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Radiation Therapy and The Heart

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Abstract:

Background: Radiation therapy represents a cornerstone in the management of breast cancer, contributing significantly to improved local control and survival outcomes. However, exposure of cardiac structures during thoracic irradiation has been increasingly recognized as a source of both early and late cardiovascular complications. Advances in radiotherapy techniques have reduced cardiac exposure, yet radiation-induced heart disease remains a clinically relevant concern, particularly in patients receiving left-sided breast irradiation or combined modality treatment. This review aims to summarize the mechanisms, clinical manifestations, risk modifiers, and dose-related parameters associated with radiation-induced cardiac toxicity, with emphasis on contemporary radiotherapy practices and long-term cardiovascular outcomes.

Keywords: Radiation therapy; Breast cancer; Radiation-induced heart disease; Cardiotoxicity; Cardiovascular complications; Thoracic irradiation

Introduction:

Breast cancer is the most common cancer diagnosed in women and the second most common cause of death from cancer among women worldwide. The breasts are paired glands of variable size and density that lie superficial to the pectoralis major muscle. They contain milk-producing cells arranged in lobules; multiple lobules are aggregated into lobes with interspersed fat. Milk and other secretions are produced in acini and extruded through lactiferous ducts that exit at the nipple. Breasts are anchored to the underlying muscular fascia by Cooper ligaments, which support the breast. **(1)**.

Breast cancer most commonly arises in the ductal epithelium (ie, ductal carcinoma) but can also develop in the breast lobules (ie, lobular carcinoma). Several risk factors for breast cancer have been well described. In Western countries, screening programs have succeeded in identifying most breast cancers through screening rather than due to symptoms. However, in much of the developing world, a breast mass or abnormal nipple discharge is often the presenting symptom. Breast cancer is diagnosed through physical examination, breast imaging, and tissue biopsy. Treatment options include surgery, chemotherapy, radiation, hormonal therapy, and, more recently, immunotherapy. Factors such as histology, stage, tumor markers, and genetic abnormalities guide individualized treatment decisions **(2)**.

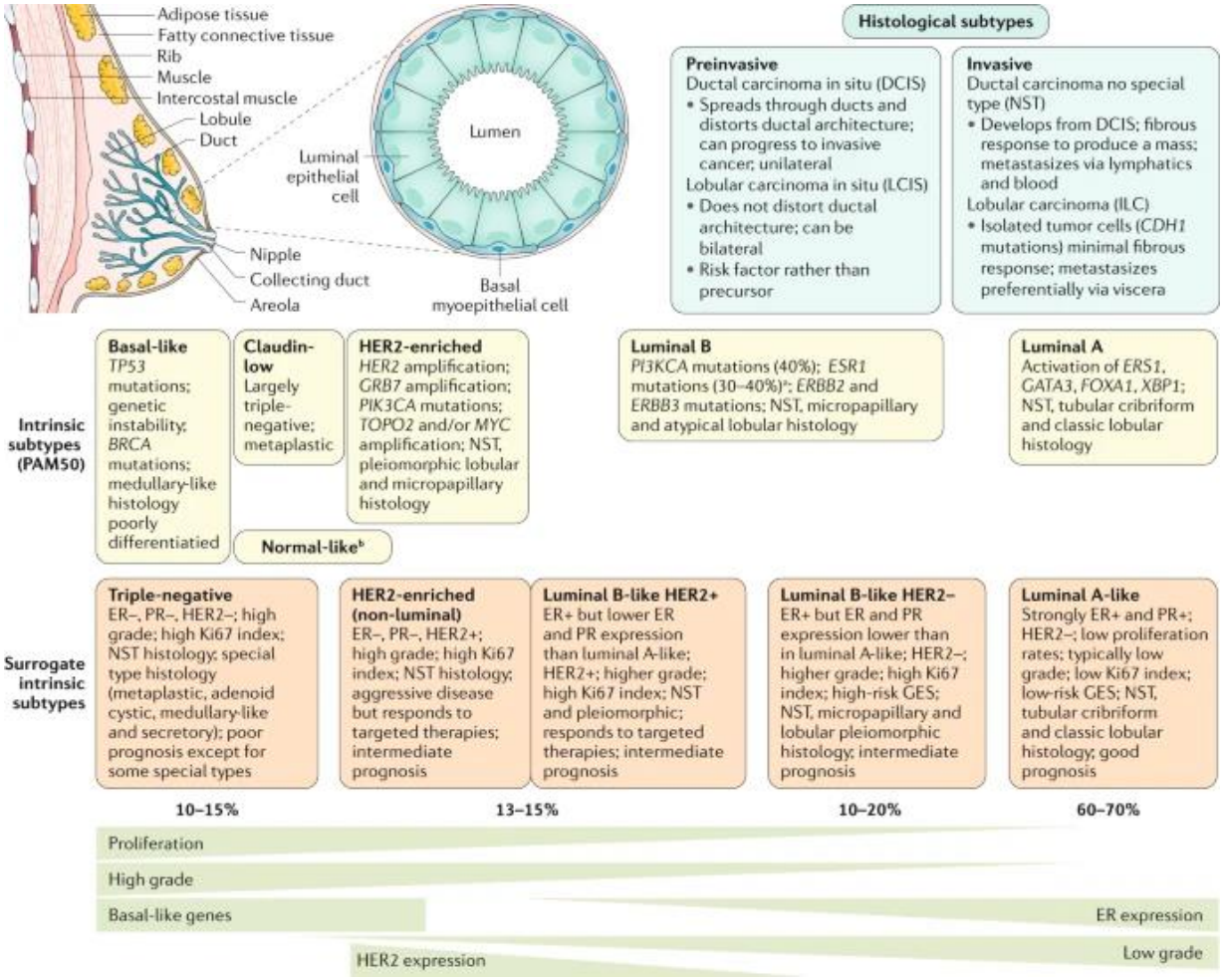

Figure 1: Breast cancer **(3).**

Treatment of BC

The treatments of breast cancer include surgery, chemotherapy, radiotherapy (RT), endocrine therapy, targeted therapy, and immunotherapy, and the therapeutic schedules require the cooperation of multiple subspecialties. For non-metastatic breast cancer, surgery-based treatment is the standard management, and chemotherapy-based preoperative systemic therapy can reduce tumor volume of the breast, making breast conservation possible, and decreasing the need for axillary lymph node dissection (ALND). Systemic treatment remains the preferred option for metastatic breast cancer, and surgery is only used for palliative therapy in selected metastatic patients **(4)**.

Treatment choice is based on the grade, stage, and BC molecular subtype to have the most personalized, safe, and efficient therapy. The grade describes the appearance of tumor cells compared to normal cells. It includes tubule differentiation, nuclear pleomorphism, and the mitotic count. The stage is used to classify the extent of cancer in the body and is defined using the TNM system comprising tumor size, lymph node status, and the presence of metastases **(5)**.

For non-metastatic BC, the strategic therapy involves removing the tumor by complete or breast-conserving surgery with preoperative (neoadjuvant) or postoperative (adjuvant) radiotherapy and systemic therapy including chemotherapy, and targeted therapy. Targeted therapy comprises endocrine therapy for hormone receptor-positive (HR+) BC and anti-HER2 therapy for HER2+ BC. Unfortunately, there is no available targeted therapy for the TNBC subtype. For metastatic BC the priority is to contain tumor spread as this type of BC remains incurable. The same systemic therapies are used to treat metastatic BC **(6)**.

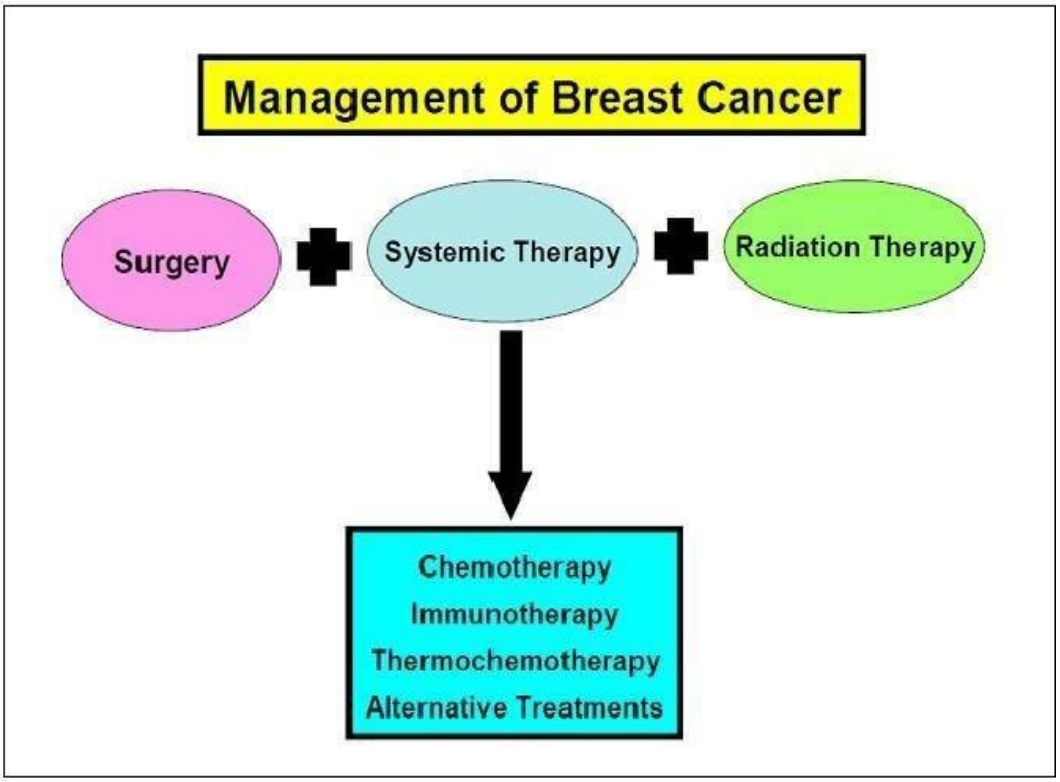

Figure 2: Management of a breast cancer **(7)**.

Radiation Therapy for BC

Radiotherapy is local treatment of BC, typically provided after surgery and/or chemotherapy. It is performed to ensure that all of the cancerous cells remain destroyed, minimizing the possibility of breast cancer recurrence. Further, radiation therapy is favorable in the case of metastatic or unresectable breast cancer. Choice of the type of radiation therapy depends on previous type of surgery or specific clinical situation; most common techniques include breast radiotherapy (always applied after BC), chest-wall radiotherapy (usually after mastectomy), and 'breast boost' (a boost of high-dose radiotherapy to the place of tumor bed as a complement of breast radiotherapy after BCS). **(8)**.

The main goal of radiation therapy is to eliminate any residual tumour cells while minimizing damage to adjacent tissues: this is achieved with dose fractionation that enables healthy cells to repair sublethal damage, as opposed to the tumour cells which are unable to repair radiation-induced damage. Modern technologies allow safe administration of radiation therapy. Thanks to computed tomography (CT)-based treatment planning, linear accelerators and new techniques such as intensity-modulated radiation therapy (IMRT), greater target dose homogeneity and sparing of normal tissue can be accomplished; these strategies help to minimize the side effects related to radiation **(9)**.

Types of Radiotherapy in Breast Cancer

Radiotherapy is generally divided into 2 broad categories of External Beam Radiation Therapy and Internal Radiation Therapy (more commonly referred to as Brachytherapy), both named so due to the method delivery; from the use of external beams directed toward the tumor or through the placement of a solid radiation source internally, within the tumor tissue or in the cavity following the removal of tumor tissue **(10)**.

External Beam Radiation Therapy utilizes beams that are produced by machines such as a linear accelerator. The beams themselves are produced by colliding high-speed particles such as electrons to a metal target such as tungsten resulting in X-ray or other high-energy ionizing rays. As opposed to Brachytherapy, External Beam Therapy is painless with most patients not having to stay in the hospital following a treatment.

EBRT can be delivered to patients using many different techniques and the commonly used techniques and sources of radiation are given below **(11)**.

3D conformal radiotherapy (3D CRT) is a type of EBRT treatment that can target the tumor and to match the shape of the tumor itself. Compared to earlier methods, which could only target the tumor's height and width and significantly damaged the surrounding healthy tissue. The beams can be manipulated in which angles they enter to optimize the target area **(12)**.

The technique relies on the use of special imaging techniques to visualize the size, shape, margins, and location of the tumor such as computer tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET scan) or PET-CT scan. These images will then be used to fabricate a plan for the radiation to be applied to the patient. Due to the nature of detailed imaging and healthy tissue sparing, recovery will be quicker as surrounding healthy tissues receive less radiation. This also enables for larger radiation doses to be used, resulting in greater tumor shrinking efficiency **(13)**.

Intensity-modulated radiotherapy (IMRT) is a more specialized form of 3D CRT which allows more precise shaping of the radiation applied to fit the tumor. The radiation beam is divided into "beamlets", the intensity of which may be adjusted over the radiation field. This level of control allows the healthy tissue that surrounds the tumor to be spared even more than it can be through 3D CRT, as well as increasing the dose delivered. Randomized studies have shown that the use of IMRT is able to reduce toxicity in breast cancer patients **(14)**.

Volumetric Modulated Arc Therapy (VMAT) is a novel radiation therapy extension to IMRT, which allows for an optimized 3D dose distribution delivery in a single gantry rotation. It works similarly to IMRT where the radiation dose is varied through the treatment with intensity differences to allow healthy tissue sparing. Comparing VMAT to 3D CRT, VMAT offers more efficiency with the same or higher level of dose conformity while delivering a lower dose to the ipsilateral lung in breast cancer treatment. As with 3D CRT and IMRT, a high level of accuracy is maintained in targeting the tumor **(10)**.

Image Guided Radiation Therapy (IGRT) uses frequent imaging techniques in order to visualize and aid radiation therapy. This is especially useful in areas that may move and is rarely used in breast cancer treatment **(15)**.

Proton Beam Therapy (PBT) is a specialized form of radiation therapy that utilizes protons being delivered to the target rather than X-rays as seen in conventional radiation therapy. The use of this technique for breast cancer is conflicted with countries such as the United Kingdom not approving the use whereas countries such as Switzerland allow the use **(16)**.

As a relatively novel technique, more studies will be required in order to identify if the technique can provide a better solution compared to other radiation techniques. The advantage of PBT is that minimal dose is deposited past the treatment target sparing many of the organs that otherwise would have been affected in traditional Radiation Therapy techniques, specifically the heart, lungs, bones, and muscles **(17)**.

Neutron Beam Therapy, like PBT, is a specialized form of EBRT that uses neutrons. The use of NBT in breast cancer is less frequent than the past levels of use, with only a handful of countries that are still using this technique such as the United States of America, Russia, and South Africa. NBT can be of great benefit in patients where the tumors are radioresistant to conventional radiation therapy techniques; they have a higher impact on cells compared to other radiation types **(18)**.

Brachytherapy involves placement of a radiation or radiation therapy placed close to or within tumor tissue. The dosage is delivered as intracavitary, intraluminal, or multicatheter interstitial. Brachytherapy can be classed by the delivery method or by the dose given; low dose rate implant, high-dose rate implants and permanent implants or Interstitial, Intracavitary, and Intraluminal. The main advantage of brachytherapy lies within the method of delivery where the radiation is placed within the tumor tissue or the site where the tumor tissue is

removed, allowing a higher dose to be applied. In the case of Breast Cancer, the radiation is almost always given following surgical removal of the tumor **(19)**.

Brachytherapy requires easy access to the site of the tumor; here lies the advantage of brachytherapy for breast cancer as it can be routinely used following surgical removal of the advances in 3D scanning that allows visualization to make access to the tumor site. American Brachytherapy Society guidelines for brachytherapy suggest that women 45 or above diagnosed with DCIS or early-stage invasive breast cancer with lumpectomy are appropriate candidates for brachytherapy **(20)**.

Additional guidelines from American Brachytherapy Society also include that the patient's cancer is **(10)**:

- Hormone-receptor positive or negative
- Node-negative
- Have not invaded the lymphovascular system
- Has a negative or a clear margin

Interstitial Brachytherapy is a type of brachytherapy which involves implanting hollow tubes, needles, or wires that are radioactive to the tumor site or the area where the tumor was removed. This is one of the main types of brachytherapy used in breast cancer compared to other types. Interstitial brachytherapy can be delivered using a single or multi-catheter device, in which a remote afterload is performed following the puncture **(21)**.

Intracavitary Brachytherapy is when the radiation is placed within the body cavity. It is of great significance in breast cancer as it can be carried out, following mastectomy or lumpectomy. Intraluminal Brachytherapy is most commonly used in hollow organs where the radiation is delivered through the means of a tube or an applicator of some sort to the lumen of the target organ**(10)**

The main advantage of Brachytherapy is the fact that it can spare a lot of the healthy tissue surrounding the tumor and reduce the side effects that may come with External Beam Therapy**(22)**

Contraindications to Radiotherapy

In the treatment of early breast cancer, it is important to consider both general and specific contraindications to radiation therapy

Table (1): Contraindications to Radiotherapy (9)

General	**Patient's inability to access a radiotherapy centre** **Neurological/orthopaedic conditions (upper limb functional limitations, inability to keep still, etc.)** **Severe lung disease** **Severe cardiac disease for left-sided breast tumours** **Germline TP53 mutations (Li-Fraumeni syndrome)**
Specific **AbsoluteRelative**	Pregnancy Patient's inability to maintain stable treatment position Active connective tissue diseases (systemic lupus erythematosus, dermatomyositis and scleroderma) Quiescent connective tissue diseases (systemic lupus erythematosus, dermatomyositis and scleroderma) Very large breast volume Previous thoracic irradiation

	Genetic predisposition to breast cancer

The patient's ability to access a radiotherapy centre in relation to their general physical and psychological performance status and their logistical situation should be assessed before conservative surgery is planned. It should be kept in mind that some neurological or orthopaedic conditions such as severe upper limb functional limitations or neurodegenerative disorders like Parkinson's disease can compromise the setup and ability to safely deliver the radiation treatment.

Specific contraindications to radiation treatment are traditionally divided into absolute and relative **(9)**

- Pregnancy is an absolute contraindication to breast radiotherapy for its teratogenic risk (abortion, malformations, growth retardation and radiation-induced cancers). Before starting treatment, it is mandatory to ensure that women of childbearing age are not pregnant, and pregnancy must be prevented during the radiotherapy course. When a breast cancer diagnosis occurs during pregnancy, conservative surgery may be considered, and radiotherapy is usually postponed until after delivery, although the delay of the commencement of WBI might have some impact on efficacy. However, the possibility of receiving chemotherapy during pregnancy, as of the end of first trimester, may play a role on local control
- Patients' inability to maintain a stable treatment position (advanced Parkinson's disease, advanced essential tremor, etc.) is an absolute contraindication because it prevents the correct execution of radiation treatment.
- Li-Fraumeni syndrome is an absolute contraindication because, in these patients, ionizing radiation exposure increases the incidence of second malignancies.
- Relative contraindications are shown below:
- Connective tissue diseases involving the skin such as systemic lupus erythematosus, dermatomyositis and scleroderma, if quiescent, represent a relative contraindication and, if active, might be an absolute contraindication because of the amplification of reported toxicity. Rheumatoid arthritis is not considered a contraindication to radiation therapy. Moreover, new radiotherapy approaches, such as partial-breast irradiation, which reduces the irradiated volume, could be promising to improve the feasibility and tolerability of radiotherapy in patients with connective tissue diseases and will probably help to overcome the unresolved concerns about radiotherapy indications for patients with connective tissue diseases **(23)**.
- Severe lung disease with impaired respiratory capacity.
- Severe cardiac disease for left-sided breast cancers.
- The irradiation of very large breasts can be difficult due to the difficulty in reproducing the setup of dose delivery and the inhomogeneity of dose distribution, with a possible negative impact on post-treatment cosmesis. In these particular situations, radiation in the prone position or lateral decubitus position or, in selected patients, accelerated partial-breast irradiation (APBI) might be considered **(24)**.
- Previous thoracic irradiation, although not an absolute contraindication, should be assessed with caution and may be considered for PMRT or treatment of recurrent disease. The previous radiotherapy details (technique, volumes, dose and fractionation) and the interval between previous irradiation and the new planned treatment must be carefully evaluated before re-irradiation is undertaken. In case of re-irradiation, lower doses and smaller volumes are employed in order to limit normal tissue injury **(25)**.
- Women with a known genetic predisposition to develop cancers should be handled with care because of the increased risk of radiation-induced cancers (e.g. carriers of germline mutations in genes involved in the DNA damage repair pathway) **(26)**.

Adverse Effects of Radiation Therapy

Acute radiation damage predominantly involves rapidly proliferating cells, e.g., epithelial surfaces of the skin or digestive tract. Radiation damages the stem cells, which manifests when tissues are lost as part of normal cell turnover, but there is inadequate replacement by stem cells due to radiation damage **(27)**.

This results in a break in the protective barrier - commonly in the skin, oral mucosa, and gastrointestinal tract, especially 1-5 years within the completion of radiotherapy. Subsequently, compensatory hyperplasia within stem cells results in recovery. Therefore, symptoms resolve over a few weeks.

When acute damage fails to heal completely and persists into the late period, such lesions are consequential late effects. Such effects are more commonly seen in regimens that involve chemotherapy in combination with radiotherapy, where tissues fail to repair due to concomitant cytotoxic effects from chemotherapy **(27)**.

Late complications occur in tissues with slow turnover, e.g., brain, kidney, liver, the wall of the intestine, subcutaneous tissue, fatty tissue, and muscle. Consequences of radiation in such tissues include fibrosis, atrophy, necrosis, and vascular damage - telangiectasia and carcinogenesis. Late effects are a result of a complex interplay of various cytokines and adaptive cellular processes. Damage to vasculature results in increased permeability and subsequent release of vasoactive cytokines, TGF-beta, and fibrin, promoting collagen deposition. Most of these tissues or organs have a threshold dose above which late effects increase **(28)**.

Leucocyte adhesion to damaged endothelial cells results in the formation of thrombi and subsequent distal ischemia, which results in distal atrophy and necrosis. Further cell loss may perpetuate the cytokine storm and dysregulated cellular interactions. The type of cytokines released depends on the tissue type and is responsible for the differential response of tissues to irradiation. e.g., the predominant response in the lungs is fibrosis, while in the brain, the predominant response is necrosis **(29)**.

Radiation therapy and the heart

Radiation therapy is an important component in the treatment of cancer. It may play a role as an adjuvant, neoadjuvant, palliative, or definitive therapy, with or without concurrent chemotherapy.

Radiation is most commonly delivered as a local/regional treatment by an external beam consisting of photons, electrons, protons, or heavy particles but may also be delivered via brachytherapy (where a sealed radiation source is placed adjacent to the target) or systemically via unsealed sources. The side effects of radiation therapy are a function of the tissues included in the radiation field. Treatment of diseases within the thoracic region, such as Hodgkin lymphoma, lung, and breast cancer, carries the risk of radiation-induced cardiovascular toxicity (RICT).**(30)**.

Side effects of therapeutic radiation to the heart and coronary vessels include pericarditis, coronary artery disease (CAD), arrhythmias, cardiomyopathy, valvular dysfunction, and heart failure. Pericarditis and pericardial effusions are potential short-term toxicities that may occur during or within the weeks following treatment. Long-term side effects may present in the months to years after radiation therapy, possibly as late as 20 years or more post-treatment. Late toxicities include CAD, valvular heart disease, and heart failure **(31)**.

Major risk factors that increase the likelihood of RICT include higher radiation doses, adjuvant treatment with cardiotoxic chemotherapy, irradiation of the left side of the thorax, and the presence of pre-existing cardiovascular disease. Studies have correlated the mean dose of radiation received by various heart sub-structures to the incidence of major adverse cardiac events (MACE), such as hospitalization for heart failure, myocardial infarction, and even cardiac death. Given the importance of radiation therapy in treating cancer and the high prevalence of cardiovascular disease in Western populations, numerous preventive measures have been suggested and used in clinical practice, such as dose limitation, proton and particle therapy, conformal radiation therapy, and deep-inspiration breath-hold technique **(32)**.

Physiology of radiation-induced heart disease

Radiotherapy exerts its cardiac effects through different mechanisms, depending on the specific cardiac structure affected. Pathologically, its effect on the coronary vessels appears similar to atherosclerosis. Radiation injury to the coronary endothelial cells causes oxidative injury and release of proinflammatory/profibrotic cytokines, which in turn leads to collagen deposition and proliferation of endothelial cells, smooth muscle cells, and myofibroblasts. Radiotherapy can also affect the myocardium, inducing microvascular damage that results in proinflammatory changes and eventual myocardial cell death. Consequently, myocardial tissue is eventually replaced with fibrotic tissue consisting of proliferating collagen bands. These changes can ultimately result in cardiac ischemia, congestive heart failure, and cardiac wall motion abnormalities visible on echocardiogram. Electrical conduction abnormalities may also be seen, including arrhythmias, conduction blocks, and dysfunction in the autonomic nervous system **(33)**.

The pericardium is another cardiac structure susceptible to RT damage. Pericarditis is a known complication of RT that can present in the acute or chronic setting. Acute pericarditis is characterized by a pericardial exudative effusion in the pericardial sac. This can manifest clinically as pleuritic chest pain, tachycardia, and even cardiac tamponade. Chronic pericarditis is characterized by fibrin deposition in the pericardial space, leading to collagen deposition and pericardial fibrosis. The most severe form of chronic pericarditis is constrictive pericarditis, which typically presents 10 or more years after radiotherapy. The definitive treatment is pericardial stripping or pericardiectomy, although it is associated with poor outcomes **(34)**.

Valvular disease characterized by fibrosis and calcification is another possible consequence. The exact incidence of radiation-induced valvular disease is unclear, but one report indicated that clinically significant disease was especially likely at doses above 30 Gy. It can lead to either stenosis or regurgitation and is commonly seen in the aortic valve more than in the mitral or right heart valves. For patients with clinically significant aortic valve disease, surgical replacement has been associated with improved survival regardless of cancer status. Minimally invasive techniques, such as transcatheter aortic valve replacement and MitraClip procedures, may provide relief for patients who are poor surgical candidates **(35)**.

Confounding Factors

Older Radiotherapy Techniques

Substantial improvements in RT techniques have occurred over the last half century. Radiotherapy equipment has improved from older orthovoltage and cobalt machines to higher energy megavoltage linear accelerators, which allow for a lower integral dose to normal structures. Other improvements in RT delivery, including the use of multileaf collimators and field-in-field techniques, have allowed for enhanced control of radiation delivery**(36)**.

Improvements in imaging, dose calculations, and disease knowledge have also resulted in reduced doses. Imaging improvements ushered in the transition from 2-dimensional (2D) imaging with plain film x-rays to 3D imaging with computed tomography. Three-dimensional imaging at the time of treatment planning enhanced visualization of the entire heart. Combined with improved dose/therapy calculations using computerized modeling software, the improvements in imaging allowed physicians to measure the actual dose being received by the heart **(37)**.

The increase in clinical knowledge has resulted in decreased doses to the heart. For example, older field designs for breast cancer included coverage of the internal mammary and supraclavicular nodal regions, even for patients at low risk of nodal involvement. For lymphoma, treatment shifted from RT alone (with larger fields and higher doses) to combined modality treatment with chemotherapy and RT (smaller fields and lower doses). Better understanding of which patients benefit from additional RT doses/coverage yielded risk-adapted treatment options; only patients at risk for recurrence and cancer mortality are treated with more aggressive RT **(38)**.

With these improvements, radiation oncologists are now able to customize a treatment plan based on an individual patient's anatomy and minimize dose to the heart. There is evidence that these improvements have

resulted in reductions in cardiotoxicity. A SEER-Medicare analysis of breast cancer patients from 1973 to 1989 found that the absolute risk of left breast cardiac mortality decreased with each period, from 13% (1973–1979) to 9.5% (1980–1984) to 5.8% (1985–1989) **(39)**.

Systemic Therapy

Systemic chemotherapy also has cardiotoxic effects that may confound the effects of RT. Anthracycline chemotherapy has a prominent role in the treatment of breast cancer and is a mainstay of treatment in HL, but it has well-documented cardiotoxic effects. In an insurance database study of 16,000+ breast cancer patients, 4.6% of patients receiving anthracyclines developed heart failure at a median of 8 months compared to 4% for those not receiving anthracyclines (P = .048). The hazard ratio was 1.53 for anthracyclines; other risk factors included increased Charlson/Deyo comorbidity scores, hypertension, and valvular disease **(39).**

Almost all patients with HL receive an anthracycline-based regimen. In an analysis of nine randomized trials of more than 6,000 patients treated with anthracyclines and RT, both mean heart radiation dose and cumulative dose of anthracyclines were significant predictors of cardiovascular disease **(40)**.

Breast cancer patients include patients that express HER2. HER2-targeted therapy (eg, trastuzumab) can result in cardiac dysfunction. However, unlike with anthracyclines, cardiotoxicity for trastuzumab is not dose dependent and is often reversible with treatment discontinuation because it causes dysfunction rather than necrosis. In an insurance database study of roughly 16,000 breast cancer patients, the rate of heart failure among those treated with trastuzumab was 8.3% compared with 2.7% for those who were not treated with trastuzumab (HR 2.01, P < .001). The introduction of trastuzumab after anthracyclines has been found to further increase these risks. Since HER2-targeted therapy is a relatively new treatment option, it is unclear how the combination of trastuzumab, anthracyclines, and RT would affect the risks of heart disease **(41)**.

Pre-Existing Comorbidities

Across all malignant diagnoses, pre-existing comorbidities and cardiac risk factors have been found to independently increase the risk of heart disease. In a study of breast cancer patients from Denmark and Sweden, women with other previous circulatory diseases, diabetes, chronic obstructive pulmonary disease, tobacco use, or high body mass index had a higher rate ratio of radiation-induced heart disease (1.92). In a systematic literature review of roughly 40,000 breast cancer patients, continued smoking increased the risk of RT-related cardiac mortality compared to nonsmokers or former smokers (8% vs 1.8%, respectively) **(42)**.

In a cohort of HL survivors in the Netherlands, smoking, hypertension, diabetes, and hypercholesterolemia all increased the risk of cardiovascular disease in addition to the effects of RT and anthracyclines. A different case-control study of HL survivors found that the risk of coronary heart disease after chemoradiation was independently increased when patients had risk factors for coronary heart disease (diabetes, hypertension, hypercholesterolemia) **(43)**.

In NSCLC, both pre-existing cardiac disease and mean heart dose were associated with higher rates of cardiac events on multivariable analysis of multiple clinical trials. However, even when removing patients with pre-existing cardiac disease, increased mean heart dose remained significantly associated with grade ≥ 3 cardiac events. In a separate analysis of radiation dose-escalation trials for NSCLC, coronary artery disease was associated with increased risk of cardiac events on univariable analysis. Unfortunately, this was not examined independently on multivariable analysis **(44)**.

Radiation dose parameters

Typically, mean heart dose has been the parameter of interest when discussing RT dose to the heart. However, mean heart dose may be acting as a surrogate for radiation dose with regard to specific cardiac substructures. If the dose to specific substructures is elevated, the mean heart dose will generally also be elevated. On the other hand, it is possible that the mean dose to the entire heart may be low, but specific structures (such as the coronary vasculature) may be receiving high doses that may predispose a given patient to cardiotoxicity. For example, in a dosimetric study of 50 patients with left-sided breast cancer, there was excellent correlation between

mean heart dose and left anterior descending (LAD) artery dose. However, for every 1 Gy increase in mean heart dose, the mean LAD dose increased by 4.82 Gy, indicating that mean heart dose may potentially be serving as a surrogate for LAD dose **(45)**.

Conversely, the review by Darby et al. found that coronary artery doses were not significantly associated with the rate of ischemic heart disease events after the mean whole heart dose was taken into account. Again, this model used prototypical patient anatomy and did not account for individual patient data. It is clear that the dose to the LAD and coronary vasculature can vary from patient to patient (due to individual anatomic variation) or even from treatment to treatment for one patient (due to setup/positioning errors caused by breathing and heartbeats) **(46)**.

It is also possible that the dose delivered to different cardiac substructures may predict different types of cardiotoxicities. In a review of 125 HL patients, a whole heart model of dose outperformed a coronary artery model when all types of cardiotoxicities (including pericardial disease, conduction disorders, valvular disease, and ventricular function abnormalities) were evaluated. However, when looking at events due to ischemic cardiotoxicity, the coronary artery-based model was superior to the whole heart model **(47)**.

Clearly, further research is needed to fully elucidate the parameters most predictive of cardiac dysfunction. In the meantime, it appears reasonable to record both the dose to the whole heart as well as to specific cardiac substructures to allow for comprehensive data collection and subsequent analysis **(40)**.

Cardiovascular Effects of Radiation Therapy:

Radiation therapy is a crucial component of cancer treatment, with specific doses measured in Gray (Gy) and Sievert (Sv), units reflecting absorbed radiation and biological effectiveness. This literature review explores the clinical significance of radiation-induced cardiac toxicity (RICT), a concern both in the short and long term. The median time to diagnosis of RICT is approximately 19 years, emphasizing the need for comprehensive understanding and proactive management **(48)**.

Dose-Dependent Cardiac Impact:

The heart's susceptibility to radiation is dose-dependent, with doses exceeding 40 Gy linked to increased post-radiation mortality. Intriguingly, harmful effects are observable even at lower doses (2 Gy), suggesting an absence of a "safe" threshold for cardiac radiation. Additional risk factors, such as age at treatment, left-sided irradiation, and co-administration of certain drugs, amplify cardiovascular risks, emphasizing the complexity of RICT **(49)**.

Diverse Cardiac Manifestations:

RICT presents a diverse range of cardiac manifestations, spanning acute to delayed effects. Acute pericarditis and effusions may arise during or shortly after irradiation, while delayed pericarditis, often associated with doses >40 Gy, can progress to restrictive pericarditis and diastolic heart dysfunction. Late complications include valvular disease, myocardial damage leading to cardiomyopathy, arrhythmias, and accelerated atherosclerosis, collectively contributing to long-term cardiovascular morbidity **(50)**.

Radiation-Induced Valvular Disease and Cardiomyopathy:

Valvular disease emerges as a late complication, with fibrosis and thickening occurring asymptomatically for over 15 years. Left-sided valves are particularly susceptible, leading to stenosis, regurgitation, or a predisposition to endocarditis. The myocardium undergoes progressive damage, culminating in diffuse fibrosis and potential development of restrictive cardiomyopathy and systolic heart failure. The risk is heightened with combined radiation and certain chemotherapeutic agents **(51).**

Arrhythmias and Atherosclerosis:

Arrhythmias surface as late effects, with damage to cardiac nodes manifesting years after treatment completion. Atherosclerosis worsens due to radiation-induced inflammation, escalating the risk of coronary artery disease (CAD). The left anterior descending artery (LAD) receives particular attention, with an established

association between its dose and major adverse cardiac events (MACE). Patients with pre-existing CAD risk factors face an increased likelihood of MACE after thoracic radiation therapy **(52).**

Radiation-Induced Cardiotoxicity:

Radiation therapy, a cornerstone in cancer treatment, comes with the potential risk of inducing cardiotoxicity, a concern rooted in complex underlying pathways that impact the heart at the cellular and molecular levels. Understanding these mechanisms is crucial for devising strategies to mitigate cardiac damage associated with radiation **(53)**

Cellular and Molecular Mechanisms:

At the cellular level, ionizing radiation sets in motion a cascade of events that directly influence cardiac cells. The primary instigator is DNA damage, occurring as a result of radiation-induced ionization and the subsequent generation of reactive oxygen species (ROS). This assault on the cellular genome triggers a series of responses, including activation of stress signaling pathways and cell cycle arrest. The delicate balance between cell survival and death is disrupted, leading to cell dysfunction or demise **(54).**

Molecularly, radiation-induced damage extends beyond DNA to encompass proteins and lipids. Proteins crucial for cellular function may undergo modifications, impairing their normal activity. Lipid peroxidation, a consequence of ROS generation, further contributes to cellular dysfunction. These intricate molecular interactions form the groundwork for subsequent inflammatory processes **(55).**

Inflammatory Responses:

Radiation-induced damage serves as a potent trigger for inflammation within the cardiac tissue. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukins, are key players in this response. The immune system, recognizing cellular distress signals, mobilizes inflammatory cells to the affected area, intensifying the local inflammatory milieu **(56).**

This orchestrated immune response, while initially aimed at repairing damaged tissue, can paradoxically contribute to further harm. Prolonged inflammation may result in chronic activation of immune cells, fostering a microenvironment conducive to fibrosis **(57).**

Fibrosis:

A pivotal consequence of radiation-induced cardiotoxicity is the development of fibrosis, a process characterized by excessive deposition of extracellular matrix components. Fibrosis alters the structural integrity of the heart, compromising its ability to function optimally. Myofibroblasts, stimulated by the inflammatory cascade, play a central role in the formation of fibrotic tissue **(33)**.

The fibrotic changes in the myocardium can lead to stiffening of the cardiac muscle, impeding its ability to contract and relax effectively. In the context of radiation-induced cardiotoxicity, this fibrotic transformation is a major contributor to the development of restrictive cardiomyopathy and diastolic heart dysfunction **(58).**

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