Breast cancer represents one of the most common non-cutaneous malignancies among women with over 1.4 million cases diagnosed annually worldwide [1]. Due to improvements in surgical techniques, systemic therapy options, and radiation therapy, long-term cause-specific survival has improved significantly over the past few decades [2,3]. With the increasing use of radiotherapy and the larger number of women surviving for many years after treatment, more patients are at risk of developing chronic toxicities associated with their care. While some of these toxicities may be minor, chronic toxicities including arm edema and/or shoulder dysfunction can alter quality of life while toxicities to the heart carry the potential for reduced survival [4]. Cardiac toxicity following radiotherapy can manifest itself as arrhythmias, pericarditis, congestive heart disease, ischemic heart disease (myocardial infarctions), or valvular disease with the pathogenesis of these entities suggested to be fibrosis/damage of the AV node and conduction system, inflammation, fibrosis, accelerated atherosclerosis, and fibrosis respectively [5,6].

A recent study by Darby et al., used a population-based case-control model to look at major coronary events and ischemic cardiac deaths following breast cancer radiotherapy in a cohort of 2158 women. The study reported that major coronary events increased linearly with the mean dose delivered to the heart (7.4%/Gy). This increase began within 5 years of treatment regardless of existing cardiac risk factors [7]. While hypothesis generating, the impact of these findings is uncertain since patients analyzed were treated beginning in the 1950s (radiation techniques at that time are not comparable to current standards of care) and since techniques for measuring cardiac dose were not standardized. The methodology for calculating cardiac dose at that time was based on average anatomy and not patient specific anatomy, and required simply superimposing radiation therapy isodose lines over average anatomy. Although the study’s findings are not practice changing in scope, they are thought provoking and suggest that increased efforts to minimize cardiac dose in breast cancer radiotherapy may be beneficial to patients.
Similarly, meta-analyses have found an increase in cardiac deaths following breast radiotherapy associated with the volume of the heart receiving 5 Gy [8]. In recognition of this, several techniques have been developed, particularly in left sided breast cases, to reduce dose to the heart. These techniques vary and include (1) maneuvers to increase the distance between the heart and the chest wall (i.e., timing radiotherapy with the breathing cycle or prone patient positioning) (2) using more sophisticated, advanced technologies in the delivery of radiotherapy (i.e., IMRT, or proton beam radiotherapy) to limit cardiac dose and (3) changing the traditional target of the whole breast to a more confined region (accelerated partial breast irradiation or intraoperative radiotherapy). Therefore, the purpose of this analysis is to provide an updated review of contemporary techniques available for cardiac protection/avoidance in breast cancer radiotherapy.

Methods

This analysis was conducted to comprehensively review frequently utilized cardiac dose sparing techniques for breast cancer radiotherapy. No formalized literature review protocol was created or followed. Eligibility criteria for this review included published studies in the English language evaluating patients with breast cancer between the years 2000 and 2013 with an assessment of cardiac protecting techniques. For studies addressing dosimetric endpoints, mandatory information included the number of patients, techniques utilized, and outcomes. For clinical studies, required information included the number of patients reviewed, radiation techniques employed, whether there was a comparison arm, and clinical outcomes (recurrence, toxicities, and cardiac outcomes). Due to heterogeneity among studies, cardiac sparing was evaluated through three different mechanisms: (1) Anatomic data (i.e., distance to heart, volume of heart in field), (2) Cardiac dose volume histogram data (V<sub>0.5</sub>, mean, maximum cardiac doses), and (3) Normal tissue complication probability. A 13 year interval of publication was chosen in order to focus on more recent literature which included modern techniques though older studies that provided background for techniques were included. Sources of information for the review included Medline/PubMed, those found in references from the major articles identified, and articles known to the authors. The PubMed search was conducted by a single author (C.S.) to identify any and all articles addressing cardiac protecting radiation techniques with the following MeSH headings: breast, heart, cardiac, radiation therapy, intensity modulated, prone, partial breast, breath hold, gating, and intraoperative. When multiple updates from a single institution were available, the most recent publication was utilized. All searches were completed by November 1, 2013.

Based on the initial searches, a total of 352 articles were identified including: 12 articles that were known to the authors and 340 identified from the literature search. Each of the eligible studies were evaluated independently by a single author (C.S.) with data from selected studies extracted including the type of study (prospective vs. retrospective), institution, number of patients, follow-up, radiation therapy technique, and outcomes. Studies were excluded due to poorly defined technique, or outcomes presented that were not within the scope of the review. Of the 46 studies identified for breath hold/gating, 25 were found to have sufficient data for inclusion. Of the 38 articles identified for the prone technique, 19 were found to have sufficient data for inclusion. Of the 174 studies identified for intensity modulated radiation therapy (IMRT), 33 were found to have sufficient data for inclusion. Thirty-nine studies evaluating proton beam therapy were identified and 9 with sufficient and relevant data were included. With regard to partial breast irradiation 108 articles were identified and 30 had sufficient data to be included.

Results

Multiple cardiac dose protection and/or avoidance techniques were identified in the search. However, only six key techniques were consistently utilized and studied and represent the focus of this review: These techniques include: (1) timing the delivery of radiotherapy with the breathing cycle, (2) prone patient positioning, (3) intensity modulated radiation therapy (IMRT), (4) proton beam radiotherapy (PBT), and (5) partial breast irradiation techniques including accelerated partial breast irradiation (APBI) and single-fraction, intra-operative radiation (IORT). Table 1 presents a summary of each technique and Table 2 the data supporting each technique and key dosimetric findings.

Timing of radiotherapy with the breathing cycle

The impact of the respiratory cycle on cardiac exposure in breast cancer radiotherapy was documented over two decades ago. Using CT scans, several studies demonstrated that with inspiration, cardiac volumes exposed to radiation are reduced as the heart typically moves away from the chest wall [9–12]. Subsequent studies confirmed that moderate-deep inspiration breath hold (MDiBH) represents the ideal point of cardiac displacement [10–12]. Initial clinical experience with the technique on 5 patients demonstrated feasibility and reproducibility of this approach with an average of 2.5 deep breaths per treatment being typically required and a treatment time of 18.2 min [13].

With the development of more reproducible techniques, additional studies compared cardiac dosimetry between free breathing and breath hold techniques in left sided breast cancer cases. A series from Denmark confirmed a reduction in the cardiac V<sub>50</sub>, of 80–90% with deep inspiration breath hold and a reduction in the left anterior descending coronary artery median dose. Also, a cardiac MRI analysis from the group at William Beaumont Hospital demonstrated significant reductions in left ventricular dose with active breathing control (ABC), which was confirmed by subsequent series [14–23]. The largest study of 319 patients confirmed these findings with reductions in cardiac V<sub>20Gy</sub> and V<sub>40Gy</sub> along with a reduction in mean cardiac dose [24]. These results have also been reproduced in the post-mastectomy setting even with the incorporation of treatment of the regional lymphatics [20,25–27].

Two techniques were identified that are commonly utilized for breathing cycle management. The first is the ABC technique where patients are simulated and subsequently treated using MDiBH. A recent randomized trial comparing the ABC technique with voluntary breath hold found no difference in cardiac or left anterior descending artery doses, though the study included only 23 patients [28]. A related technique uses respiratory gating with chest wall sensors to trigger delivery of radiation therapy based on respiratory expansion of the thorax [25]. Prospective data have demonstrated the comparability of this technique to MDiBH and with 233 patients treated, consistent reductions in cardiac dose metrics have been noted [19]. At this time, there are insufficient data to recommend one breathing cycle management technique over others; however, the data do demonstrate that a moderately deep breath hold is the key to achieving the greatest cardiac sparing.

Breath hold and respiratory gating techniques are estimated to reduce cardiac mortality by 4.7% compared with free breathing techniques in left sided patients with a median cardiac mortality normal tissue complication probability (NTCP) of 0.1% [14]. Recent studies have looked at combining breath hold techniques with the use of IMRT and have found further reductions in cardiac dose (V<sub>20Gy</sub> to the heart and LAD) when both are applied [29]. An additional comparison of 3D conformal radiotherapy with breath hold versus free breathing IMRT found significant reductions in all

Cardiac sparing techniques in breast RT

November 1, 2013.
Summary of studies on cardiac protection.

<table>
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<tr>
<th>Technique</th>
<th>Cardiac sparing mechanism</th>
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<tr>
<td>Breath hold Prone position</td>
<td>With inspiration, distance from chest wall to the heart increases Breast falls away from chest wall Increases distance from the heart to RT beam</td>
<td>(1) Decreased cardiac volume in field [9–11,18,20–23,30] (2) Reduced mean, maximum, ( V_{5Gy}, V_{10Gy}, V_{15Gy} )</td>
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<td>Intensity modulated radiation therapy Proton beam irradiation Accelerated partial breast irradiation Intraoperative radiotherapy</td>
<td>Computerized leaves and dose planning algorithms allows for shaping of radiation field to limit cardiac dose Utilizes difference in properties of protons compared with photons to allow for reduced dose fall off Smaller target volume allows for possible decreased dose to the heart</td>
<td>(3) Reduced left anterior descending dose [17,25,27,29–30] (4) Reduced cardiac mortality probability (4.8% vs. 0.1%) [14]</td>
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**Abbreviations:** RT = radiation therapy.

**Prone patient positioning**

The prone positioning technique was developed for patients with large, pendulous breasts to allow the breast to fall away from the chest wall. This provides the opportunity for the edge of the radiation beam to be positioned further away from the heart (i.e., increasing the distance from the heart) and potentially reducing cardiac dose [31,32]. An analysis of 100 patients (53 with left-sided cancers) comparing prone versus supine treatment from New York...
University found that prone positioning reduced the in-field heart volume by 12 cc in 90% of patients [33]. However, it should be noted that this is not a consistent finding [34]. For example, a recent comparison of prone and supine whole breast irradiation (WBI) found that while the prone technique reduced cardiac dose in 19 of 30 patients, it actually increased cardiac dose in 8 of 30 patients [35]. Similarly, a planning study of 18 patients found no significant difference in heart sparing between the prone and supine positions with the utilization of IMRT [36]. A subset analysis in this study demonstrated a benefit to the prone position in those patients with large breast volumes, while no benefit or a decrement was noted for prone positioning in those with smaller breast volumes, which was confirmed by several other series [37–40]. A recent dosimetric study attempting to quantify the benefit in subsets of breast volumes found no improvement in cardiac V<sub>50</sub> in all breast volumes including large breasts (>700 cc) [41]. Although there have been imaging studies suggesting a potential increase in cardiac dose with prone techniques when including the chest wall, this has not been validated by recent dosimetric studies [32–34].

One concern regarding the prone technique is the reproducibility of the technique and potential for increased dose to normal tissues including the heart based on poor set up [42]. However, recent data have shown that the technique is reproducible and can be improved with cone beam CT [43]. While daily CBCT could increase the cardiac dose, algorithms have been analyzed to minimize the dose to 5–6 mGy per scan though no data could be found on the implications of such doses on cardiac outcomes [44].

While initial research suggested a potential for increased dermatitis with the prone technique, more recent data have confirmed a reduction in lung dose with the technique and clinical and cosmetic outcomes equivalent or superior to traditional supine techniques [45–47]. A Phase I/II study from New York University demonstrated the feasibility, low rates of acute toxicities, and cardiac sparing capabilities of the prone technique in a series of 91 patients [47]. The largest long-term study comes from the Memorial Sloan Kettering Cancer Center with 248 patients and a median follow-up of 4.8 years. Acute and chronic skin toxicity profiles were low but no comparison to the supine technique was made and no cardiac outcomes provided [48,49]. Moving forward, long term follow up is needed with cardiac outcomes evaluated as a specific endpoint; while a randomized trial with a cardiac morbidity endpoint would be extremely costly and difficult to power, recent data from a randomized trial have demonstrated the feasibility of SPECT imaging to detect changes in cardiac perfusion 6 months following radiotherapy and this could be incorporated into follow up testing of future breast radiotherapy trials [50].

A recent dosimetric analysis from Rush University demonstrated that when adding a third field for regional nodal irradiation, prone treatment reduced lung doses but provided no benefit to cardiac dosimetry (ventricular V<sub>50</sub> and mean dose) compared with supine treatment [51]. At this time, it remains unclear if comprehensive breast and regional nodal irradiation is feasible and reproducible in the prone position, a potential limitation of this technique.

**Clinical scenarios:** At this time, the value of the prone technique for cardiac protection is less clear than breathing techniques and IMRT; a subset of patients that may benefit are large breasted patients based on subset analyses and data demonstrating reduced toxicities with large breasted patients receiving prone treatment [47,48]. Prone techniques can be combined with IMRT and APBI as well.

### Intensity modulated radiation therapy

Intensity modulated radiation therapy (IMRT) has become the standard of care in the management of prostate and head and neck cancer and has shown promise as a cardiac sparing technique for breast cancer patients as well (particularly those with left-sided lesions) [52,53]. IMRT was initially developed with a forward planned technique but more recently has been used employing the inverse planning method [52]. Initial studies from Stanford University demonstrated an improvement in dose homogeneity in the breast as well as reduction in cardiac dose with IMRT in left sided cancer patients, though a small number of patients was evaluated [53]. Further studies have confirmed improved cardiac dosimetry with IMRT when treating the whole breast alone, breast and regional nodal volumes, and the chest wall and regional nodal volumes after mastectomy compared with 3D-CRT tangential therapy. These benefits are similar to those seen with breathing techniques and more consistent than prone techniques with respect to improvements in (1) high dose volumes of the heart receiving RT (maximum cardiac dose and volume receiving high dose), (2) the volume of the heart receiving 5 Gy, and (3) the mean cardiac dose compared with 3D-CRT and (4) reduced cardiac NTCP [54–61]. More detailed studies have found that IMRT reduces dose specifically to the coronary arteries and left ventricle compared with traditional treatment [62,63].

When examining the role of IMRT in locally advanced breast cancer, IMRT has been shown to provide significant reductions in low dose and high dose cardiac dose parameters as well as in the mean cardiac dose. This has been demonstrated even when employing regional irradiation with or without internal mammary treatment and independent of breast reconstruction technique [64–69]. When comparing standard tangential fields using cardiac shielding, IMRT was still associated with greater reductions in high dose cardiac volumes [70]. NTCP modeling has also found that IMRT is associated with low probabilities of heart complications [71,72]. Importantly, studies demonstrate that IMRT can be delivered in an efficient and reproducible manner such that the benefits in cardiac dose sparing are preserved.

Multiple IMRT techniques have been developed with each showing significant improvement in cardiac dose metrics compared with 3D-CRT (both when treating the whole breast alone or when including regional lymph nodes). Field-in-field techniques for whole breast IMRT have been found to be the most cardiac dose sparing of the techniques utilized [73–77]. IMRT may further reduce cardiac dose when combined with the prone technique [36].

While the dosimetric benefits of IMRT have been demonstrated, limited data examining cardiac outcomes with long-term follow-up using IMRT are available [78]. A large study of 495 patients confirmed a consistent cardiac sparing benefit dosimetrically with IMRT utilization, with no difference in cardiac dose sparing between community and academic practices [79]. A series of 354 patients with three-year follow-up found that with IMRT, rates of local recurrence were 3% with low cardiac V<sub>15Gy</sub> mean dose, and left ventricular doses though no cardiac outcomes were presented [80]. Further refinements in IMRT planning allow for reductions not only in mean heart dose but also in dose to the anterior myocardial region and left ventricle (areas at highest risk of cardiac morbidity from radiotherapy) [81,82]. More modern studies are identifying which patients benefit most from IMRT based on numerous cardiac metrics such as heart distance, cardiothoracic ratio, and breast size [83]. Concurrently, other studies are examining the volume of low dose delivered with IMRT and suggest that these are similar or reduced compared to 3D-CRT [83,84].

**Clinical scenarios:** IMRT represents a proven technique to provide cardiac protection and has been demonstrated to be efficacious in academic and community settings. It is a technique that can be used in all left sided breast cases to improve cardiac dosimetry; a patient subset that may benefit further is larger breasted patients due to improvements in homogeneity with data.
supporting reductions in acute and chronic toxicities with breast IMRT in large breasted women [85]. IMRT can also be used in conjunction with breathing techniques, prone set up, and APBI.

Proton beam radiotherapy

Proton beam radiotherapy represents a technique that allows for the reduction in dose to structures beyond the target volume based on the characteristics of the proton particle. The rapid dose fall off beyond the Bragg peak allows for a potential reduction in dose to critical adjacent structures and a reduction in acute and late toxicities. While primarily utilized for pediatric cancers, base of skull tumors, and re-irradiation, there are some studies suggesting a role in cardiac dose reduction with PBT for breast cancer [86]. Initial dosimetric studies evaluating single field PBT found that while no difference in mean breast dose was noted with protons compared with conventional photon or IMRT treatment, a suggestion for a reduction in maximum cardiac dose was noted [87]. When evaluating patients requiring regional treatment, small dosiometric studies have suggested that PBT may reduce the cardiac NTCP compared with conventional and IMRT techniques and reduce cardiac $V_{20}$Gy and $V_{50}$Gy [87–89]. With recent innovations in proton beam delivery, studies have demonstrated that intensity modulated proton therapy (IMPT) can further reduce cardiac dose compared with 3D-CRT and IMRT (i.e., lower $V_{50}$Gy and $V_{20}$Gy) [90,91]. Current studies are addressing the feasibility of PBT in the post-mastectomy setting [92,93]. One significant concern regarding protons is the increased costs associated with the technology. However, a recent study has suggested the potential for this technique to be more cost effective as the costs associated with the technology are reduced over time [94].

Clinical scenarios: At this time, in light of the limited data available and high costs associated with treatment, we do not advocate for proton therapy as a modality to provide cardiac dose sparing off-protocol.

Partial breast irradiation

Partial breast techniques offer an alternative method to reduce cardiac doses. By treating only the lumpectomy cavity and a margin surrounding it, the volume irradiated is decreased and the distance from the target volume to the heart increased. One concern is that many partial breast techniques incorporate hypofractionation potentially increasing the risk of cardiac morbidity due to the low $\alpha/\beta$ of cardiac tissues [95]. However, recent reviews of hypofractionation in breast cancer radiotherapy suggest that hypofractionated techniques have not been associated with increased cardiac morbidity based on published data to date [96,97].

Accelerated partial breast irradiation (APBI) is one form of partial breast irradiation and can be delivered with interstitial brachytherapy, applicator-based brachytherapy or external beam techniques. APBI is primarily utilized in early stage breast cancer with long-term survival rates of 90% or greater [98]. As a result, minimizing cardiac dose and future cardiac morbidity remains a significant concern in these patients. To date, long-term data have confirmed the clinical efficacy of the technique with randomized, prospective, and retrospective data confirming excellent local control, and cosmesis with side effects that are comparable or reduced compared to WBI [98–100]. With interstitial brachytherapy, catheters are placed and loaded around the lumpectomy cavity. Employing high dose rate (HDR) brachytherapy, the high dose volume can be targeted away from the chest wall and heart [98]. Applicator based brachytherapy also employs HDR brachytherapy and can also limit dose to the chest wall and heart [101,102]. With regard to external beam APBI, larger margins are required to account for breathing motion and treatment set-up uncertainties not typically seen with brachytherapy. However, instead of the traditional tangential fields used with WBI, multiple beam arrangements have been devised (including non co-planar fields) to limit dose to the heart [103].

Interstitial brachytherapy has the longest follow up of any APBI technique to date. Dosimetric studies have demonstrated low cardiac doses with modern, image-guided techniques [104,105]. For example, Major et al. evaluated 49 patients treated with multi-plane interstitial APBI and found the mean cardiac dose to be 21% of prescription dose in left sided patients ($n = 20$) with a mean $V_{50}$Gy of 12.8 cm³ with only 4 of 20 patients receiving any dose greater than 10 Gy [104]. These findings are consistent with a study from Germany that compared interstitial APBI with traditional WBI. Their results demonstrated that interstitial APBI not only reduced the volume of heart receiving low doses (5 and 10 Gy) but also the maximum dose received by small portions of the heart (DO1cc). For example, the mean maximum cardiac dose was reduced from 45.6 Gy with WBI to 12.6 Gy with interstitial APBI [106]. No long-term studies with cardiac outcomes are available at this time.

Over the past decade, applicator based brachytherapy has replaced interstitial brachytherapy as the primary brachytherapy APBI modality. A dosimetric study comparing balloon based brachytherapy with WBI found significant reductions in cardiac dosimetry from $V_{50}$ to $V_{20}$ [107]. With the advent of multi-lumen applicators, dosimetric studies have shown increased ability to shape dose clouds allowing further reductions in cardiac dose [102,108].

With respect to external beam APBI, cardiac doses remain low but are significantly impacted by distance from the lumpectomy cavity. Cavities greater than 4 cm from the heart have a $V_{50}$Gy typically $<$1% [109]. Further, a dosimetric evaluation of 29 patients found that external beam APBI reduced low and high dose volumes to the heart compared with WBI delivered with IMRT in left sided breast cancers [110]. A phantom study with advanced dose detection found that external beam APBI was associated with a reduction in cardiac dose from 2.7 Gy with WBI to 0.7 Gy. This was also confirmed in prospective studies [111–113]. More recently, IMRT has been utilized demonstrating a further reduction in cardiac dose [114]. A phase I/II study in 10 patients compared 3D-CRT APBI with IMRT APBI and WBI, using free breathing and deep inspiration breath hold. The maximum heart dose was greater than 30 Gy for WBI techniques while it was less than 5 Gy for 3D-CRT/IMRT APBI with breath hold and 8.2 Gy for 3D-CRT with free breathing suggesting that strategies used in WBI can be incorporated with APBI to further reduce cardiac dose [115].

The prone technique has also been utilized to deliver external beam APBI. Dosimetric studies from prospective trials demonstrate the ability to meet standardized cardiac dosimetric guidelines with cardiac $V_{50}$Gy being well within accepted standards [116,117]. However, a planning study found that while prone APBI reduced cardiac dose in 7 of 30 cases, it increased cardiac dose in 19 of 30 cases [117]. Also, APBI utilizing PBT has been investigated demonstrating low cardiac doses compared with 3D-CRT APBI [118–120].

A 30 patient study from William Beaumont Hospital evaluated cardiac doses using interstitial brachytherapy, applicator based (single-lumen) brachytherapy, and 3D-CRT external beam APBI techniques and found equivalent values for cardiac $V_{50}$Gy [121]. This was confirmed by a second dosimetric comparison of interstitial PBI with 3D-CRT external beam APBI that found comparable cardiac dosimetry with biologic mean doses of 0.5 and 0.7 Gy respectively [122]. An evaluation of 15 patients found that the cardiac dose was low with single-lumen applicator brachytherapy, 3D-CRT APBI, and IMRT APBI with mean $V_{50}$Gy of 12%, 4%, and 1% respectively [123].

Another partial breast technique that allows for the delivery of radiation therapy to the lumpectomy cavity region (potentially
reducing cardiac exposure) is IORT. However, at this time, data supporting this modality are far more limited than with APBI [124,125]. IORT can be delivered with 50 kVp X-rays or with electrons employing lead shielding to reduce dose beyond the chest wall [124,125]. Initial work with IORT demonstrated the dosimetric feasibility of reducing cardiac dose with IORT using 50 kVp X-rays with a tungsten coated sheet to limit dose beyond the chest wall; subsequent dosimetric studies have confirmed low maximum cardiac doses of 1 Gy [126–128]. While these data suggest a potential for reduced cardiac dose, further study is required as this technique has limited long-term follow up with respect to clinical outcomes and a lack of significant data demonstrating cardiac dose reduction.

Clinical scenarios: At this time, partial breast irradiation with APBI techniques can be offered to women with early stage invasive breast cancers and DCIS off-protocol based on consensus guidelines currently published [129]. However, in light of higher rates of local recurrence noted with IORT, we do not advocate for this technique to be used off-protocol despite the potential for improved cardiac sparing [130,131]. APBI can be used with IMRT and prone techniques as well.

Discussion

Improved long-term survival for all stages of breast cancer has prompted an increased focus on long term toxicities associated with treatment [2,3]. While population studies and pooled data from older radiotherapy series have demonstrated a potential increase in cardiac morbidity and mortality, there are significant limitations to these data [7,8]. These studies reported on patients primarily treated prior to the advent and implementation of cardiac dose sparing radiotherapy techniques and in some cases prior to even 3D conformal radiotherapy planning techniques being available [7,8]. Although limited term clinical cardiac outcome data exist utilizing current cardiac sparing techniques, dosimetric data available are favorable. These data consistently demonstrate significant reductions in cardiac doses at both low and high dose measures [8]. At the present time, women with left sided breast cancers should be offered some form of cardiac dose sparing technique when feasible. This should be applied both in patients treated with breast conserving therapy or mastectomy (with or without regional nodal irradiation). No particular technique has been found to be significantly superior to any other and multiple options can be applied concurrently; further, it is unlikely that one method will emerge as the dominant cardiac dose sparing technique. It is important that future studies follow cardiac outcomes. While it is difficult and costly to follow patients beyond 10 years to assess for cardiac events, alternatives including SPECT perfusion imaging and biomarkers offer the potential for short term surrogates of late cardiac events [50,132–134]. Currently, biomarkers represent a new way to identify potential cardiac injury secondary to radiation therapy with inflammation pathways, and TGF-B among the pathways being evaluated [132–134]. This will allow for a more optimal assessment of cardiac risk, to determine if new and possibly lower cardiac dose thresholds are required and to clarify both clinical and technical risk factors associated with the development of cardiac events [135].

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References


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