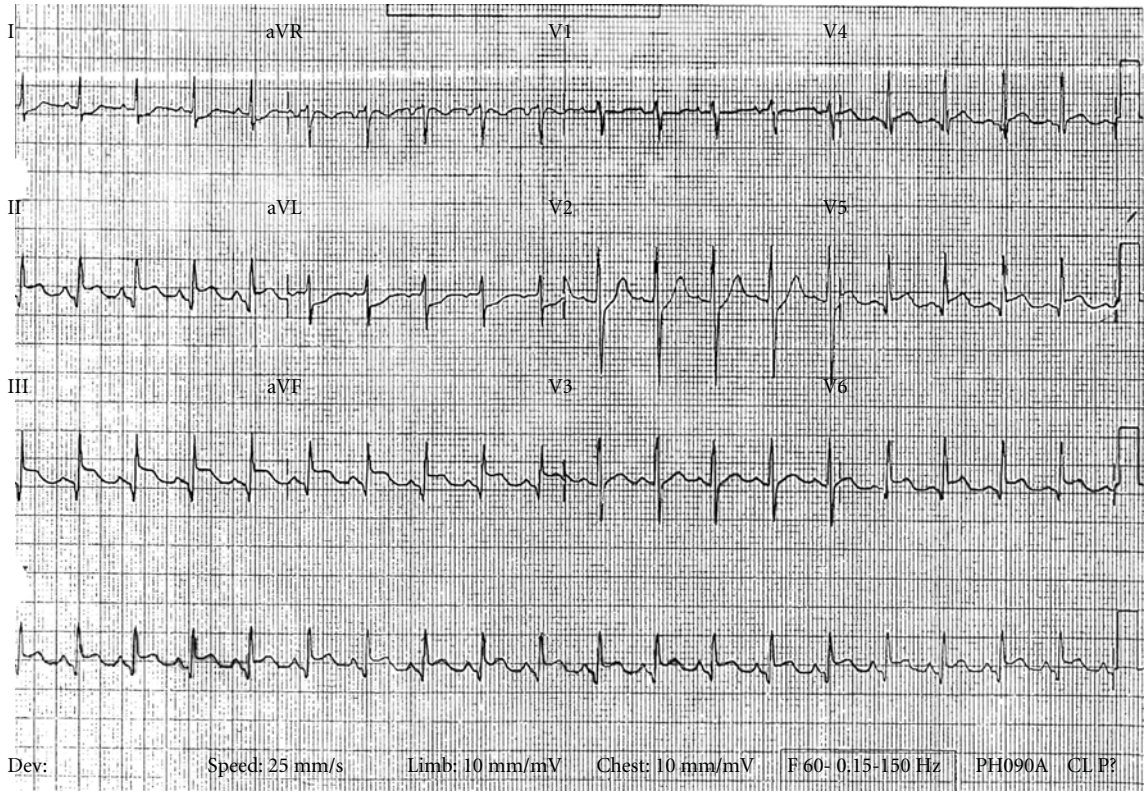
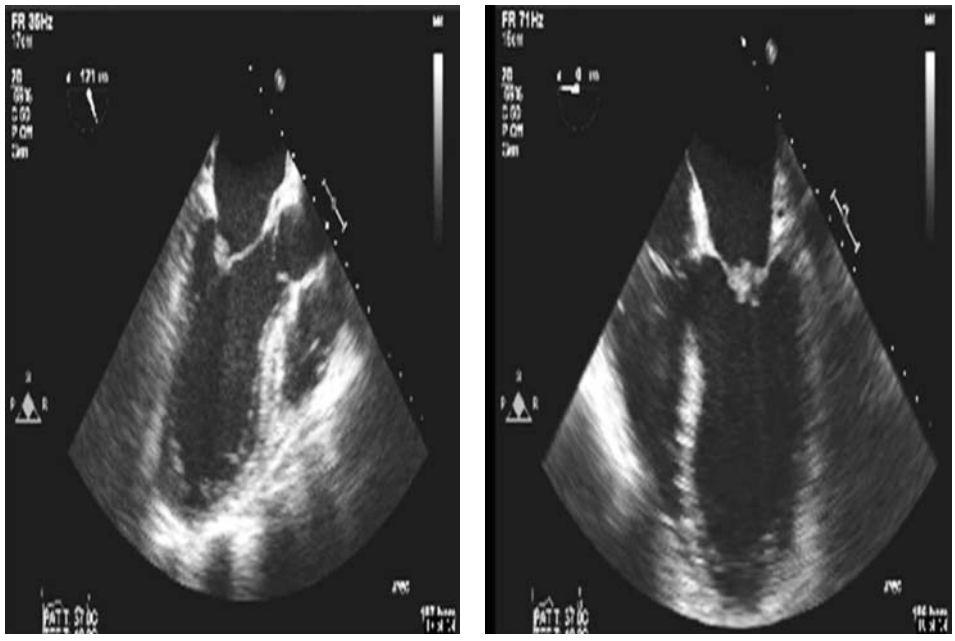


Figure 1: A 12-lead electro cardiogram showing ST elevations in lead II, III, AVF, V5, and V6.



(a) (b)

Figure 2: A transesophageal echocardiogram showing vegetation on the mitral valve.

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Case Report

Recurrent Syncope in a Cancer Patient: A Case Report and Review of the Literature

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A 59-year-old male with invasive squamous cell carcinoma of the left preauricular region, treated with several chemotherapy regimens and radiation therapy, was admitted for recurrent syncopal episodes. He was found to be suffering from neurocardiogenic reflex-mediated syncope secondary to mechanical compression of the carotid baroreceptors and glossopharyngeal nerve by the tumor. We discuss the pathophysiology of this case and the available treatment options.

1. Case

A 59-year-old Caucasian male with invasive squamous cell carcinoma of the left pre-auricular region was admitted for recurrent syncope over a period of four weeks. He was previously treated with radiation therapy and two chemotherapy agents, Cisplatin and Cetuximab. He described brief prodromal symptoms of lightheadedness and diaphoresis prior to each episode. He regained consciousness in less than one minute and quickly returned to his baseline mental status. Upon arrival to the emergency room after his first episode, his pulse was 65 beats per minute (bpm) and his blood pressure was recorded as 64/42 mm Hg. He was managed with aggressive fluid resuscitation, including three liters of intravenous fluids, and Trendelenburg positioning. After this first episode, follow-up blood pressure recordings were in the normal range within the first one to two hours. 24 hours later, he was no longer symptomatic and was back to his baseline physical and mental status. On a second occasion he was more profoundly affected, and his first systolic blood pressure recorded in the emergency room was 46 mm Hg and his pulse ranged from 46–57 bpm. Upon presentation during this event he was confused and his blood pressure took longer to recover despite similar treatment with intravenous fluid resuscitation and Trendelenburg positioning. However, similar to the first episode, 24 hours later he was back to his baseline.

On no occasion was his syncope associated with head turning or neck compression. He did have longstanding neuropathic pain located in the posterior nasopharynx and the left side of his face. As his disease had progressed, he also developed pain with swallowing; however, there was no exacerbation in his symptoms surrounding the syncopal episodes. Several events occurred while he was supine.

Further testing including orthostatic blood pressure measurements, electrolyte measurements, an electrocardiogram, and echocardiogram revealed no abnormalities. A Holter monitor recording preceding one of his syncopal episodes showed sinus pauses of up to 2.1 seconds. These pauses were frequent and were associated with prodromal symptoms of diaphoresis and lightheadedness (Figure 1(a)). A few minutes later, he had a rapid drop in his sinus rate to a junctional rhythm at 33 bpm (Figure 1(b)) that culminated in a syncopal episode. Both of these symptomatic recordings, although nocturnal, began in the supine, but awake state. Formal tilt table testing and gentle carotid massage was not feasible due to the lability of his vital signs. Repeat head and neck computed tomography (CT) scan showed progression of his tumor, now completely encasing his left internal carotid artery at its bifurcation from the left common

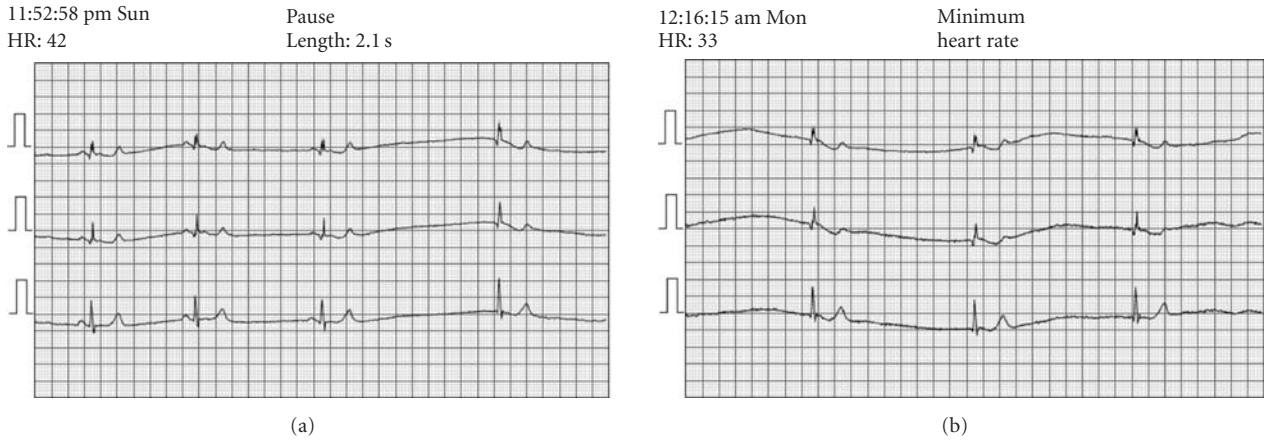

Figure 1: (a) Holter monitor recording showing sinus bradycardia at 42 bpm with sinus pauses of up to 2.1 seconds, corresponding to his prodromal symptoms while awake. (b) Holter monitor recording during a syncopal episode showing a drop in heart rate to 33 bpm.

carotid artery (Figure 2). In addition, the tumor abutted the glossopharyngeal nerve at the point of exit from the posterior aspect of the base of his skull. We concluded that the patient was suffering from neurocardiogenic reflex-mediated syncope, secondary to mechanical compression by the tumor of the carotid baroreceptors and the glossopharyngeal nerve. This syndrome has also been called a parapharyngeal space lesion syncope.

He was placed on midodrine, fludrocortisone, and sertraline to help alleviate his symptoms; however, he continued to have syncopal episodes while hospitalized that became progressively more resistant to fluid resuscitation. For example, during the first two events he experienced, his blood pressure recovered within the first one to two hours of aggressive fluid resuscitation. However, during later hospitalizations, despite the same interventions his blood pressure remained in the hypotensive range for hours. During two different episodes, he was given atropine to help increase his heart rate. His heart rate increased appropriately with this intervention; however, hypotension persisted, thus demonstrating that the vasodilatory component of his neurally mediated syncope was playing a dominant role in his events. His primary oncology team determined that he had a poor prognosis and did not have any more chemotherapy or radiation therapy options available to treat his progressive cancer. After discussion with him, he was discharged with home hospice.

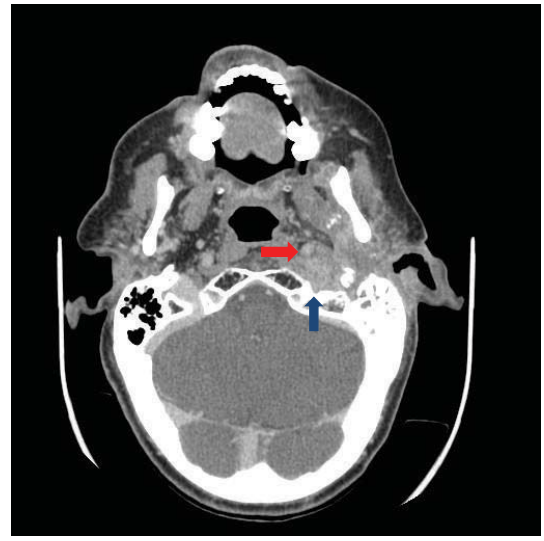

Figure 2: CT scan of the patient's head, axial image. The red arrow shows tumor encasing the internal carotid artery. The blue arrow shows tumor infiltrating the skull base where CN IX exits the jugular foramen. CN IX is not visualized clearly because of the invading tumor.

2. Discussion

2.1. Neurally Mediated (Reflex) Syncope and Carotid Baroreceptors. Neurally mediated, or reflex, syncope is the term used to describe a reflex response that leads to systemic hypotension and bradycardia. The trigger for this response can be varied in individual patients. This case illustrates a particular severe cause of neurally mediated syncope due to mechanical encroachment on the carotid baroreceptors and glossopharyngeal nerve.

The carotid baroreceptors are located at the internal carotid artery, close to their bifurcation off the common carotid artery. They are innervated by the Sinus Nerve of Hering, which is a branch of the glossopharyngeal nerve, cranial nerve (CN) IX. Sensory fibers arise from the carotid body and join the other components of CN IX at the inferior hypoglossal ganglion. The central processes of these neurons enter the skull via the jugular foramen. In its passage to the jugular foramen, CN IX passes between the internal jugular vein and internal carotid artery. It descends in front of the internal carotid artery and beneath the styloid process and the muscles connected with it. After entering the skull, CN IX eventually synapses in the nucleus tractus solitarus (NTS), which in turn modulates activity of both the sympathetic and parasympathetic neurons in medulla.

The medulla ultimately regulates autonomic control of the heart and blood vessels.

Maximal carotid sinus sensitivity normally occurs near a mean arterial pressure (MAP) of approximately 100 mm Hg. Increases in MAP increase baroreceptor firing and decreases in MAP lead to decreases in baroreceptor firing. Carotid sinus sensitivity is such that even very small changes in arterial pressure around this set point can significantly alter receptor firing, and in turn, tightly up regulate or down regulate autonomic control of the heart and peripheral vasculature [1]. In this individual, progressive disease led to tumor compression of the internal carotid artery, and the mechanical pressure caused an increase in baroreceptor firing. His medulla responded by increasing parasympathetic outflow and decreasing sympathetic outflow. Under normal physiologic conditions, baroreceptor firing has a tonic inhibitory influence on sympathetic outflow from the medulla, and in this case, the sympathetic outflow was decreased still further.

This patient's tumor also encroached upon CN IX as it exited the skull base and thus affected a second anatomical component of the neutrally mediated reflex. Direct tumor ingrowth at CN IX at the jugular foramen interrupted the sensory fibers that run along the nerve affecting parasympathetic and sympathetic outflow from the medulla. The combination of bradycardia and peripheral vasculature vasodilatation that occurs as a result of the surge in parasympathetic outflow and decrease in sympathetic stimulation culminated in his syncopal episodes.

Another pathogenic mechanism underlying the association between glossopharyngeal neuralgia and syncope is thought to be related to the close relationship that exists between CN IX and CN X [2]. Neurosurgical research suggests that ephapses, or artificial synapses, develop between CN IX and CN X, or that anomalous communications develop between the nucleus tractus sollitarus and the nucleus ambiguous centrally [3]. The presence of an irritative lesion might thus give rise to "cross talk" between the above circuits, thereby inducing bradycardia with or without a decrease in peripheral resistance, through possible mediation of the vagus nerve and carotid baroreceptor, respectively [4]. Evidence for cross talk between nerve fibers is supported by experimental findings [5].

Thus, it is likely a combination of several factors including direct tumor invasion on the carotid body and CN IX, and possible development of anomalous connections centrally involving CN X that led to our patient's syncopal episodes. The inexorable progression of his symptoms and their increasing refractoriness to resuscitation corresponds to the progressive state of his tumor.

2.2. Treatment Options for Neurally Mediated (Reflex) Syncope. The European Society for Cardiology offered a recent update on its guidelines for the management of syncope [6]. The initial steps for treating patients suffering from the common form of neurally mediated (reflex) syncope include reassurance and education about their syndrome. Other simple interventions such as educating patients to avoid trigger events, teaching them to recognize and respond to premonitory symptoms, and modifying or discontinuing medications that may cause hypotension have also proven to be beneficial. Patients that suffer from frequent syncopal episodes may require additional pharmacologic treatment.

Many drugs have been used for treatment of the various forms of neurally mediated syncope, including beta blockers and anticholinergic agents; however, the evidence for benefit in randomized clinical trials is lacking. Midodrine, an agent that stimulates alpha-1 adrenergic receptors, has shown more promise in selected patients, particularly those with predominant vasodilatory responses. Results from two small open-label randomized studies that were done on patients who suffered from recurrent neurally mediated syncope showed that midodrine was effective in reducing the number of syncopal and presyncopal episodes over the short term, and its use significantly improved patients' quality of life [7, 8].

The use of selective serotonin reuptake inhibitors (SSRI) has also been studied in patients with neurally mediated syncope. Serotonin (5-hydroxytryptamine), along with several other neurotransmitters, may play an important role in eliciting reflex syncopal reactions. Experimental animal models in rats [9] have shown that intracerebral serotonin inhibits sympathetic neural outflow during acute hemorrhage while increasing adrenal sympathetic stimulation. In rabbits, blocking serotonin receptors seemed to eliminate the hypotensive reflex during acute hemorrhage [10]. Accumulation of extracellular serotonin by SSRIs result in downregulation of neuronal transmission, thus blunting the effect of the neurocardiogenic reflex.

Paroxetine was studied in a randomized, double-blind, placebo-controlled trial in patients who suffered from recurrent vasovagal syncope (VVS) [11]. 68 consecutive patients were included and those that received paroxetine were significantly less likely to suffer from spontaneous syncope (17.6% in the paroxetine group compared to 52.9% in the placebo group) over a mean follow-up period of 25.4 months. Similar results were reported in studies evaluating other SSRIs including fluoxetine [12] and sertraline [13]. Despite success in these small trials, until their results can be duplicated in larger trials, the European Society of Cardiology is not currently recommending use of this class of agents.

Besides pharmacologic therapy, much effort has been devoted to examining whether pacemaker insertion is useful in treating various forms of neurally mediated syncope, and in particular vasovagal syncope. Five major multicenter randomized controlled trials have been done so far to evaluate the benefit of pacing in this patient population [14–18].

The first three studies [14–16] published showed a significant benefit to patients who were implanted with a pacemaker. The two most recent studies, however, showed a negative result. The largest difference in these studies was the method in which they were conducted. The initial three studies, theVPS Study [14], European VASIS trial [15] and SYDIT trial [16] were all unblinded studies. Patients were randomized to receive either a pacemaker or standard

medical therapy. In the latter two studies, the SYNPACE trial [17] and the VPS II study [18], all patients received a pacemaker, but patients were randomized to have their device either turned on or turned off.

Combining the data of these five trials, only 318 patients are studied. In addition, because the first three trials were unblinded, placebo effect and reporting bias must be taken into consideration when examining the results of these studies. While pacing may be efficacious for the bradycardic component of neurally mediated syncope, it does little to combat the accompanying hypotension. Thus, given the evidence, pacing therapy is not considered first line therapy for most patients with neurally mediated syncope, and the European guidelines state "cardiac pacing should be limited as a choice of last resort to a very selected small proportion of patients affected by severe vasovagal syncope [6]." In the subject of this case report, the vasodepressor component of his syncope overshadowed the cardioinhibitory component, thus pacing was not considered to be a reasonable treatment choice for this individual.

2.3. Treatment of Syncope in Cancer Patients. Recurrent carotid sinus syncope in head and neck cancer patients is uncommon but can present a particularly malignant form of the condition. The presumed mechanism is direct tumor compression of the carotid sinus baroreceptors or CN IX, or both, as in the case above. There are no guidelines currently in place to direct the treatment for syncope in this specific patient population. Several case reports have been published with circumstances similar to those seen in our patient. Most recently, two groups reported resolution of syncopal episodes with tumor regression with chemotherapy [19, 20]. In one case, the patient had a pacemaker placed but continued to faint. However, in both cases symptoms resolved after induction chemotherapy was begun.

Older published reports have also documented similar situations. One case report examined a group of 17 patients suffering from head and neck carcinoma with associated syncope [21]. Various treatment strategies including carotid ligation, intracranial sectioning of CN IX, and local radiation have been employed with success in individual reports. Of the 17 patients, three had pacemakers placed and this appeared to be ineffective in preventing syncope. Another report with seven patients found periarteriectomy, intracranial nerve root section, and radiation therapy to be beneficial [22].

A review from the neurosurgery literature examines treating CN IX dysfunction by surgical means. A group from France investigated patients who were suffering from syncopal episodes secondary to tumor compression of CN IX [23]. The majority of these patients were treated with neurosurgical resection of the root of CN IX, though not all surgeries were completely curative. In addition to discussing surgical options for these types of patients, the authors also discuss the importance of relief of symptoms with treatment of the underlying cause-invading tumor.

What many of these successfully treated cases have in common is achievement of regression of the underlying carcinoma, reduction in tumor burden, and relief of pressure on either the carotid baroreceptors, CN IX, or both. Pacemaker implantation has been an unsuccessful treatment strategy in this group of patients, due to a pacemaker's inability to combat the vasodilatory component of neurally mediated syncope. Other medical treatment options, like those tried in this patient, are often left to the discretion of the treating physician because there are no current treatment guidelines available. Definitive treatment and successful syncope relief depends primarily on successful tumor regression, without which the condition is likely to be inexorably disabling and perhaps fatal.

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Case Report

Primary Pericardial Sarcoma: A Case Report and a Brief Review

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There are very few cases of primary pericardial sarcomas reported in the English literature. Pericardial tumors, like other cardiac tumors, are most likely to be metastatic in nature and are an extension of primary tumors from the surrounding structures. Sarcomas are the most common primary pericardial tumors. Surgical eradication of the tumor is considered to be the treatment of choice. We are presenting a case of a primary pericardial, high-grade pleomorphic undifferentiated sarcoma that was diagnosed at our institution. We discuss the available diagnostic modalities and also shed light on alternative therapies when patients are not ideal surgical candidates.

1. Introduction

Cardiac neoplasms are either primary or secondary; in case of secondary neoplasms the most common site of origin is the lung [1]. The cardiac involvement can be endocardial, myocardial, or pericardial, but tumors only involving the parietal pericardium are not considered to be true cardiac tumors. Primary cardiac tumors are rare; the incidence is reported to be around 0.056–0.02% [1]. Malignant tumors involving the pericardium are even rarer in autopsy series, the incidence is reported to be around 0.001%. Pericardial tumors, like other cardiac tumors, are most likely to be metastatic in nature and are an extension of primary tumors from the surrounding structures.

Pericardial tumors often cause symptoms related to malignant pericardial effusion. The presenting symptoms are cough, dyspnea, chest pain, and palpitations, which are a result of the mass effect of the tumor on the cardiac chambers [2]. These tumors are of a particular concern due to the fact that overt signs and symptoms occur rather late in the course, precluding effective tumor eradication [2]. We are presenting a case of a primary pericardial, high-grade pleomorphic undifferentiated sarcoma that was diagnosed at our institution and provide a brief insight into the detection and treatment of the disease.

2. Case Presentation

A 67-year-old Caucasian gentleman presented to our institution with acute right-sided chest pain. He had been experiencing gradually worsening shortness of breath on exertion for a few months. Physical examination revealed a malnourished moderately built male with tachycardia and muffled heart sounds. Chest radiography revealed a widened mediastinum and an enlarged heart that was suspicious for a pericardial effusion. A transthoracic echocardiogram (TTE) confirmed a large anterior pericardial effusion with respirophasic blunting of the inferior vena cava but no right ventricular diastolic collapse (Figure 1). A computed tomography (CT) scan that closely followed the TTE revealed an anterior mediastinal mass arising from the pericardium, compounded by the previously documented pericardial effusion (Figure 2). Pericardial fluid cytology revealed malignant cells. CT guided fine needle aspiration cytology of the pericardial mass was done. Histopathology showed a moderately cellular, spindle cell neoplasm with pleomorphic nuclei in a myxoid background (Figure 3). The pathologists did find pseudolipoblasts, which are found in many tumors including pleomorphic liposarcomas (which can be confused with undifferentiated sarcomas [3]). Immunohistochemistry was positive for vimentin, CD163 and CD 68, other muscle

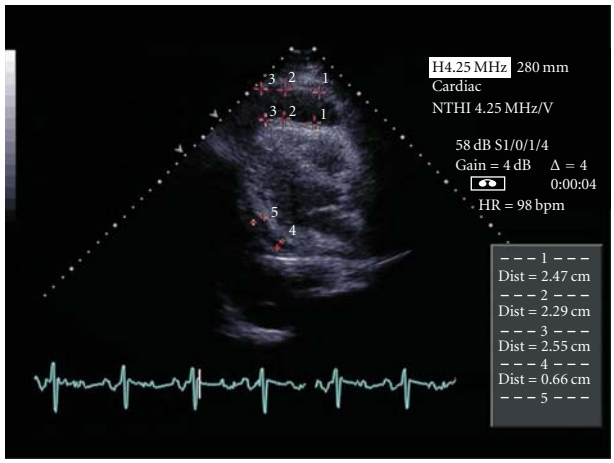

Figure 1: Echocardiographic image showing anterior and posterior pericardial effusion.

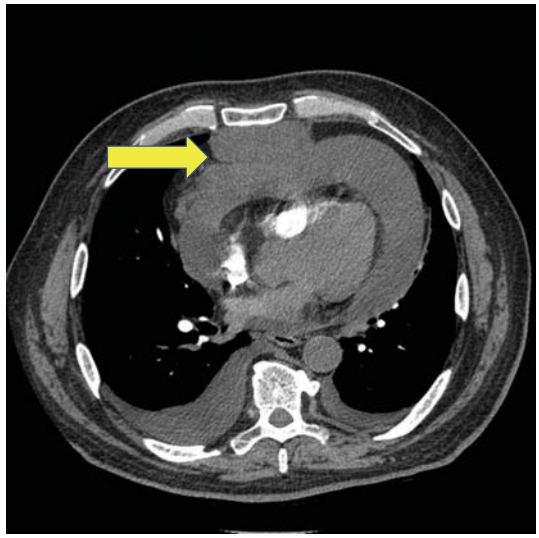

Figure 2: CT showing anterior mediastinal mass arising from the pericardium.

specific markers but melanocytic markers were negative. The tumor was diagnosed as a primary pericardial high-grade pleomorphic undifferentiated sarcoma.

Surgery is the most effective treatment for sarcoma; however our patient was not considered to be an ideal surgical candidate due to the advanced nature of his disease and poor nutritional state. Oncology was consulted and further treatment options of radiation and chemotherapy were discussed with the patient. Doxorubicin was not considered a feasible option in his case due to its cardiotoxic potential hence a decision was made to attempt a trial of imatinib mesylate and further testing of the pericardial mass for c-kit staining was done. The tumor was found to be c-kit negative suggesting that chemotherapy with imatinib was unlikely to be of benefit and the patient was started on a radiotherapy protocol. Eventually the patient succumbed to the disease in a matter of months.

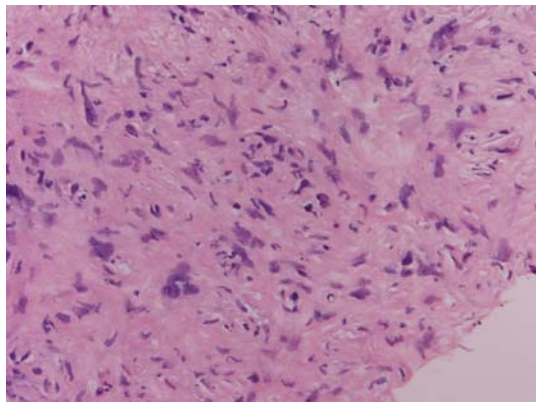

Figure 3: Histopathology showing a moderately cellular, spindle cell neoplasm with pleomorphic nuclei in a myxoid background.

3. Pathology

Sarcomas are the most common primary pericardial tumors; other tumors that involve the pericardium are mesotheliomas, lymphomas, and hemangiomas. Among the sarcomas, undifferentiated sarcomas (previously called malignant fibrous histiocytomas) are most frequent. These are thought to arise from primitive mesenchymal cells and are composed of histiocytic and fibroblastic elements in a storiform pattern. The use of immunohistochemistry, cytogenetics and molecular diagnostics has made it possible to identify other types of sarcomas including myxoid, giant cell, inflammatory, and angiomatoid sarcomas [3, 4]. Undifferentiated sarcomas are further classified into high-grade pleomorphic sarcoma, pleomorphic sarcoma with giant cells, and pleomorphic sarcoma with predominant inflammation on the basis of their histologic appearance [5]. Multiple studies have proved that undifferentiated sarcoma is but a common pathway for developing sarcomas and that a tissue of origin should be actively sought before labeling a soft tissue sarcoma as an undifferentiated sarcoma [5, 6]. Pleomorphic undifferentiated sarcomas are commonly seen in elderly males and involve the thigh, upper arm, and the retroperitoneum [3]. We have presented a high-grade pleomorphic undifferentiated sarcoma arising from the pericardium that is very rarely documented in English literature.

4. Diagnosis

In case of cardiac sarcomas, a TTE is a good initial diagnostic test to detect the associated pericardial effusion. With the use of contrast echocardiography the sensitivity of detecting malignant tumors increases due to the increased pixel intensity of tumors as compared to the surrounding myocardium [7]. Not all pericardial tumors are associated with pericardial effusion and computed tomography (CT) scan is useful in the detection of such cases. The CT scan finding of pericardial nodularity is highly suggestive of a pericardial tumor [8]. Another distinct advantage over TTE is that CT scan can

identify the dominant mass and offer guidance for biopsies of the mass [8]. Advanced modalities like multidetector CT scans and cardiac magnetic resonance imaging are gaining favor as the imaging of choice for diagnoses of pericardial sarcomas but they are expensive and their availability is limited [9]. Tissue sampling in the form of surgical biopsies provides the best odds for detection of the cell of origin. Since pleomorphic undifferentiated pattern can be found adjacent to areas of well-differentiated sarcomas in the same tumor, the distinction between pleomorphic undifferentiated sarcomas and other sarcomas can pose a difficult problem for a pathologist [10]. This makes it imperative that every effort should be made to obtain as much tissue as possible to prevent misdiagnoses. Accurate tissue diagnoses have been shown to affect prognosis since myogenic differentiation is considered to be more aggressive than some of the other pleomorphic sarcomas [6]. A surgical biopsy is fraught with periprocedural risks depending on the site of the tumor. We suggest that multiple CT-guided biopsies from different accessible sites should be preferred over open surgical biopsies [2, 6].

When such a disease process is suspected, a less invasive procedure like pericardial fluid cytology will provide information regarding the presence of malignancy. It is well accepted that pericardial fluid cytology is indicated in asymptomatic young adults who have an incidental finding of a pericardial effusion. We suggest that pericardial fluid cytology should also be extended to older individuals who do not have an obvious underlying cause for an effusion, in an effort to get a lead time advantage for diagnosing a pericardial malignancy. Positive cytology should be followed by multiple CT-guided biopsies in an effort to make an accurate tissue diagnosis, to guide treatment and also assesses the true prevalence of these tumors [6].

5. Management

Surgery is the mainstay of treatment for soft tissue sarcomas and effective tumor removal depends on the anatomic location of the tumor. Pericardial sarcomas may be amenable to removal if detected very early on but our case reflects that this may not be possible due to its covert presentation. The response of soft tissue sarcomas to radiation has been well documented and currently adjuvant radiation is recommended along with surgical resection to improve overall survival [5, 11, 12].

Chemotherapy is currently reserved for metastatic tumors and the agents of choice are doxorubicin and ifosfamide, with response rates ranging from 55–66% [13, 14]. In case of pericardial sarcomas, the use of chemotherapeutics may extend to the treatment of the primary tumor if surgery is ineffective. The use of doxorubicin in pericardial sarcomas may be restricted due to its cardiotoxicity which may confound the mass effects of the tumor and further worsen cardiac reserve. The detection of pericardial tumors should prompt clinicians to enroll these patients into studies that determine the efficacy of novel chemotherapeutics [15]. The tumor should be evaluated for the presence of specific targets (for newer experimental agents) like c-kit, epidermal growth factor receptor, vascular endothelial growth factor receptor, and platelet growth factor receptor, among others [15, 16]. Gemcitabine has shown promise in the treatment of soft tissue sarcomas that have failed anthracycline-based chemotherapeutic regimen [17, 18]. Trials with imatinib mesylate have shown some benefit in gastrointestinal soft tissue sarcomas, and ongoing multicenter trials for its use in other soft tissue sarcomas have shown modest results [19]. Further studies are needed to guide chemotherapeutic management.

6. Prognosis

Pleomorphic undifferentiated sarcomas in general have a 2-year survival rate of 60% with a high rate of recurrence and metastasis. In a series of 200 cases of undifferentiated sarcomas, the rate of recurrence after primary tumor eradication was around 44% [3]. The rate of metastasis was around 42% and correlated with the depth of the tumor spread, with deeper tumors possessing greater potential for metastasis [3]. The rates for survival, metastasis, and recurrence specific for primary pericardial sarcomas are not available. Given the close proximity of these tumors to vital structures, it is quite possible that mass effect of the tumor itself may be lethal, making metastasis and recurrence less important issues.

7. Discussion

The relative paucity of such cases makes it difficult to design management protocols specific to pericardial sarcomas. Detection starts by identification with contrast enhanced TTE, pericardial fluid cytology which should be followed by accurate tissue diagnosis with multisite CT-guided biopsies and cardiothoracic surgery consultation. Currently we believe that surgical approach should be the primary modality of treatment. However if patients are not found to be ideal surgical candidates then chemotherapy and radiation should be offered requiring a multidisciplinary approach by cardiology and oncology. Enrollment in clinical trials involving chemotherapeutic agents should always be considered in this patient population.

Conflict of Interests

The authors declare no conflict of interests.

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This paper is not under simultaneous consideration by another journal.

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