Introduction to the Cardiac Implications of Radiotherapy

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Since shortly after Wilhelm Roentgen's discovery of the X-ray in 1895 [1], ionizing radiation has been used to treat a variety of benign and malignant conditions alike. Early applications of X-rays were limited to superficial cutaneous lesions due to the underperformance of poorly penetrating low-energy beams at significant tissue depth. The discovery of naturally occurring isotopes [2] and the later development of the linear accelerator [3] allowed for more energetic penetrating photons to treat deeply seated lesions such as the visceral or brain tumors that today are routinely ablated in non-invasive fashion. With the development of high-energy beams, however, emerged a concurrent need to protect critical deep structures that might now be at risk of radiation injury.

Although contemporary radiotherapy is largely delivered using high-energy photons (i.e., X-rays and gamma rays), the physical properties of particle-based beams are routinely exploited for their dosimetric advantages. To illustrate, X-rays deposit energy along a beam path that gradually dissipates while traversing the patient, typically yielding an "exit dose" beyond the target tumor that exposes distal tissues. Protons, conversely, by virtue of having mass and charge, maximally interact with tissue at an energetically predetermined depth (the "Bragg peak"), fully depositing energy at a given depth and sparing the tissues beyond (Fig. 22.1). This fundamental property of proton-based techniques is often exploited to limit normal-tissue toxicity, as in the treatment of pediatric central nervous system malignancies where the ability to spare adjacent developing brain structures preserves cognitive function [4, 5]. Aside from photons and protons, other particle beams including electrons, neutrons, and carbon ions, among other investigational approaches, are also in use.

The central challenge of radiotherapy, as alluded to above, is striking a balance between sufficient tumor dose and adequate sparing of adjacent non-target tissues. This principle is perhaps best illustrated by the history of breast and thoracic radiation. Prior to the advent of effective systemic therapies for breast cancer, disease control was exceedingly poor and adjuvant (i.e. post-operative) radiotherapy was broadly employed following mastectomy. These early efforts typically treated the regional lymph node basins comprehensively (including the internal mammary nodes) yet lacked three-dimensional thoracic imaging or techniques that might allow for cardiac avoidance, as is standard today. Consequently, long-term follow-up of these early patients demonstrated an excess of deaths among those receiving post-mastectomy radiation, suggesting that radiotherapy was partly contributing to a reduction in survival [6]. Focused analyses from that era have variably identified the causes of excess mortality among those receiving radiation as acute myocardial infarction [7] or "cardiovascular disease" more generally, prompting modifications to field design and a reconsideration of the appropriate risk–benefit considerations [8].

Cardiotoxic sequelae were similarly observed, if more dramatically, among patients with Hodgkin lymphoma who relied extensively on nodal irradiation prior to the advent of contemporary systemic regimens [9]. Often young at the time of radiation, these patients sustained elevated cardiac doses from wholesale treatment of the mediastinal lymph nodes and were broadly reported to exhibit an increased risk of valvular disease, atherosclerosis, and cardiomyopathies [10–13].

As evidence for the cardiac implications of radiotherapy mounted, a seminal study conducted by Darby et al. yielded what has now become a landmark finding [14]. In a population-based case–control study among 2168 women who underwent breast cancer radiotherapy, rates of major coronary events appeared to increase linearly with mean

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R. M. Steingart et al. (eds.), *Atlas of Imaging in Cardio-Oncology*,
https://doi.org/10.1007/978-3-030-70998-3_22

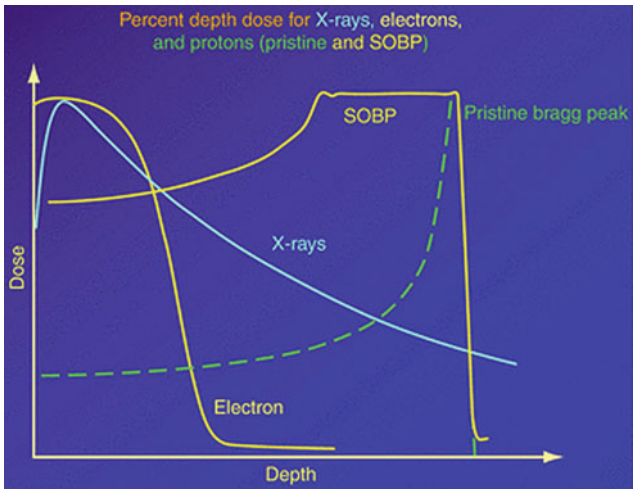

Fig. 22.1 Percent depth dose for X-Rays, electrons, and protons (Pristine peak and spread-out Bragg peak—SOBP). (From Hasson et al. [23]; with permission from Springer Nature.)

heart dose by 7.4% per gray (95% CI 2.9 to 14.5). Whereas mean heart doses in this outdated cohort ranged significantly higher than currently allowable limits, the report was particularly notable for demonstrating that there is no lower bound below which radiation ceases to influence cardiac risk. Mindful of these findings, contemporary practice has significantly mitigated heart dose and concomitant cardiovascular risk as discussed below.

To revisit the utility of adjuvant breast radiation since the early days when cardiac avoidance was not practicable, a series of landmark trials recently evaluated the benefits of comprehensive adjuvant radiation for breast cancer in the context of contemporary planning techniques and a nuanced appreciation for cardiac risk. The MA.20 [15] and EORTC 22922 [16] trials randomized patients to receive regional nodal irradiation following lumpectomy or mastectomy and, in contrast to the historical findings above, both trials observed a 3–5% disease-free survival benefit to treating the regional lymph nodes among appropriate breast cancer patients. Notably, despite treating the internal mammary nodes in both studies, the rate of cardiac adverse events was exceedingly rare (0.9% on MA.20) and was not significantly different in either study between those receiving radiation or not.

Thoracic radiotherapy for lung cancer has also been illustrative of the cardiac implications of radiotherapy. In the seminal RTOG 0617 trial of dose-escalation for unresectable stage III non-small-cell lung cancer (NSCLC), investigators evaluated whether a radiation dose of 74 Gy could improve disease control as compared to the prevailing 60 Gy standard dose [17]. To the surprise of many, the study revealed that the investigational 74 Gy conferred a potential decrement in survival, counter to the trial hypothesis and opposing the otherwise notable trends of improved disease control with higher doses in NSCLC. Much has since been written about this failure of dose-escalation, with many positing that higher doses do effect improved tumor control, but that an excess of mortality arises from the concomitant cardiopulmonary effects of radiation [18, 19].

Several studies have attempted to elucidate the underlying pathophysiology of radiation induced cardiac disease. In an autopsy series that included 27 cases [20], Veinot and Edwards identified pericardial injury in 70%, with effusion and tamponade in a subset. Similarly, radiation-associated valvular disease was identified in 71% of patients (mean dose 46 Gy), with 25 examined valves (8 aortic, 9 mitral, 5 tricuspid, and 3 pulmonary) all showing diffuse cusp or leaflet fibrosis without evidence of post-inflammatory change such as chronic inflammation or neovascularization, suggesting an alternate pathway to fibrotic injury from radiation. Perhaps most notably, 16 subjects had evaluable myocardium with 10 (63%) harboring interstitial fibrosis attributable to radiation injury, while 13 had evaluable coronary arteries with 2 young men (26 and 44 years old) showing significant narrowing via atherosclerosis or fibrointimal thickening attributable to radiation damage. Coronary disease in these two subjects was noted to be "disproportionately severe" in light of their non-radiation risk factors. Thus, radiation induced heart disease putatively affects every cardiac substructure, and subsequent studies have suggested that tissue fibrosis represents the unifying etiologic pathway [21].

Indeed, the implications of cardiac radiation exposure have now set the stage for a burgeoning industry of cardiac avoidance devices and techniques that are commonly used in clinical practice. Among these are prone immobilizers for breast cancer, allowing patients to be treated in the prone position as gravity is used to displace the target breast tissue away from the underlying heart (Fig. 22.2). The respiratory cycle can also be exploited to optimize cardiac positioning away from a nearby target. This approach uses respiratory gating, or the Deep-Inspiration Breath-Hold (DIBH) technique, whereby breathing is monitored via imaging or spirometry and radiation is delivered only during the most favorable anatomic phase of the respiratory cycle (Fig. 22.3). In breast radiotherapy, for example, treatment is often delivered during end-inspiration when the lungs are maximally inflated and the heart is displaced postero-inferiorly relative to the target internal mammary nodes which may otherwise be mere millimeters from the right ventricle during end exhalation (Fig. 22.4). These techniques, along with advanced planning modalities such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc radiotherapy (VMAT) (Fig. 22.5), are routinely brought to bear in mitigating the cardiac and normal-tissue effects of radiation.

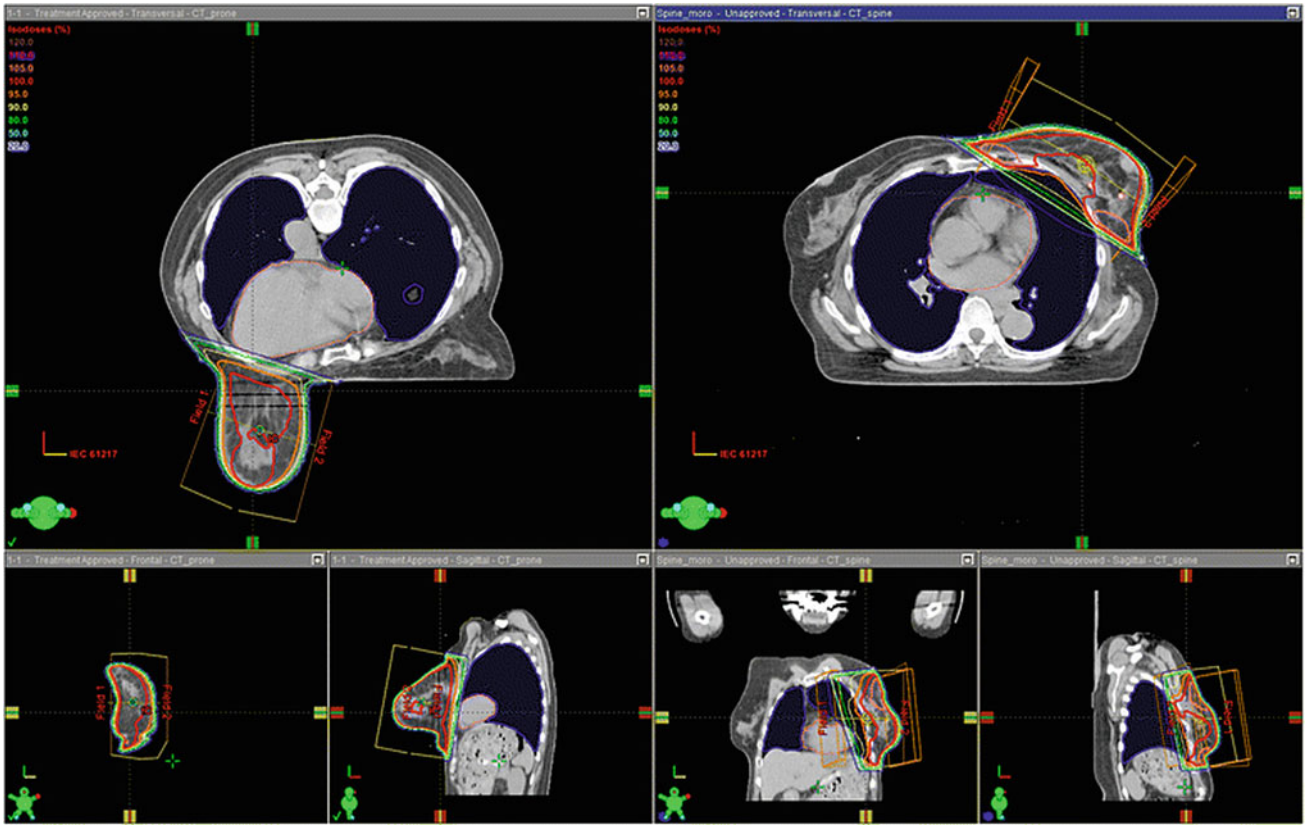

Fig. 22.2 Prone breast radiotherapy [22]. Typical dose distributions of a patients with a pendulous breast. For each patient, opposing tangential fields were set up to irradiate planning target volume in both supine and prone positions. (From Takahashi et al. [22]; Creative Commons Attribution 4.0 International License, https://creativecommons.org/licenses/by/4.0.)

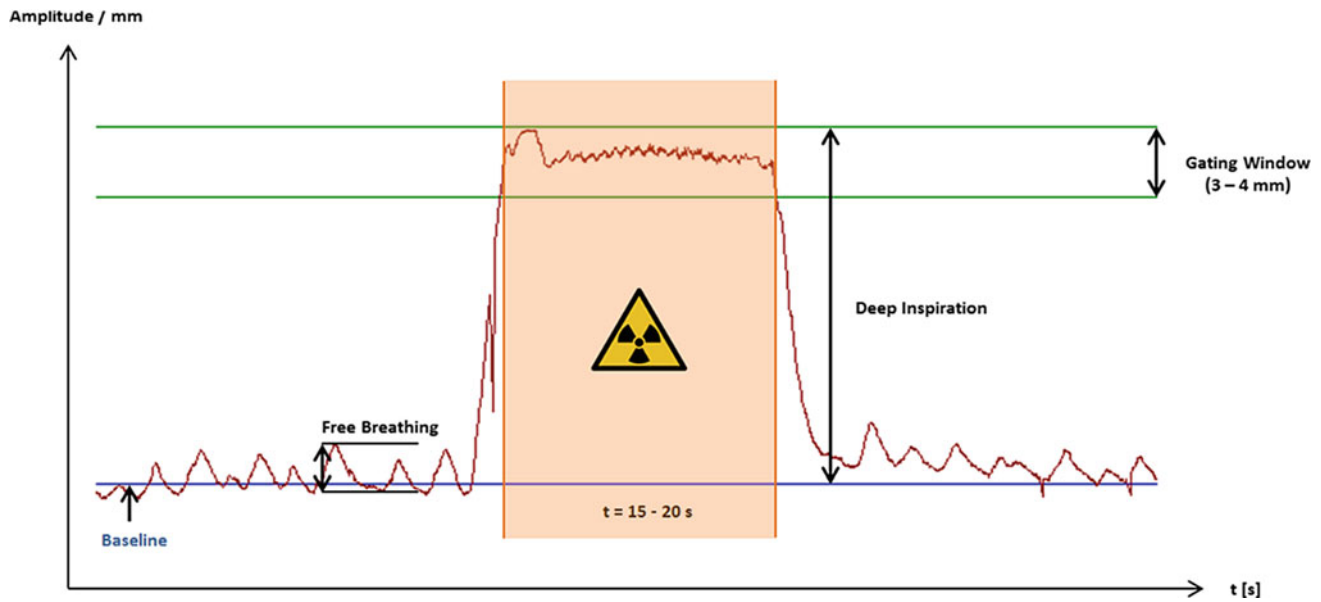

Fig. 22.3 Respiratory gating. The respiratory cycle is monitored using surface imaging and radiation is delivered during either deep-inspiration breath-hold (as below) or, alternatively, during any desired portion of the respiratory cycle. The beam can be automatically activated and deactivated as the surface anatomy enters or exists the specified "gating window" that corresponds to the desired respiratory phase. (From Schönecker et al. [24]; Creative Commons Attribution 4.0 International License, https://creativecommons.org/licenses/by/4.0.)

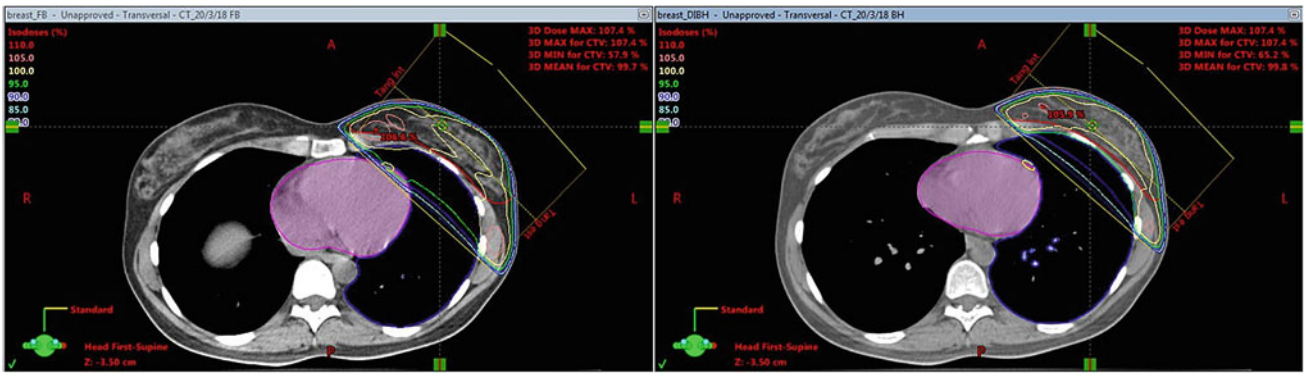

Fig. 22.4 Typical dose distributions from a free-breathing plan (left) and a deep-inspiration breath-hold (DIBH) plan (right). Note that neither the heart (magenta) nor the left anterior descending artery (yellow) is within the radiation fields in the DIBH plan. (From Aiello et al. [25]; with permission from Springer Nature.)

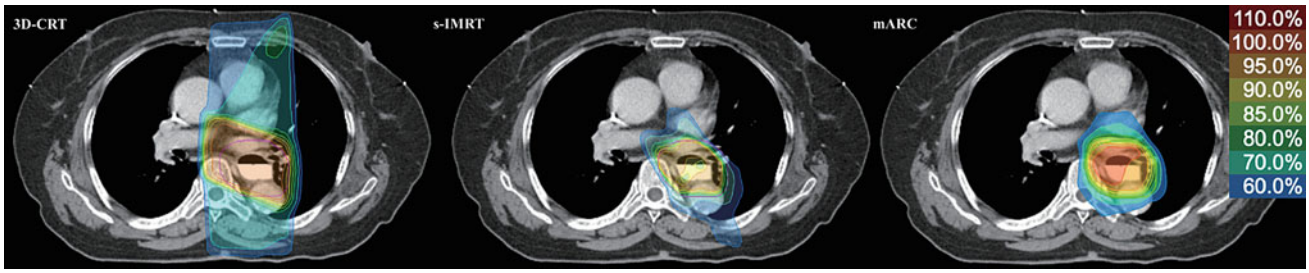

Fig. 22.5 Comparison of 3D, IMRT, and VMAT for the radiotherapeutic targeting of esophageal cancer. Note the extent of radiotherapy dose to adjacent structures in the 3D plan (using anterior and posterior beams) in comparison to the VMAT (mARC) plan using a modulated arc of radiotherapy. (From Choi et al. [26]; Creative Commons Attribution 4.0 International License, https://creativecommons.org/licenses/by/4.0.)

Thus, while there is no tumor that cannot be controlled with a sufficiently high dose of radiation, the countervailing sensitivity of adjacent structures may limit the feasibility of delivering an adequately ablative dose. The heart represents one such limiting organ, with potential for radiation injury to each cardiac substructure. As a result, contemporary radiation approaches employ combinations of advanced particle beams, novel beam shaping techniques, and patient positioning to limit cardiac toxicity while precisely targeting thoracic-based malignancies including tumors of the breast, lung, and mediastinum. Meanwhile, substantial efforts are underway to optimize prophylactic and therapeutic approaches to mitigate radiation-associated cardiac injury, and to prolonging survival via oncologic and cardiac approaches alike.

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