Radiation Therapy (RT) has been critical in cancer treatment regimens to date. However, it has been shown that ionizing radiation is also associated with increased risk of damage to healthy tissues. At high radiation doses, varied effects including inactivation of cells in treated tissue and associated functional impairment are seen. These range from direct damage to the heart; particularly, diffuse fibrosis of the pericardium and myocardium, adhesion of the pericardium, injury to the blood vessels and stenosis. Cardiac damage is mostly a late responding end-point, occurring anywhere between 1 and 10 years after radiation procedures. Cardiovascular disease following radiotherapy was more common with radiation treatments used before the late 1980s. Modern RT regimens with more focused radiation beams, allow tumors to be targeted more precisely and shield the heart and other healthy tissues for minimizing the radiation damage to normal cells. In this review, we discuss radiation therapeutic doses used and post-radiation damage to the heart muscle from published studies. We also emphasize the need for early detection of cardiotoxicity and the need for more cardio-protection approaches where feasible.

Keywords: radiation therapy, proton therapy, heavy ion radiotherapy, ionizing radiation cardiotoxicity, charged particle therapy, cardiovascular disease, radiation damage to the heart

INTRODUCTION

Cancer associated heart disease has become a prominent cause of mortality in the industrialized world (1). Modern treatment using radiotherapy has resulted in a dramatic improvement in the chances of cancer patient’s survival. While the high energy ionized radiation treatment successfully kill cancer cells, they at the same time harm healthy cells, leading to several side effects including increased cardiovascular disease in cancer survivors (2).

It is well known that nuclear industry workers and survivors of nuclear catastrophes have a significantly higher incidence of cardiovascular diseases than the general population (3–5). For the last couple of decades, it had been found that radio therapy (RT) increases the risk of associated radiation related cardiac damage in cancer survivors (6). However, a significant increase of death rate in the follow up after 10 year was found in patients post radiation therapy (7). Later studies also revealed that radiotherapy increased the cardiovascular mortality in women treated for left breast compared to those who are treated only to the right breast from earlier studies during 1970s and 1980s (8). Several population studies show that RT induced heart disease develops very slowly and often seen around 15 years after the first exposure to radiation (9).

Subsequent studies have focused on the risk of radiation-induced heart mortality as a linear-quadratic function at moderate dose levels (10) and at high dose levels a more linear response (11–13). However, no threshold dose studies have been reported; we therefore suggest that the radiation dose exposed to the heart must be minimized and limited as there is no such thing as safe radiation dose to the heart.
Studies to-date show that radiation-associated cardiac disease emerged from studies of breast cancer (14) and Hodgkin’s lymphoma (15, 16). There exists enough scientific evidence to now support radiation-related heart injury as a direct effect of RT to the chest (8) (Early Breast Cancer Trialists’ Collaborative Group, EBCTCG-2000). At doses above 30 Gy, heart disease may occur within a year or two of radiation exposure with concomitant increase in the risk factors for cardiovascular disease with higher radiotherapy doses. At lower doses, the latency period is longer and can extend to more than a decade (17). Cardiovascular disease as a direct side effect of radiation was more common with radiation treatment regimens used before the late 1980s. Newer radiation protocols with lower radiation doses and more focused radiation beams allow tumors to be targeted more precisely and shield the heart and other healthy tissue from direct impact of radiation. In this review we discuss radiation induced damages to the heart tissue and effectiveness of current approaches to minimize the damage.

RADIATION INDUCED CARDIAC DAMAGE

A study of radiation doses used between the 1950s and the 1990s comparing whole heart doses for left vs. right-sided breast cancer indicate that heart doses for left-sided were higher than that for the right. The dose range was shown to be 13–17 Gy for the left breast and 2–10 Gy for the right (18). Breast radiotherapy practiced in the 1970s and 1980s resulted in more exposure to the myocardium of the heart and thereby damage, which was higher when left breast was treated (Table 1). Higher cardiovascular mortality following irradiation of the left breast as opposed to the right has been attributed to this difference (19). Swedish cancer registry documents increased mortality from myocardial infarction for patients treated for Hodgkin’s disease with older clinical trials that are higher than that for the right (17). Cardiovascular disease as a direct side effect of radiation was more common with radiation treatment regimens used before the late 1980s. Newer radiation protocols with lower radiation doses and more focused radiation beams allow tumors to be targeted more precisely and shield the heart and other healthy tissue from direct impact of radiation. In this review we discuss radiation induced damages to the heart tissue and effectiveness of current approaches to minimize the damage.

RADIATION INDUCED VASCULAR CHANGES

It is well documented that RT induces vascular endothelial dysfunction, which ultimately results in clinical cardiovascular events, manifesting many years after completion of therapy (51). Radiation induced heart conditions are described in selected studies (Table 3). The linkage of senescence of endothelial cells and atherosclerosis has been well established (68). In the preclinical setting, irradiation of the heart has been associated with endothelial cell dysfunction leading to accelerated atherosclerosis (69).

A more focused study with rodent models indicate that the radiation causes microvascular damage. Microvascular damage is manifested by a decrease in capillary density, resulting in chronic myocardial ischemia and fibrosis, whereas macrovascular disease is due to an accelerated onset of age-related atherosclerosis (70). Experimental data (53) lead to formulation of two possibilities for a mechanistic explanation of increased death from coronary artery dysfunction that follows exposure to radiation. The first, being radiation increases the frequency of myocardial dysfunction by affecting the biological pathway of age-related atherosclerosis. The second that radiation reduces the heart’s tolerance to acute infarctions due to damage to the microvasculature, thereby increasing lethality. These two possible explanations may be contiguous and not necessarily exclusive acting together to produce heart disease.
TABLE 1 | Relative risk of Cardiac mortality after radiation for left vs. right breast cancer laterality at 95% Confidence Interval (CMR, Cardiac Mortality Ratio).

| Diagnosis | <10 years | 10–14 years | ≥15 years |
|-----------|-----------|-------------|-----------|
| 1973–1982 | 1.2 (1.04–1.38) | 1.42 (1.11–1.82) | 1.58 (1.29–1.95) |
| 1983–1992 | 1.04 (0.91–1.18) | 1.27 (0.99–1.63) | NA |
| 1993–2001 | 0.96 (0.82–1.12) | NA | NA |

TABLE 2 | Selected studies with significance for heart condition post radiation treatment.

| Author-year | Tissue/neoplasm | Average dose to heart (Gy) (mean, range) | Heart studies (endpoints) | Sample size |
|-------------|-----------------|----------------------------------------|---------------------------|------------|
| Cohn et al. (6) | Hodgkin’s, breast, cervix, esophagus | 1.5–9 | Pericardial effusion/Cardiac Damage | 21 |
| Brosius et al. (21) | Hodgkin’s | 3–8.8 | Thickened pericardia, interstitial myocardial fibrosis, fibrous thickening of mural and valvular endocardium | 16 |
| Applefeld and Wiernik (22) | Hodgkin’s thorax | 3–4 | Constrictive or occult constrictive pericarditis, abnormal hemodynamic response, coronary artery disease, left ventricular dysfunction | 48 |
| Orzan et al. (23) | Hodgkin’s, lymphoma, breast, seminoma | 45–122 | Aortic stenosis, regurgitation, pericardial effusion, constrictive pericarditis, mitral/tricuspid regurgitation, myocardial infarction, pericardial effusion | 15 |
| Veinot and Edwards (24) | Hodgkin’s thorax | 1.3–4 | Pericardial fibrosis, constrictive pericarditis, endocardial fibrosis, and valvular dysfunction, non-ischemic myocardial fibrosis, obstructive coronary artery disease with myocardial ischemia, damage to the great vessels and conduction system dysfunction | 27 |
| Darby et al. (12) | Breast | 4.9 (0.03–27.72) | Myocardial infarction, coronary revascularization, ischemic heart disease | 2,168 (936 cases, 1,205 control) |
| Erven et al. (25) | Breast/chest wall | 5 | Decrease in cardiac strain and strain rate | 75 |

CHARGED PARTICLE THERAPY AND HEART

Particle radiation therapy applied today uses more advanced techniques and safer approaches. About 137,518 (by 2014) patients worldwide were treated with particle therapy between 1954 and 2014, 86% of which were treated with protons and 14% with carbon ions and with other particles (71). Between 2014 and 2016, in just 2 years, the total number of patients treated with particle therapy increased by 27% or 36,994 new patients to a total of 174,512 (by 2016), about 27% increase. This includes a 37% increase in new carbon ion therapy patients from 15,736 (in 2014) to 21,580 (in 2016) by 5,844. On the other hand, proton therapy patients were increased by about 26% from 118,195 (in 2014) to 149,345 by about 31,150 patients worldwide. This is a significant increase in the total number of patients who are treated with more precise radiation treatment options. A study for the late effects of radiotoxicity to the heart from this new class of patient database after 5 and 10 years is of great importance for detailed studies and assessment. Such studies are anticipated and expected to dominate the published literature in the next few years. More details of the ion therapy data worldwide are shown in Figure 3 for protons and carbon ions and in Table 4 for all other particle therapy patients.

Adjuvant breast radiotherapy dramatically reduced radiation dose to the heart and substantially decreased the risk of death from cardiovascular heart disease (72, 73). More efficient planning with CT scanners and accurate delivery with IMRT could be ways to protect the heart and lungs from unintentional radiation (74).

Radiation treatment with x-rays and gamma particles, which emit high energy electromagnetic radiation is absorbed completely into the target tissue, resulting in an increase of radiation dose per tissue depth. Proton and heavy ions such as carbon ions which constitute charged particles, deposit minimal energy at the entrance of the body where their velocity is greater and deposit most of the energy at the end of its range (as planned and calculated for the Bragg peak) in the tumor. Charged particles therefore present a newer advancement to RT to achieve lower and more targeted dose to tumor and reduce organ at risk (OAR). Since cardiac damage is a late event, long term follow-up data to study its effects on the heart are limiting. Charged particles operate by delivering high energy more effectively than x-rays or gamma particles, therefore they have an advantage of...
exhibiting a higher control of the tumor, lower probability of damage to healthy tissue, low risk of complications and a good prognosis for a rapid recovery after therapy (75); thus it is most promising for cardio-protection than conventional radiotherapy.

Proton therapy may spare radiation exposure to the heart and reduce cardiotoxicity (18). The main benefit of proton therapy in breast cancer is to spare the heart from direct radiation exposure (76). The heart dose is dramatically reduced in proton therapy. A study on left breast cancer treatment using intensity radiotherapy and proton therapy using normal tissue probability showed that proton therapy has less radiation dose and damage to the heart (77). However, whether the cardiovascular disease is reduced in breast cancer survivors from proton therapy remains unclear. An underlying study will reveal whether proton therapy decreases radiation induced cardiovascular disease in breast cancers.

In addition to the advantage of proton therapy, carbon therapy delivers higher linear energy transfer radiation (LET). High LET radiation increases radiation sensitivity to radioresistant cancer and overcomes the oxygen enhancement ratio (OER). Carbon ion therapy has also been used to stage I breast cancer without surgery at National Institute of Radiological Science (NIRS; Chiba, Japan) (78). Significant sparing of normal tissue has been demonstrated with IMRT (Intensity-modulated radiation therapy) proton treatment (79, 80), such that the dose delivered to 90% of the cochlea was reduced from 101.2% with conventional x-rays to 33.4% for IMRT beams and 2.4% for proton beams. Dose calculations to the heart recorded a reduction from 72.2% with conventional x-rays to 29.5% with IMRT and merely 0.5% with protons (Figure 2).

### TABLE 3 | Radiation induced heart conditions for selected studies.

| Radiation study | Observed condition | Description |
|-----------------|--------------------|-------------|
| Muroos and Toole (52); Stewart et al. (53) | Arteriosclerosis | Thickening of heart wall and loss of elasticity |
| Gujral et al. (54) | Cardiac valve diseases | Heart Valve Abnormalities |
| Posner et al. (55) | Cardiac arrhythmias | Irregular Heart Rate |
| Stewart et al. (56); McChesney et al. (57) | Cardiomyopathy | Heart muscle becomes enlarged, thick or rigid |
| Wright and Bresnan (58); Ivanov et al. (59); Morris et al. (60); Smith et al. (61) | Cerebrovascular disease | Lack of oxygen to brain through blood |
| McReynolds et al. (62); Gyenes (63); Darby et al. (12) | Ischemic heart disease | Cholesterol plaque build-up in arteries, blocking flow of blood and oxygen |
| Morton et al. (64); Morton et al. (65); Brosius et al. (21); Posner et al. (63); Mill et al. (66); Stewart and Fajardo (67) | Pericarditis | Inflammation of the pericardium |

### NON RADIATION APPROACHES FOR PREVENTING DAMAGE TO THE HEART

Just as any other disease-prevention, mitigation, and treatment of radiation-induced cardiac injury also demands early detection. The sequences of events leading to cardiac damage that

![FIGURE 1](image1) Age at first radiation treatment from 15 years through 74 years are shown with calculated Absolute Excess Risk (AER) per 1,000 patients is depicted with data from Swerdlow et al. (48). Higher the age, the greater the risk with about 50% around age 45 years and almost 100% by age 65 years.
result from radiation are of several facets. To identify an early detection marker to predict risk of radiation induced cardiovascular disease is a key to prevent the late effects. Ionizing radiation induce premature aging in cultured endothelial cells (ECs) can be seen as increased apoptosis and expression of inflammatory markers (81) which \textit{in vivo} are associated with EC dysfunction and atherosclerotic plaque formation (82). It has been also reported that the biological effects of ionizing radiation exposure activate NF-$\kappa$B, and reduces anti-inflammatory gene expression, which \textit{in vivo} are pro-atherogenic conditions (83). Also, p90RSK is a unique serine/threonine kinase with two distinct functional kinase domains (84) that has been well characterized for its role in heart failure (85, 86). Perhaps, phenomena can be used as an early detection marker of radiation induced late cardiovascular diseases.

Pharmaceutical approach to prevent RT-related cardiac injury - since the endothelium of the vasculature is thought to be one target for injury induced by radiation, pharmaceutical interventions to maintain endothelial functions are one potential strategy to mitigate and treat radiation-induced cardiac damage. The pharmaceutical drug \textit{Captopril}, which is currently used to treat hypertension and congestive heart failure because of its function as angiotensin-converting enzyme (ACE) inhibitor, has been known to be able to prevent structural changes to the heart, when administered after radiation exposure (20 Gy), but there is no evidence seen in its ability to prevent the decline in cardiac function (87). However, ACE inhibitors are not evaluated for cardio protective ability with lower doses of radiation (10 Gy or lower). Similarly, the drug \textit{Simvastatin}, a lipid-lowering medication for lowering cholesterol has been observed to be capable of decreasing the radiation-associated injury to rats (88). However, critical data is lacking for understanding the ability of Simvastatin to mitigate cardiac damage following radiation (89). The plant polyphenol curcumin has been shown to have a potent anti-inflammatory and antioxidant properties (90).

Cardiac muscle toxicity can result in a concomitant loss of cardiac muscle and deterioration of the vasculature, ultimately resulting in cardiac failure. Current heart failure care can alleviate symptoms but cardiac myocytes that are killed during cancer therapies cannot be replaced or regenerated with current pharmaceuticals administered to-date. In light of the fact that most pharmaceutical interventions have not yet been demonstrated to be effective to repair cardiac damage, there arises a need for early detection of cardiac toxicity (91) and development of a new generation of therapeutics that are better able to more effectively prevent the cardiac injury caused by existing cancer therapeutics (92).

Cell based therapy to prevent RT-related cardiac injury—it has been investigated as a possible future treatment strategy for heart failure patients. Co-culturing stem cells with primary cells in \textit{vitro} followed by injecting \textit{in vivo} have demonstrated the ability of stem cells to engraft and differentiate into cells of cardiac nature. Myocytes isolated from cardiac tissue of rats have been shown as capable of inducing cardio-myogenic differentiation of endothelial progenitor cells (93, 94) and mesenchymal stem cells (95, 96). Mesenchymal stem cells injected into hearts of pig (97) or sheep (98) following myocardial infarction, have been shown to engraft long-term, express muscle-specific proteins as well as cells of vascular and smooth muscle origin (98). Despite the expression of cardiac proteins which are good indicators of cardiac differentiation, data is lacking for the stem cell’s ability for differentiating into heart cells \textit{in vivo}, alluding to the fact that merely injecting stem cells into heart may not be the best approach for cardiac muscle regeneration.

Activating stem cells residing within the heart may hold more promise as a therapeutic intervention strategy for heart regeneration. Scientific data exists for the ability of resident cardiac stem cells toward differentiating into the cardiac lineage. More specifically, the percentage of this population of dividing cardiac stem cells are shown to be increased in hearts undergoing acute infarction and those with end-stage cardiomyopathy when compared with normal cardiac tissue. Additionally, these cardiac stem cells display an increased commitment toward differentiation to the cardiac myocyte, smooth muscle and endothelial cell lineages within the infarcted and end-stage hearts as compared to hearts without abnormality or disease (99–101). Ongoing research is currently aimed at this differentiation process for understanding how to selectively increase the population of cells capable of regeneration which have highly sought after value for their functionality. Therefore, perhaps the best cell source for heart muscle regeneration is most likely the resident, cardiac stem cells if the proportion that becomes a thriving functioning heart cells could be enhanced. Further studies are needed to develop the cell based therapy specially targeted RT-induced cardiac injury.

**TABLE 4** | Total number of patients who received treatment with protons, carbon, pion, helium, and other ions around the world through 2017.

| Country   | Protons | Carbon | Pion | Helium | Other | All     |
|-----------|---------|--------|------|--------|-------|---------|
| Belgium   | 21      |        |      |        |       | 21      |
| Canada    | 196     | 367    |      |        |       | 563     |
| China     | 1,239   | 563    |      |        |       | 1,802   |
| Czech Rep.| 1,538   |        |      |        |       | 1,538   |
| England   | 3,020   |        |      |        |       | 3,020   |
| France    | 13,903  |        |      |        |       | 13,903  |
| Germany   | 8,556   | 2,870  |      |        |       | 11,426  |
| Italy     | 846     | 816    |      |        |       | 1,662   |
| Japan     | 23,842  | 17,331 |      |        |       | 41,173  |
| Poland    | 167     |        |      |        |       | 167     |
| Russia    | 7,061   |        |      |        |       | 7,061   |
| South     | 2,799   |        |      |        |       | 2,799   |
| Sweden    | 1,716   |        |      |        |       | 1,716   |
| Switzerland | 8,106 | 503    |      |        |       | 8,609   |
| Taiwan    | 439     |        |      |        |       | 439     |
| USA       | 75,896  | 230    | 2,054| 433    | 78,613|         |
| Grand total| 149,345| 21,580| 1,100| 2,054  | 433   | 174,512|

Data is adopted from PTCOG, Particle Therapy Co-Operative Group (https://www.ptcog.ch/).
FIGURE 2 | A comparison of radiation treatment via spinal axis and the estimated dose received at the heart for X-Ray, IMRT, and Proton procedures. Data is adopted from St Clair et al. (80).

FIGURE 3 | Depiction of worldwide patients treated with protons and carbon ions as of 2017 indicating largest number patients treated with protons (75,896) in the US and patients treated with carbon ions (17,331) in Japan. Data is adopted from PTOOG, Particle Therapy Co-Operative Group (https://www.ptcog.ch/).
CONCLUSIONS

From various studies reviewed for this publication, it is evident that age at first radiation exposure plays a prominent role in cardiovascular related damage. The younger the age at first treatment, the greater the protection of the heart tissue and hence the lower is the risk. On the other hand, the older the age at first treatment the risk is significantly higher and the repercussions onset at an earlier time. It is also noted that by age 45–50 years, the risk of cardiovascular related damage risk increases by about 50%. This is of significant importance for general public and further studies and assessment by sex and treated conditions are to be published at a later time. We recommend more comprehensive long-term studies to be considered and evaluated as a function of time (up to ten years and beyond), sex (M/F), and radiation dose and type administered for various target sites.

A new class of radiation treatment procedures with particle therapy will be of greater challenge ahead in the years to come. At a rapid pace, nearly 20,000 patients per year during recent five years with ion therapy (protons and carbon) pose a potential challenge of cardio toxicity studies in near future. It is essential to establish the radiation related toxicity to the heart from particle therapy; it is believed that particle therapy is a rapidly growing approach for most cancer treatment protocols around the world.

Very likely it would be desirable for oncology research to encourage both medical and scientific explorations within the cardiac care and research communities to extend their follow-up for a greater period of time to discern any unforeseen cardiac complications which at present are most likely under-reported. Nonetheless, current radiation protocols far surpass the previous regimes in providing more radioprotection to critical organs including the heart. Much of the radiation related cardiotoxicity is associated with the use of traditional radiation approaches and older methods whereas the advanced modern therapies including particle therapy might reduce the immediate cardiac damage drastically. Advanced particle radiotherapy holds the promise for moving forward toward enhancing the efficacy of tumor cell killing and lowering the risk of cardiac complications from traditional radiation treatment approaches.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American heart association. Circulation (2017) 135:e146–603. doi: 10.1161/CIR.0000000000000485
2. Abe J, Martin JE, Yeh ET. The future of onco-cardiology: we are not just side effect hunters. Circ Res. (2016) 119:896–9. doi: 10.1161/CIRCRESAHA.116.309573
3. McGeoghegan D, Binks K, Gillies M, Jones S, Whaley S. The non-cancer mortality experience of male workers at British nuclear fuels plc, 1946–2005. Int J Epidemiol. (2008) 37:506–18. doi: 10.1093/ije/dyn018
4. Wakeford R. Radiation in the workplace-a review of studies of the risks of occupational exposure to ionising radiation. J Radiol Prot. (2009) 29:A61–79. doi: 10.1088/0952-4746/29/2A/505
5. Azimzadeh O, Azizova T, Merl-Pham J, Subramanian V, Rakhi MV, Moseeva M, et al. A dose-dependent perturbation in cardiac energy metabolism is linked to radiation-induced ischemic heart disease in Mayak nuclear workers. Oncotarget (2017) 8:9067–78. doi: 10.18632/oncotarget.10424
6. Cohn KE, Stewart JR, Fajardo LF, Hancock EW. Heart disease following radiation. Medicine (1967) 46:281–98. doi: 10.1097/00005792-19670500-00003
7. Cuzick J, Stewart H, Petro R, Baum M, Fisher B, Host H, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep. (1987) 71:15–29.
8. Darby SC, McCague P, Taylor CW, Petor R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol. (2005) 6:557–65. doi: 10.1016/S1470-2241(05)70251-5
9. Roychohoudri R, Robinson D, Putcha V, Cuzick J, Darby S, Mollner H. Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. BMC Cancer (2007) 7:9. doi: 10.1186/1471-2407-7-9
10. Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ (2010) 340:b5349. doi: 10.1136/bmj.b5349
11. Bhattacharya S, Asaihthambly A. Ionizing radiation and heart risks. Semin Cell Dev Biol. (2016) 58:14–25. doi: 10.1016/j.semcdb.2016.01.045
12. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. (2013) 368:987–98. doi: 10.1056/NEJMoa1208825
13. van Nimwegen FA, Ntenta G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood (2017) 129:2257–65. doi: 10.1182/blood-2016-09-740332
14. Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, et al. A systematic review of epidemiological associations between low and moderate doses of ionizing radiation and late cardiovascular effects, and their possible mechanisms. Radiation Res. (2008) 169:99–109. doi: 10.1667/RR1070.1
15. Hancock EW. Heart disease after radiation. N Engl J Med. (1983) 308:588. doi: 10.1056/NEJM198303103081010
16. Maraldo MV, Giusti F, Vogliosi IR, Lundemann MM, van der Kaaij A, Ramadan S, et al. Cardiovascular disease after treatment for Hodgkin’s lymphoma: effects of radiation therapy on circulatory disease risk. J Vasc Interv Radiol. (2017) 28:1039–1044. doi: 10.1016/j.jvir.2016.01.004
17. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiotherapy. JAMA (2003) 289:2851–7. doi: 10.1001/jama.290.21.2831
18. Taylor CW, Nisbet A, McGale P, Darby SC. Cardiac exposures in breast cancer radiotherapy: 1950–1990s. Int J Radiat Oncol Biol Phys. (2007) 69:1484–95. doi: 10.1016/j.ijrobp.2007.05.034
19. Raghunathan D, Kylee MI, Hassan SA, Yusuf SW. Radiation-induced cardiovascular disease. Curr Atheroscler Rep. (2017) 19:22. doi: 10.1007/s11883-017-0658-x
20. Rutqvist LE, Johannson H. Mortality by laterality of the primary tumour among 55,000 breast cancer patients from the Swedish Cancer Registry. Br J Cancer (1990) 61:866–8. doi: 10.1038/bjc.1990.193
21. Brosius FC III, Waller BE, Roberts WC. Radiation heart disease: analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med. (1981) 70:519–30.
22. Applefeld MM, Wiernik PH. Cardiac disease after radiation therapy for Hodgkin's disease: analysis of 48 patients. Am J Cardiol. (1983) 51:1679–81.
23. Applefeld MM, Wiernik PH. Cardiac disease after radiation therapy for Hodgkin’s disease: analysis of 48 patients. Am J Cardiol. (1983) 51:1679–81.
24. Orzan F, Brusca A, Conte MR, Presbitero P, Figliomeni MC. Severe coronary artery disease after radiation therapy of the chest and mediastinum: clinical presentation and treatment. Br Heart J (1993) 69:496–500.
25. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. Hum Pathol. (1996) 27:76–73.
26. Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol. (2003) 45:55–75. doi: 10.1016/S1040-8428(01)00227-X
27. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, van ’t Veer MR, Baaijens MH, de Boer JP, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood (2007) 109:1878–86. doi: 10.1182/blood-2006-07-03405
28. Erven K, Jovic S, Plaggenolm P, Sweldens C, Jurgut R, Wildiers H, et al. Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys. (2013) 85:1172–8. doi: 10.1016/j.ijrobe.2012.09.022
29. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. Nat Rev Clin Oncol. (2012) 9:688–99. doi: 10.1038/nrct onc.2012.194
30. Fass D. Three-dimensional conformal radiotherapy. Sci Med. (1998) 5:6–15.
31. Erven K, Jovic S, Plaggenolm P, Sweldens C, Jurgut R, Wildiers H, et al. Acute radiation effects on cardiac function detected by strain rate imaging up to 14 months in breast cancer patients. Int J Radiat Oncol Biol Phys. (2011) 79:1444–51. doi: 10.1016/j.ijrobe.2010.01.004
32. Liem X, Chira C, Fourquet A, Campana F, Peurien D, Fournier-Bidoz P, et al. Early detection of subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys. (2011) 81:569–76. doi: 10.1016/j.ijrobe.2011.01.044
33. Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, et al. Accelerated partial breast irradiation consensus statement from the American society of breast surgeons MammoSite (R): final analysis of the American society of breast surgeons MammoSite(R) breast brachytherapy registry trial. Ann Surg Oncol. (2013) 20:3279–85. doi: 10.1245/s10434-013-3158-4
34. Remouchamps VM, Lets N, Vicini F, Sharpe MB, Kestin LL, Chen PY, et al. Initial clinical experience with moderate deep-inspiration breath hold using an active breathing control device in the treatment of patients with left-sided breast cancer using external beam radiation therapy. Int J Radiat Oncol Biol Phys. (2003) 56:704–15. doi: 10.1016/S0360-3016(03)01001-5
35. Strahl H, Zurl R, Langsenlehner T, Kapp KS. Wide tangential fields including the internal mammary lymph nodes in patients with left-sided breast cancer. Influence of respiratory-controlled radiotherapy (4D-CT) on cardiac exposure Strahlenther Onkol. (2009), 185:155–60. doi: 10.1007/s00066-009-1939-2
36. McIntosh A, Shoushtari AN, Benedict SH, Read PW, Wijesooriya K. Quantifying the reproducibility of heart position during treatment and corresponding delivered heart dose in voluntary deep inhalation breath hold for left breast cancer patients treated with external beam radiotherapy. Int J Radiat Oncol Biol Phys. (2011) 81:569–76. doi: 10.1016/j.ijrobe.2011.01.044
37. Jin X, Yi J, Zhou Y, Yan H, Han C, Xie C. Comparison of whole-breast helical tomotherapy with intensity-modulated radiotherapy in head-and-neck cancer patients: comparative analysis of dosimetric and technical parameters. Med Dosim. (2011) 35:73–44. doi: 10.1016/j.meddos.2011.08.003
38. Swanson T, Grills IS, Ye H, Entwistle A, Teahan M, Letts N, et al. Six-year experience routinely using moderate deep inspiration breath hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. Am J Clin Oncol. (2013) 36:24–30. doi: 10.1097/COC.0b013e3182382fe481
39. Cheng Y-J, Nie X-Y, Ji C-C, Lin X-X, Liu L-J, Chen X-M, et al. Long-term cardiovascular risk after radiotherapy in women with breast cancer. J Am Heart Assoc. (2017) 6:e005633. doi: 10.1161/JAHA.117.005633
40. Wondergem J, Strootman EG, Frolich M, Leer JW, Noordijk EM. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque in the dog. Ann ICRP. (2003) 45:55–75.
41. Posner MR, Cohen GI, Skarin AT. Pericardial disease in patients with cancer: a collaborative British cohort study. J Natl Cancer Inst. (2007) 99:206–14. doi: 10.1093/jnci/djk029
42. Bresnan MJ, Leong PS, Leong PS, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque in the dog. Ann ICRP. (2003) 45:55–75.
43. Costi L, Fogliata A, Bolsi A, Nicolini G, Bernardi J. Three-dimensional conformal vs. intensity-modulated radiotherapy in head-and-neck cancer patients: comparative analysis of dosimetric and technical parameters. Int J Radiat Oncol Biol Phys. (2004) 58:617–24. doi: 10.1016/j.ijrobe.2003.09.059
44. Dhillon D, Pathak A, Franck D, Latorzeff I, Jimenez G, Fondard O, et al. Early detection and prediction of cardiotoxicity after radiation therapy for breast cancer: the BACCARAT prospective cohort study. Radiat Oncol. (2016) 11:54. doi: 10.1186/s13014-016-0627-5
45. Wondergem J, Strootman EG, Frolich M, Leer JW, Noordijk EM. Radiation-induced cerebrovascular disease in children. J Med Imaging Radiat Oncol. (2012) 56:464–72. doi: 10.1111/j.1754-9485.2012.02405.x
46. Rutqvist LE, Johannson H. Mortality by laterality of the primary tumour among 55,000 breast cancer patients from the Swedish Cancer Registry. Br J Cancer (1990) 61:866–8. doi: 10.1038/bjc.1990.193
99. Urbanek K, Torella D, Sheikh F, De Angelis A, Nurzynska D, Silvestri F, et al. Myocardial regeneration by activation of multipotent cardiac stem cells in ischemic heart failure. Proc Natl Acad Sci USA. (2005) 102:8692–7. doi: 10.1073/pnas.0500169102

100. Crile, G. Jr. Results of simple mastectomy without irradiation in the treatment of operative stage I cancer of the breast. Ann Surg. (1968) 168:330–6. doi: 10.1097/00000658-196809000-00003

101. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med. (1985) 312:674–81. doi: 10.1056/NEJM198503143121102

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