Chapter

06

Radiation-Induced Heart Disease

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6.1. Introduction

Cardiovascular diseases are a major cause of morbidity and mortality among the general population. They account for 30% to 50% of all deaths in most developed countries.

Radiation therapy (RT) has significantly improved the disease-specific survival of patients with early-stage breast cancer, Hodgkin Lymphoma (HL), and other malignant tumors in the thoracic region. Moreover, it has also been shown to increase overall survival in breast cancer recently. Several studies observed large cohorts of cancer survivors with late cardiovascular complications and a prolonged survival after delivery of RT (alone or in combination with other techniques)[1, 2]. Similar effects were observed in other cancer survivors who received thoracic RT, but data is scarce.

Any component of the heart (pericardium, myocardium, heart valves, coronary arteries, or capillaries) can be damaged if a sufficiently high dose of radiation is administered in a large volume of the heart. Pericarditis is a typical acute manifestation of damage produced by radiation. Conversely, chronic pericardial disease, coronary artery disease, cardiomyopathy, valvular disease, and conduction abnormalities can be observed years or decades after treatment delivery. Few studies have assessed the effects of delivering specific radiation doses to the whole heart or to specific structures[3, 4].

The potential cardiotoxicity of RT motivated the development of improved RT techniques to minimize irradiation to the heart. The new techniques aim to decrease the incidence of delayed complications, but it remains to be seen whether there is still some residual risk. Because cardiac injury may appear years or decades later, prolonged follow-up is essential to detect cardiac events due to RT.

In this chapter we will review current RT treatments for breast cancer and thoracic lymphomas, as well as pediatric patients and esophageal cancer, and their impact the toxicity of the heart.

6.2. Frequency and Prevalence

A dose-dependent increase in cardiovascular damage after thoracic RT has been proven in several studies, especially in lymphoma and breast cancer. Hodgkin's disease relative risks of radiation induced heart disease (RIHD) in cancer survivors have been documented: > 6.3 for RIHD, 4.2-6.7 for ischemic heart disease, and 2.2-12.7 for cardiac death. As regards breast cancer survivors, the relative risk of radiation-related cardiotoxicity is 2-5.9 times for RIHD, 1-2.3 times for ischemic heart disease and 0.9-2 times for cardiac death. The relative risk of RIHD is proportional to time of exposure and radiation dose[5]. Subclinical abnormalities are more common, and are noted in up to 50% of patients, depending on the sensitivity of the endpoint considered and the associated comorbidities.

The estimated cumulative incidence of radiation-related cardiotoxicity is 10% to 30% by 5-10 years after RT[6]. The most common non-malignant cause of death for these groups of patients who

have received chest RT is cardiovascular disease. Exact prevalence of RIHD in not known because of available data arising from retrospective single-center studies, with old RT techniques used. Patients with previous history of CAD were excluded, and no baseline pre-RT imaging were available. Modern approaches to the delivery of more targeted and lower-dose RT will likely lead to a reduction in the frequency of cardiac complications of RT.

6.3. Pathophysiology

Damage to blood vessels seems to be the main pathophysiologic sign of most cardiotoxicity manifestations. The generation of reactive oxygen species that disrupt DNA strands may be at the origin of this injury. Secondary inflammatory changes then lead to fibrosis[7].

Histologic features of radiation-related cardiotoxicity are diffuse fibrosis in the interstitium of the myocardium with normal-looking myocytes and narrowing of capillary and arterial lumens[8]. Irregularities of endothelial cell membranes, cytoplasmic swelling, thrombosis, and rupture of the walls are also present. Endothelial dysfunction is sometimes considered as a precipitating factor in cardiac sequelae. It is probably a combination of impaired endothelial function, stimulation grow factors, and eventual fibrosis[9, 10]. Myocytes capillaries are reduced by approximately 50%, leading to myocardial cell death, ischemia, and fibrosis. The adipose tissue of the outer layer of the heart is replaced by dense collagen and fibrin, which may result in pericardial fibrosis[11].

These alterations may have various effects:
- **Coronary artery disease** (CAD). CAD is caused by the narrowing and blockage of coronary arteries. Typical events observed in atherosclerosis can also be observed in these cases, including replacement of damaged cells by myofibroblasts and deposition of platelets. Generally, lesions are consistently longer, more proximal, smoother, concentric, and tubular[12]. The distribution of arteries affected by RT reflects the dose distribution. For instance, damage to the left anterior descending artery and the right coronary artery is more commonly observed in patients receiving mediastinal RT for HL. The coronary ostium is often affected and arterial narrowing is commonly proximal[13].
- **Fibrotic changes with or without calcification may be observed in the cusp or leaflets of valves.** Left-sided changes to valves are more common than right-sided changes irrespective of the relative dose distribution of RT[14]. Incidence of valvular dysfunction has been reported during the 20 years following mediastinal RT of Hodgkin disease. In addition, valve retraction has been reported to appear at an early stage of valvular dysfunction. It causes regurgitation and valves may become significantly thickened, calcified, and stenotic later on. It was suggested that the mitral and aortic valves were affected

more than the pulmonary and tricuspid due to the existence of a higher pressure on the left side of the heart[15].
- **Myocardial fibrosis.** It can compromise cardiac compliance and lead to diastolic dysfunction[16]. Myocytes cell division relatively improves the myocardium resistant to irradiation. In spite of this, diffuse interstitial fibrosis occurs involving damage to the capillary endothelial cells. There is evidence that diastolic dysfunction is seven times more common in individuals treated with thoracic RT population than in community-control subjects. The presence of diastolic dysfunction is also associated with stress-induced ischemia, a worse prognosis, and event-free survival[17].
- **Fibrosis of conduction system cells can predispose to dysrhythmia**[18]. Studies have reported several abnormalities along the entire conduction system, including varying degrees of atrioventricular block, sick sinus syndrome, prolonged QTc, supraventricular arrhythmias, and ventricular tachycardia. Right-bundle branch block is more common than left-bundle branch block after RT. This is probably due to a higher irradiation exposure of the right ventricle in its anterior location. Some studies have reported dysfunction of the autonomic nervous system (causing persistent tachycardia), loss of circadian heart rhythm, and respiratory phasic heart rate variability after irradiation[19].
- **Acute pericardial effusions.** They are characterized by fibrous adhesions, high protein count, and an increase in serum inflammatory markers. **Chronic pericarditis** may be observed even in patients that did not experience an acute event. Fibrotic fusion and thickening of the visceral and parietal layers in the presence of a tense effusion in the free pericardial space is referred to as effusive-constrictive pericarditis and has been well-reported in radiation-treated cancer survivors[20].

6.4. Risk Factors

Various risk factors for RT-related cardiac toxicity have been identified. Among these: total radiation dose; dose per fraction; volume of heart irradiated; areas of the heart treated; left-sided tumors; anterior or left-sided chest irradiation; presence and extent of tumor in or next to the heart; lack of shieldings; and concomitant administration of cardiotoxic systemic agents (such as anthracyclines and trastuzumab). There seems to be no entirely safe minimum radiation dose and increasing doses appear to augment the effects of radiation. The risk can be observed within the first five years after RT and it may remain high for at least 20 years. Specific patient-related factors may increase the risk of radiation-related cardiotoxicity: short age at the time of treatment and presence of other risk factors for coronary heart disease (i.e., hypertension, smoking, increased body mass index, hypercholesterolemia, diabetes mellitus, pre-existing cardiovascular disease, and a positive family history). High-risk patient definition is anterior or left-sided chest irradiation with ≥ 1 risk factors for RIHD. Evidence shows large inter-individual variations

in susceptibility to treatment-related toxicity and genetic variation in susceptibility to radiation-related cardiovascular disease[21].

6.5. Challenges in Defining Volumes

Treatment Volume in Radiation Oncology

The *International Commission on Radiation Units and Measurements* (ICRU) report 62 published in 1999 shows how to design a gross tumor volume (GTV) and clinical target volume (CTV), which is expanded to create a planning target volume (PTV).

Volume Definition: several imaging studies are used to perform a three-dimensional (3D) simulation study: a computed tomography (CT) simulator, a positron emission tomography (PET) simulator or a magnetic resonance imaging (MRI) simulator. GTV (prechemotherapy or postchemotherapy) should be outlined on the simulation study.

CTV determination takes into account GTV, subclinical involvement, adjacent organs constraints, accuracy of imaging, changes in tumor volume, and spread patterns of disease. Internal target volume (ITV) is the CTV plus a margin encompassing uncertainties in position, size and shape of the CTV within the patient. This target is very relevant due to respiratory movements. Modern technology (four-dimensional CT simulation, and new linear accelerators (linacs), increase the accuracy of treatment and they help decrease the size of ITV **(Figure 6.1).**

Figure 6.1. Tangent fields irradiation (3D-CRT) for whole breast, regional nodes, and boost to tumor bed after conservative surgery

The third volume, the planning target volume (PTV), allows for uncertainties in planning or treatment delivery. It is a geometric concept designed to ensure that the RT dose is actually delivered to the CTV.

Heart Volume as Organ at Risk

RT planning must always consider critical normal tissue structures, known as organs at risk (OARs) that can be next to PTV and could suffer the effects of RT. Dose-volume histograms enable ascertaining the expected normal tissue complication probability **(Figure 6.2).**

Despite the known associations of radiation with long-term cardiac effects, no consistent dose-volume correlations have been found. This is likely due to the lack of detailed dosimetric studies with precise cardiac subregion volume delineation.

Delineation of the clinically relevant substructures of the heart is challenging because no imaging modality clearly shows these structures, and in most cases CT is used in RT treatment planning. It may be difficult to differentiate the superior heart border with the large vessels or differentiate cardiac and respiratory cycles, mostly in the craniocaudal direction[22]. Newer imaging tools, such as MRI, may be able to better identify cardiac subregions, but their application to RT planning is limited. Cardiac structures can be defined anatomically and/or based on functionality, but it is not clear which area of the heart is functionally most important for RT-induced toxicities.

A cardiac atlas has been developed and validated in improving the contours and permitting better accuracy and concordance of contours, which led to improved dose-reporting. This proposal can be used in any treatment which could potentially deliver radiation to an area of the heart. Using guidelines for heart delineation and dose-volume constraints on the heart and its subareas would be possible to have a better understanding about the causative effects of RT on cardiac mortality and morbidity, and minimizing risks[23].

6.6. Cardiotoxicity and Breast Cancer

RT is used as treatment after breast-conserving surgery, and it is also prescribed after mastectomy. The primary objective of this adjuvant RT is to reduce local recurrence in these patients through eradication of residual disease and overall survival in selective groups of patients[1, 24].

Patients should be immobilized with their ipsilateral arm abducted and externally rotated. In this position the CT treatment planning is taken to precisely delineate the target volume and risk organs (heart, lung, skin…). The beam arrangement and selection of photon or electron energies over these volumes enables administration of prescription dose to the target treatment and avoiding or minimizing normal tissue exposure **(Figure 6.3).**
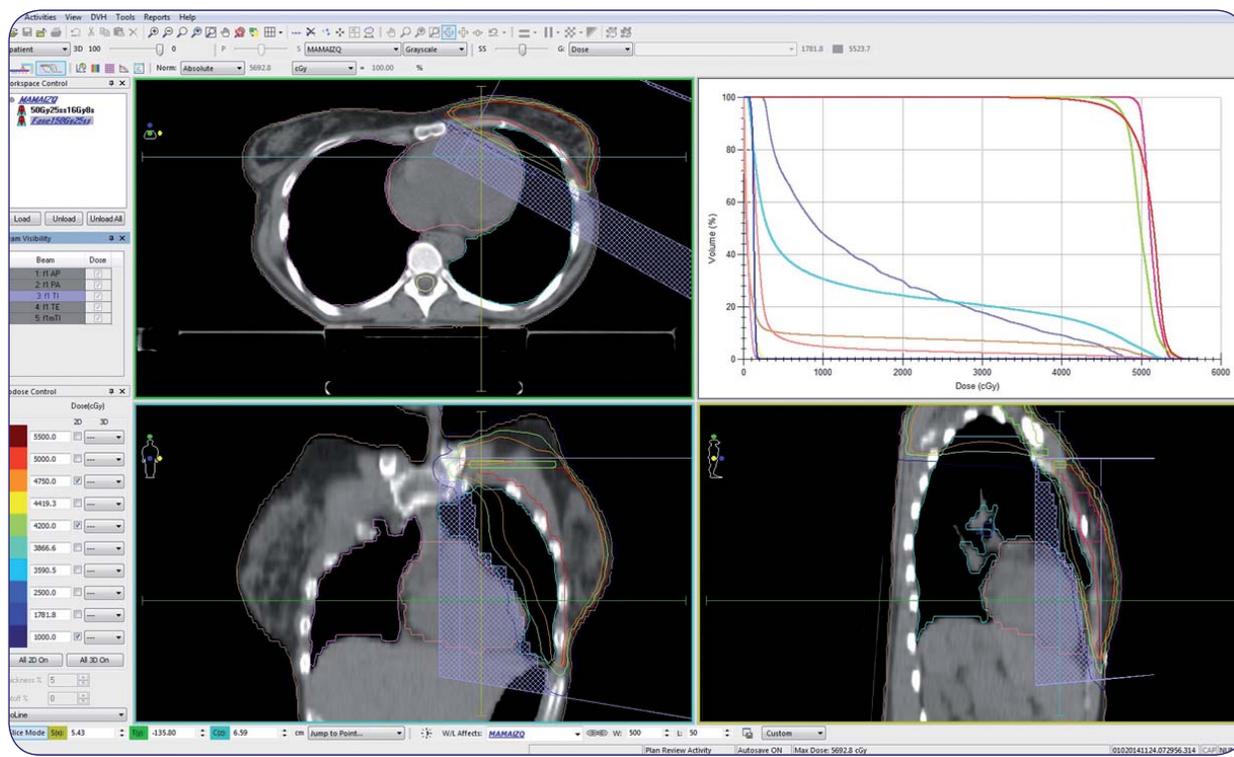
Figure 6.2. Modern linear accelerator device (high-energy X-Rays) for external beam radiation treatments
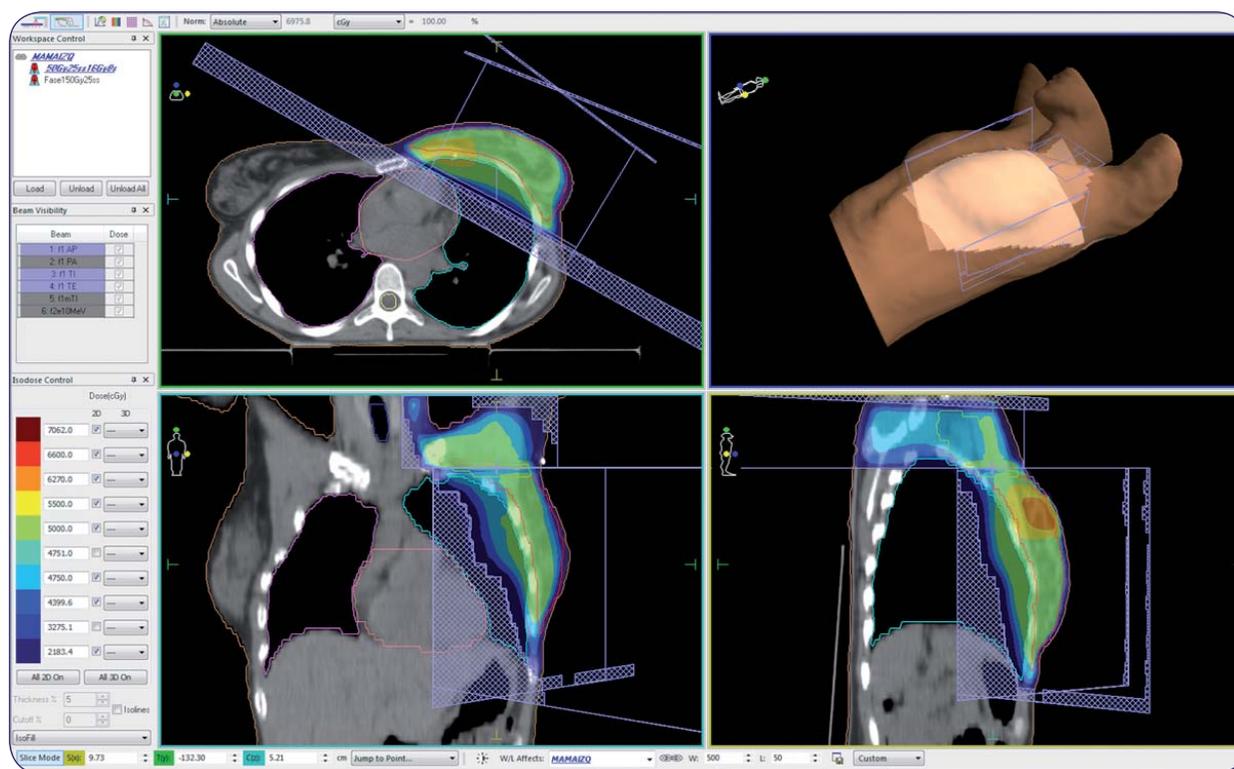

Figure 6.3. Tangent photon beams set up (3D-CRT) in supine position for whole breast and regional nodes irradiation after surgery. Dose-volume histogram evalution showing dose to target and normal structures

Treatment planning for tangential breast irradiation has shown that using CT-based conformal tangential irradiation the amount of heart and lung can be spared compared to standard tangential irradiation, with up to 50% reduction of average excess cardiac mortality risk in left-sided breast cancer patients[25].

Regarding the radiation dose and schedule for conserving treatment as well as post mastectomy, conventional treatment is delivered to the whole breast/chest wall with or without draining lymphatic nodes (axillary apex/supraclavicular fossa/internal mammary) to a total dose of 45 Gy to 50 Gy in 1.8 Gy to 2 Gy daily fractions[26].

It has long been known that RT for breast cancer may induce heart toxicity and it is still important to investigate the magnitude of the risk of cardiovascular disease after RT for breast cancer[13]. With contemporary tangential breast or chest wall RT, doses higher than 20 Gy are received to some parts of the heart in nearly half the patients.

There is a significant correlation between some parameters (cardiothoracic ratio, breast volume and distance of the inferior field border to diaphragm) and irradiated heart volume, as well as irradiation of inner-quadrant, is associated with a significant increase in cardiovascular mortality even with contemporary RT techniques[27]. Large breast size is related to a higher percentage of heart tissue receiving high doses and is the most important parameter to correlate with the maximum heart distance and the irradiated heart volume receiving 10, 20 and 40 Gy. For detection of patients which could benefit from a more sophisticated RT planning breast size and cardiothoracic ratio may be useful[28].

Risk-Increasing Factors in Breast Cancer

Several epidemiology studies have shown that radiation is an independent risk factor for death from cardiovascular disease at > 10 years after chest RT for breast cancer, but evidence suggests that the risk of RIHD may be increased by individual patient cardiac risk factors and cardiotoxic chemotherapy [13, 29, 30, 31]. Few studies have analyzed the role of baseline cardiac risk factors on the increase in RIHD many years after irradiation in patients with RT-treated early breast cancer. Then, further studies are needed to investigate the consequences of radiation exposure in this large population of patients with long life expectancy.

The impact of age is unclear, but some studies suggest that the risk of RIHD is 6.5 times higher in women irradiated for breast cancer at age 35 or younger than in the general population[31].Other studies comparing age > 60 years[32] *versus* age < 60-60 years[31] noted an association with myocardial infarct.

Smoking and RT synergistically increased fatal myocardial infarct (hazard ratio [HR] = 3.04 *versus* no smoking/no RT) in ≥ 10 years breast cancer survivors[31]. Hypertension and left-sided RT have a similar effect on causing coronary artery disease (CAD) (HR = 11.4 *versus* right-sided RT without hypertension)[33].

It seems to be that low high-density lipoprotein (HDL) cholesterol and high low-density lipoprotein (LDL) cholesterol are CAD risk factors; elevated very-low-density lipoprotein (VLDL) triglycerides also has an additional risk factor for CAD for women[34]. No studies have analyzed the relationship between low HDL cholesterol and high LDL cholesterol and RT for increasing radiation-associated heart disease.

Systemic drugs such as anthracyclines, trastuzumab, taxanes, tamoxifen, and letrozole have increased over the last few decades and these may potentiate the radiation's effects on the heart[35]. Radiation increases the risk of cardiotoxic effects of certain chemotherapeutic agents, such as anthracyclines[36]. In breast cancer, anthracycline-containing chemotherapy regimens are very common. It is known that anthracyclines without RT have a cumulative dose-dependent risk of congestive heart failure and dilated cardiomyopathy. This interaction appears to be dependent on the total cumulative dose of anthracyclines[37].

The study by Harrigan, *et al.* (*ASTRO,* 1996) analyzed patients diagnosed with breast cancer who underwent RT and doxorubicin-containing chemotherapy and concluded that radiation doses absorbed by the heart in conjunction with doxorubicin increased the risk of developing cardiac injury. Adjuvant therapy with anthracicline-containing regimen is never administered concurrently with chest wall or breast irradiation. On the other hand, previous chest RT may increase the susceptibility to anthracicline cardiotoxicity. Furthermore, an additional risk of congestive heart failure from RT in combination with non-anthracyclin chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) has been indicated (HR = 1.85 *versus* RT only) at retrospective study[31].

Trastuzumab combined with chemotherapy improves outcome in HER2-positive breast cancer. Halyard, *et al.* analyzed 1,503 irradiated patients with early breast cancer and positive receptors HER2. They concluded concurrent treatment with trastuzumab and RT does not increase the risk of cardiotoxicity. The short median follow-up time may preclude the evaluation of long-term cardiac toxicities[38].

A large phase III trial of the tamoxifen *versus* aromatase inhibitor letrozole showed increased cardiac events in the letrozole arm at a median follow-up of 26 months[39] which persisted in subgroup analysis at 51 months[40]; however, the study has not addressed the relationship between hormone therapy and RT.

Radiation Risk Factors and Heart Tolerance Dose in Breast Cancer

The effects of radiation on the heart rise with increasing doses of radiation, and there does not appear to be any minimum radia-

tion dose that is entirely safe[41]. The increased cardiac risk can be seen within the first five years and remains elevated for at least 20 years. Women with significant risk factors for a major coronary event may be at particularly increased risk.

The effect of radiation dose to the heart was evidenced in a population-based case-control study carried out by Darby, *et al.*[4] that included 2,168 women with breast cancer treated with surgery and RT from 1958 to 2001. The study included 963 women who suffered a significant coronary event following their treatment. These women were compared with 1,205 matched controls that received similar therapy but did not have a cardiac event following breast cancer treatment. RT records were reviewed and the dose of radiation to the heart estimated for all patients. The authors concluded there was increased risk of major coronary events following RT for all time periods. The estimated mean dose of radiation to the heart was 4.9 Gy; in women with a left-sided breast cancer, the dose of radiation to the heart was greater (6.6 *versus* 2.9 Gy). The risk of a coronary event increased progressively with the radiation dose, with an increase of 7.4% for each 1 Gy of radiation to the heart. Prior history of ischemic heart disease was associated with an increased risk of a cardiac event after treatment for breast cancer (ratio 6.67, $p < 0.001$), as well as other factors like diabetes, other circulatory disease, or a left-sided breast cancer (risk ratios 1.88, 3.23, and 1.32, respectively).

This study did not analyze other cardiac complications of cardiac irradiation and only a few patients received cardiotoxic systemic therapies, which might increase the risk associated with RT.

Furthermore, additional evidence comes from tumor registry studies that have analyzed the rate of heart complications in breast cancer survivors[42, 43, 44, 45, 46]. These studies have given conflicting results but suggest that there is an increase in cardiac events in women with left-sided breast tumors, because the right-sided cancers group received lower doses of radiation on the heart compared with the left-sided group. Three of the larger studies did not analyze the potential impact of heart radiation based upon the laterality of the tumor.

In one study, outcomes from 115,000 women who received adjuvant RT from 1973 to 2001 were analyzed in the *Surveillance, Epidemiology, and End Results* (SEER) Database[30]. Cardiac mortality was significantly higher in women irradiated with left-sided breast cancers between 1973 and 1982 and the difference was greater with longer follow-up (cardiac mortality ratio for left-sided *versus* right-sided cancers 1.20, 1.42, and 1.58, for < 10, 10-14, and > 15 years, respectively). However, patients treated between 1983 and 1992 did not show any statistically significant differences and none of the patients treated from 1993 onwards had 10-year follow-up. Therefore, this decrease in excess cardiac mortality may be due to improvements in RT techniques, shorter follow-up, or other unknown factors.

In a second SEER database study, 27,283 patients with breast cancer treated with adjuvant RT between 1973 and 1989 were analyzed[42]. For women diagnosed from 1973 to 1979, 15-year mortality rate from ischemic heart disease for women with left-sided was significantly higher than the right-sided cancer tumors group (13.1% *versus* 10.2%). For women diagnosed between 1980 and 1984, and between 1985 and 1989, 15-year mortality rates did not show any statistically significant differences between left-sided *versus* right-sided tumors (9.4 *versus* 8.7%, and 5.8 *versus* 5.2%, respectively). The overall incidence of death from cardiac disease decreased substantially with the later cohorts.

Another large study with a total of 4,456 women who survived at least five years after treatment of a breast cancer from 1954 to 1984 were followed up for mortality until the end of 2003, for over 28 years on average[47]. The cause of death being cardiovascular disease was observed in 421 patients, including cardiac disease in 236. Women who had received RT had a 1.76-fold (95% confidence interval [CI]: 1.34 to 2.31) higher risk of dying of cardiac disease and a 1.33-fold (95% CI: 0.99 to 1.80) higher risk of dying of vascular disease than patients who had not received RT. Women who had been treated with RT for a left-sided breast cancer had a 1.56-fold (95% CI: 1.27 to 1.90) higher excess mortality due to cardiac disease than those treated for a right-sided breast cancer. This difference may rise with increasing follow-up, even after 20 years. This study confirmed that RT, as delivered until the mid-1980's, increased the long-term risk of dying of cardiovascular diseases.

The absolute increase in risk of a major coronary event or death from ischemic heart disease is small. An interesting case-control study compared women treated with radiation for breast cancer who had a major coronary event with those did not have a coronary event[4]. The calculated risk for a 50 year-old woman with no other cardiovascular risk factors of dying of ischemic heart disease prior to age 80 years would increase from 1.9 to 2.4% if her heart received a mean dose of radiation of 3 Gy, and the risk of having one acute or more coronary event would increase from 4.5% to 5.4%. If the mean dose to the heart were 10 Gy, the risk of dying would increase from 1.9% to 3.4%, and the risk of having at least one major coronary event would increase from 4.5% to 7.7%.

Many other studies about overall morbidity and mortality frequencies confirm that the effect of radiation on the heart is small compared with the benefit potentially derived from such treatment in appropriately selected patients[31, 48, 49, 50, 51].

Radiobiology and Dosimetric Constraints in Breast Cancer

The different anatomy structures of the heart make the understanding of heart damage very difficult; therefore, limited data exist regarding the relationship of damage to particular struc-

tures and clinical presentation[52]. Delineation of the clinically relevant sub-regions of the heart on CT without contrast enhancement is imprecise; and even newer imaging tools, such as MRI are still able to identify cardiac subregions[22]. All this make it impossible to define which region is functionally most important for RT-induced toxicity. Since it is not known whether a relatively high radiation dose to a small volume or the much lower average dose to the whole heart is responsible for heart toxicity it is necessary to consider both, dose and irradiated heart volume, in 3D-treatment planning for correlating with clinical outcomes[53].

In 1991, some investigators pooled their clinical experience and information regarding partial organ tolerance doses and produced the "Emami paper" which was considered a guideline for physicians for treatment planning purposes[54]. With newer advanced techniques the heart volume included in the treatment volume has been reduced, but even with this it is possible to avoid cardiac irradiation completely, and a segment of the LAD coronary artery within the treatment volume is frequently included[55, 56, 57].

Different models are used to estimate the association between dosimetric parameters and heart complication risks, usually based on dose-volume histograms (DVHs). This one does not consider the different fraction schedules, that is a variable considered for heart damage. These simplest models estimate the risk of using metrics such as 2.5 Gy for the whole heart, mean dose or heart maximum. There are other mathematic models to predict the probability of induced cardiac toxicity, such as the Lyman-Kutcher-Burman (LKB) model[58], the normal tissue complication probability (NTCP) model, the so-called RS model (relative serial-ity model)[59, 60] and generalized equivalent uniform dose (GEUD). The Lyman model describes the probabilities of complications for uniformly irradiated whole or partial organ volumes. The RS model considers a response of an organ with a mixture of serial and parallel functional subunits.

In patients with **breast cancer** it is recommended that the irradiated heart volume be minimized to the greatest possible degree without compromising target coverage. In many cases, conformal blocking and breath-hold techniques can essentially eliminate the heart from the primary beams of radiation. If NTCP models for cardiac mortality are used, it should be considered that an NTCP value ≥ 5% could compromise the beneficial effect on survival of RT[30].

Another predictor frequently used is the maximum heart distance (MHD) which is related to the NTCP for cardiac mortality, but no association with cardiovascular disease risk has been found.

The *Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)* translates the estimates provided by Emami, *et al.* in a clinically useful manner[61]. *QUANTEC* proposed a conservative

approach, predicting that a V25 < 10% of the heart will be associated with a < 1% probability of cardiac mortality at 15 years after RT. Other parameters reported by *QUANTEC* related to acute pericarditis are: V30 < 46% and median heart dose < 26 Gy.

Even though perfusion defect as a clinical endpoint is questionable, evidence of subclinical myocardial injury has been demonstrated and might be relatively common. The irradiated volume of the left ventricle seems to be the most important predictor of a perfusion defect. Despite these efforts, many questions still remain. Normal tissue tolerance is an extremely complex issue and multifactorial in nature. There continues to be an urgent need for comprehensive and collaborative research and the dose-volume parameters defined in this chapter should only be used as a guide.

Currently, there is no evidence that successful treatment of traditional cardiac risk factors will alter the natural history of RIHD, so it is prudent to optimize patient cardiovascular risk profiles[62, 63].

Hypofractionated Breast Radiation Therapy

In British practice, and other countries influenced by the United Kingdom, there is wide-ranging experience on the hypofractionated whole breast irradiation as adjuvant treatment for breast cancer with excellent results. This translates into a reduction in total dose and the number of fractions compared to a conventional treatment, shrinking the duration of the total treatment and it's costs and increasing in convenience[64, 65, 66]. Over this past decade some randomized clinical trials have shown that shorter schedules (40-44 Gy in 15-16 fractions) for some breast cancer patients have similar results on long-term local control and overall survival compared with a conventional fractionation schedule[67, 68].

A critical concern for hypofractionated treatment has been whether exposure of the heart to a larger dose per fraction could lead to an increase in future risk for late cardiac events over the risk with standard dose, but reports available today do not suggest an increased risk in ischemic heart disease or cardiovascular mortality attributable to an increased daily dose, even if a propensity-score model balancing risk factors for cardiovascular disease between RT schedule groups is used. It is important to consider the follow-up of these trials ranges from 5 to 12 years[64, 65, 67, 69, 70].

Some authors suggests that hypofractionated RT for breast might be safer for the heart than conventional regimens[71]. In contrast, the latest guidelines issued by the *American Society for Radiation Oncology* suggest that short treatments should be avoided when the heart is in the RT field due to uncertainty regarding the potential late effects on cardiac function[72].

A longer follow-up of randomized trials to define the risk for heart adverse events due to cardiac tissue is very sensitive to radiation regardless of the fractionation used.

Radiation on Internal Mammary Lymph Nodes

The treatment of internal mammary lymph nodes (IMLN) with additional RT may improve overall survival prospects, disease-free and distant metastasis-free survival in some breast cancer patients[73]. Before 1980, IMLN irradiation was delivered using the anterior photon field or "hockey stick" technique, with a significant portion of the heart exposed to radiation treatment and the subsequent association between the uses of anterior fields and increased cardiac mortality[32].

One common method consists of using a 15º to 25º obliqued electron field over the medial chest wall and IMLN. Another version of this technique called "split-electron beam technique" uses a higher-energy electron superiorly and a lower-energy electron inferiorly, both matched to the chest wall tangents of photons.

Historically, IMLN radiation was associated with cardiac morbidity as reported in the *Early Breast Cancer Trialist Group* study[13]. RT to the IMLN increases the dose to the heart regardless of the radiation method used, and this issue should be especially considered when potentially cardiotoxic drugs are given as adjuvant treatment. Internal mammary chain RT delivers heart doses of 3 to 17 Gy for left breast treatments and 2 to 10 Gy for right-sided irradiation[74]. Nevertheless, until now linkage between current RT over IMLN and excess cardiac death or cardiotoxicity rate has been demonstrated[73].

Most evidence about cardiac toxicity associated with RT in breast cancer comes from studies based on outdated radiation technology, but recently studies have shown no significant difference in cardiac mortality between patients diagnosed after 1980 and those who received RT for left- *versus* right-sided breast cancers[30]. Several advanced techniques are available for keeping the dose to the heart considerably lower. Dosimetric studies have shown that these techniques differ in regard to cardiac dose and coverage of the IMLN, and produce a different distribution in radiation dose in individual patients[75, 76].

The fear of late cardiac toxicity as longer seems to be a relevant argument against RT to the IMLN. The exception is those patients who receive trastuzumab or other anti-HER2-targeting drugs, since they have an increased risk in cardiac toxicity and the long-term follow up in combination with RT to the IMLN is still missing.

Advanced Technology on Radiation Therapy in Breast Cancer

Most results about cardiac toxicity after breast RT are based on patients treated with techniques (2D-RT) not comparable to current standards of care and the methods for measuring cardiac dose were not standardized (based on average anatomy and not patient-specific anatomy). For this reason the impact of these findings is uncertain. Lately there has been major interest in minimizing the cardiac dose in breast cancer RT. Therefore, several techniques have been developed, particularly in left-sided breast cases, to reduce the dose to the heart[77]. These techniques vary and include:

- **Advanced radiotherapy technologies to limit cardiac dose (i.e., IMRT or proton beam radiotherapy).** Intensity-modulated radiotherapy (IMRT) is a newer method of RT based on multiple intensity levels for any single beam obtaining tighter distributions, compared with conventional RT, avoiding close proximity organs at risk and increasing tumor control through an escalated dose in the target.
  The benefits of this new technology in breast cancer over tangential RT needs further research with a longer follow-up period and provision of data on late toxicity and disease recurrence rates[78], as well as identifying which patients benefit most from IMRT[28].
  The information available nowadays about IMRT came from studies that have shown improved cardiac dosimetry with IMRT for the whole breast alone, breast and regional nodal volumes, chest wall and regional nodal volumes after mastectomy and with or without internal mammary nodes compared with 3D-CRT tangential therapy. However, these benefits are similar to those observed with breathing techniques with respect to improvements in different parameters (maximum cardiac dose and volume receiving high dose, heart volume receiving 5 Gy, mean cardiac dose and cardiac tissue complication probability) compared with conventional 3D-RT[76, 79].
  In the whole breast irradiation with IMRT, field-in field techniques have been found to be the most cardiac dose-sparing of the techniques utilized[80]. Proton beam radiotherapy (PBT) enables a reduction in dosage to the critical adjacent structures and subsequently, a reduction in acute and late toxicities through the rapid dose fall off beyond the target based on the characteristics of the proton particle. Thus, PBT reduces cardiac dose compared with 3D-CRT and IMRT[81]. However, the role of this technique is limited because of the quality of available data and its higher cost.
  But the role of this technique is limited due to poor availability and high costs.
- **Maneuvers to increase the distance between the heart and the chest wall (i.e., timing radiotherapy with the breathing cycle or prone patient positioning).** The impact of the respiratory cycle on cardiac exposure in breast cancer RT was documented using CT scans. During inspiration, the heart moves away from the chest wall decreasing radiation exposure to the cardiac volume[83]. Moderate-deep inspiration breath hold is considered the ideal point of cardiac displacement[84].
  Comparing cardiac dosimetry between free breathing and breath hold techniques in left-sided whole breast and chest wall radiation has demonstrated a significant reduction in left

ventricular dose (V20, V40 and mean cardiac dose) and left anterior descending coronary artery median dose[85, 86, 87].

There are two techniques available: **active breathing control** (ABC) where patients are simulated and treated using moderate-deep inspiration breath hold, and **respiratory gating** using chest wall sensors to trigger delivery of RT with respiratory expansion of the thorax. At this time, there is insufficient data to recommend one option over the other, but the combination of breath hold techniques with the use of intensity modulated radiation therapy (IMRT) have found further reductions in cardiac dose[88].

Prone position increases the distance of the radiation beam from the heart, especially on large and pendulous breasts, reducing cardiac doses[89].

This technique for shielding heart tissue is less proven than breathing techniques and/or IMRT. The combination with IMRT and accelerated partial breast irradiation (APBI) can be an option to improve dosimetric results in large-breasted patients.

A potential limitation of this technique is if a comprehensive breast and regional nodal irradiation is feasible and reproducible in the prone position, but maybe this problem can be improved with cone beam CT[90, 91].

- **More confined region as target (APBI or intra-operative radiotherapy).** Partial breast techniques, treating only the lumpectomy cavity and surrounding a margin, reduce the irradiated heart volume and increase the distance from the target volume to the heart compared to the whole breast irradiation delivered with other techniques like IMRT[92]. Normally, this is used in combination with hypofractionated schedules as accelerated partial breast irradiation (APBI). They can be delivered with interstitial brachytherapy or external beam techniques for early stage breast cancer achieving high dose volume away from the chest wall and heart[93].

Among different irradiation techniques, 3D-RT APBI appears to be the safest with less probability of cardiovascular events in the future[94], but this is significantly dependent on the distance between the heart and the lumpectomy cavity. Cavities more than 4 cm from the heart have a V5 Gy typically < 1%[95]. In order to reduce cardiac dose, IMRT can be incorporated into APBI.

Another partial breast technique that potentially reduces cardiac exposure is intra-operative radiation (IORT), with low maximum cardiac doses of 1 Gy[96].

While these techniques may suggest a reduction in cardiac dose, further studies are required as these techniques have limited long-term follow up with respect to clinical outcomes. In addition to this, these techniques have a very limited use, usually off protocol and based on consensus guidelines currently published.

No particular technique has demonstrated to be significantly superior to any other and multiple options can be applied depending on different factors. It is unlikely that one method will emerge as the dominant cardiac dose-sparing technique.

6.7. Cardiotoxicity and Other Thoracic Tumors

RT is the basic tenet for **other thoracic tumors** treatment like esophageal and lung carcinoma, usually in combination with chemotherapy. Little information is available about long-term cardiac toxicity in this type of tumors due to unfortunately short overall survival and follow-up to evaluate cardiac complications. Due to the proximity of the esophagus, bronchial structures and lungs to the heart, cardiac exposure is unavoidable resulting in high doses of radiation being administered to the heart and pericardium.

Radiotherapy or radiochemotherapy using high doses in this context can cause benign pericardial effusions[97] and myocardial perfusion abnormalities, but there is no available information about future cardiac events[98].

6.8. Cardiotoxicity and Hodgkin Lymphoma

RT of supradiaphragmatic lymphoma includes in most cases portions of heart. Those patients are long-term cancer survivors because of therapeutic benefits from RT, but they may be subject to late cardiotoxicity. When these patients are irradiated during childhood, the risk of cardiovascular complications increases.

Multiple studies have demonstrated a significant increase in cardiotoxicity in Hodgkin lymphoma survivors:

- **EORTC.** Mediastinal irradiation increases valvular disorders, ischemic heart disease and heart failure, and this risk can be greater with use of anthracyclines. Median time at diagnosis was 19 years after radiation treatment[99].
- **Canadian study.** Doxorrubicin combined with RT increases cardiac morbidity than mediastinal RT alone[100].

Risk of death from myocardial infarction is reported in Hodgkin lymphoma patients who were irradiated with supradiaphragmatic fields or treated with anthracyclines[101, 102, 103]. This risk persisted beyond 20 years[104, 105].

Diastolic dysfunction caused by mediastinal irradiation is reported in two studies, with worse cardiac event-free survival.

- 282 patients irradiated with a minimum of 35 Gy at the thorax; 14% developed diastolic dysfunction 18 years after[17].
- In another series, 54% of mediastinal-irradiated patients had echocardiographic evidence of left ventricular dysfunction[106]. Valvular abnormalities are also described in 43% of patients in this retrospective study.

Heidenreich PA, *et al.* have observed a 34-fold increase incidence of aortic regurgitation > grade 2 in 26% of asymptomatic Hodgkin lymphoma treated with a mean dose of 43 Gy. This risk persisted beyond > 20 years[107]. These patients need longer follow-up to detect mitral regurgitation, aortic regurgitation and aortic stenosis. Conduction defects and autonomic dysfunction because of fibrosis radiation-induced are reported years after therapy for Hodgkin lymphoma[106].

Pericarditis rarely occurs with modern doses and radiation techniques. Acute pericarditis is uncommon; however, chronic pericarditis may appear from months to years after RT. A total of 80% of cases resolve spontaneously.

Risk Factors in Hodgkin Lymphoma

The risk of cardiac damage may depend on the patient, such as age and known cardiovascular factors. They may also depend on the RT (total dose, dose per fraction, volume of radiation field, and treatment technique). The combination of mediastinal RT and anthracyclines increases cardiotoxicity by 7.9% 25 years after treatment[99].

However, risk factors modulating the acute effects of cardiac radiation are hardly known. It appears that the cumulative dose and its fractioning determine acute and chronic cardiac effects of RT. In the past, pericarditis used to be the most common side effect in patients receiving traditional RT for Hodgkin's disease[6]. Dose restriction to 30 Gy with lower daily fraction, different weighting of radiation fields, and blocking of the subcarinal region have been reported to reduce the incidence of pericarditis from 20 to 2.5% whilst, in doses > 30 Gy, the risk of RIHD becomes apparent, the nature and magnitude of lower doses is not well characterized nor is it clear whether there is a threshold dose below which there is no risk[10, 101].

Pediatric Patients

Two studies examining cardiotoxicity in patients irradiated in childhood. They exhibit increased heart failure when cardiac doses for radiation ≥ 15 Gy[108, 109]. However, modern imaging 3D-planning, new radiation technology, and combined treatment with chemotherapy have enabled decreased dose and volumes of RT.

Treatment Volume in Hodgkin Lymphoma

Over the years, nodal areas to treat have changed and, therefore, volumes have decreased:
- Involved RT field (IFRT): Clinically affected areas.
- Regional RT (RRT): IFRT + unaffected adjacent areas.
- Extended RT field (ERT): IFRT + several nodal areas (Mantle).
- Total nodal irradiation (TNI): Mantle + inverted Y.
- Total irradiation subnodal (TISN): pelvic-TNI.
- Involved nodal RT (INRT).

The current trend is to use IFRT. Data from Campbell, *et al.*[110] support further targeted field reduction from IFRT to INRT as a component of adjuvant therapy for early HD and no statistical difference in progression-free survival and overall survival at 10 years has been found.

Treatment Dose in Hodgkin Lymphoma

Until the late 1980's, the dose administered to Hodgkin's lymphoma patients was 35-45 Gy. Currently, the recommended dose is about 30 Gy (20-40 Gy), and 1,8-2 Gy per fraction **(Figure 6.4).**
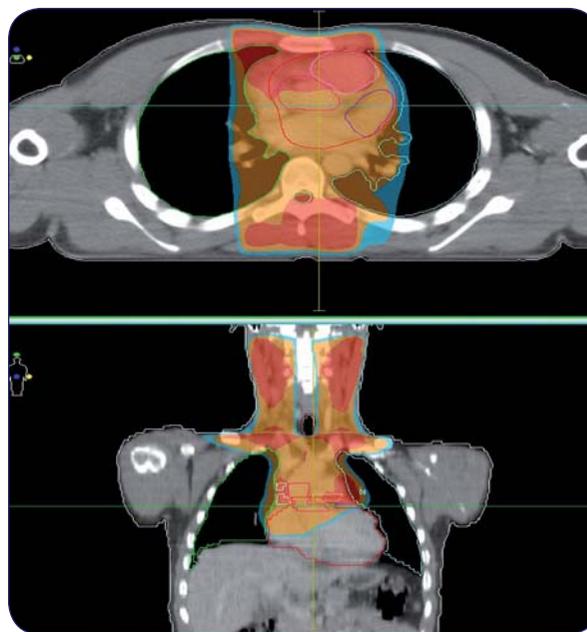

Figure 6.4. Example of dose distribution achieved with 3D-CRT (3D conformal radiotherapy)

A total of 42 to 45 Gy was the dose associated with deaths from heart disease, in the Stanford children and adolescents Hodgkin lymphoma (HL) series[101]. Aortic and mitral stenosis and regurgitation are more frequent after 30 Gy[106]. Whole heart doses above 30 Gy, increased rate of cardiac mortality. Cardiac apex dose > 12 Gy was associated with coronary artery disease. Pericarditis is observed with pericardium dose > 26 Gy and V30 > 46%, and also when a dose per fraction is > 2 Gy. It is recommended that the volume of myocardium receiving 35 Gy should be below 30% (V35 < 30%)[111].

Key Points

- The radiobiology of heart damage is not well understood due to the presence of various radiosensitive structures and their topographic heterogeneity. It still needs to be deter-

mined what part of the heart is most radiosensitive and what the heart tolerance dose is.

- It is clear that thoracic radiation, particularly administered with older treatment paradigms, increases cardiovascular related mortality in the long term. Changes in the incidence of cardiac morbidity and mortality represent the gold standard endpoints for evaluating the risk of RT-induced cardiotoxicity.

- Most studies that have not found an increased risk of cardiovascular disease were characterized by a follow-up of approximately 10 years. Increase in the frequency of cardiovascular disease is a "late effect" that may only become apparent many years or even decades after RT. Those analyses that looked at cohorts with longer follow-up have observed an increase in toxicity.

- The benefit of RT has been extensively tested in terms of local control and survival. It is useful to consider that heart constraints values should be used for guidance and they must be considered in relation to the probability of tumor control and the specific patient situations.

- Older RT techniques used to treat patients with malignancies involving the thorax clearly caused an increase in cardiovascular morbidity and mortality. Such treatment involved exposure of large volumes of the heart to high doses of radiation. Newer treatment techniques reduce both the dose of radiation and the volume of heart within the RT field and related cardiac mortality risk. The RT field and dose determine the amount of incidental irradiation to the heart. Improvements in RT technique significantly decreased the amount of incidental radiation received by the heart. These technical advances substantially reduced the incidence of cardiovascular complications compared with older studies. RT planning and treatment delivery methods that reduce both the volume and dose of incidental cardiac irradiation should be employed whenever possible, especially in left-sided breast cancer.

- When RT is appropriate in addition to systemic chemotherapy, the minimum necessary total dose of anthracycline and the lower necessary dose of RT should be administered. Particular caution is indicated when RT is used in patients who have or will receive known cardiotoxic agents, such as an anthracycline or trastuzumab.

- Because classical coronary heart disease risk factors such as smoking, elevated lipid levels and hypertension appear to increase the risk of RT-induced heart disease, efforts should be made to screen for and eliminate these factors in patients who have received cardiac irradiation; other risk factors such as hypertension, hyperlipidemia, smoking and pre-existing cardiovascular disease may increase the risk of cardiotoxicity following RT.

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