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REVIEW – CLINICAL ONCOLOGY

The impact of modern radiotherapy on long-term cardiac sequelae in breast cancer survivor: a focus on deep inspiration breath-hold (DIBH) technique

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Abstract

Introduction One of the most feared side effects of radiotherapy (RT) in the setting of breast cancer (BC) patients is cardiac toxicity. This side effect can jeopardize the quality of life (QoL) of long-term survivors. The impact of modern techniques of RT such as deep inspiration breath hold (DIBH) have dramatically changed this setting. We report and discuss the results of the literature overview of this paper.

Materials and methods Literature references were obtained with a PubMed query, hand searching, and clinicaltrials.gov.

Results We reported and discussed the toxicity of RT and the improvements due to the modern techniques in the setting of BC patients.

Conclusions BC patients often have a long life expectancy, thus the RT should aim at limiting toxicities and at the same time maintaining the same high cure rates. Further studies are needed to evaluate the risk–benefit ratio to identify patients at higher risk and to tailor the treatment choices.

Keywords Breast cancer · Modern RT · Intensity-modulated radiotherapy · Deep inspiration breath hold · Late effects · Late sequelae · Cardiac toxicity · Secondary cancer

Introduction

In the management of cancer patients, it is of paramount importance to achieve optimal loco-regional control of disease, but at the same time trying to minimize the complications, especially long-term sequelae. This approach can be even more difficult in thoracic oncology, due to "critical" organs at risk (OARs). Breast malignancies are the most common cancer in women (Siegel et al. 2017). Postoperative radiotherapy (RT) after breast-conserving surgery or mastectomy is an essential component of breast cancer treatment and significantly decreases the risk of ipsilateral breast recurrences and reduces breast cancer-specific mortality (McGale et al. 2014; Beadle et al. 2009). In accordance with the advances in surgical options, systemic treatments and RT, long-term survival for breast cancer patients has significantly improved over recent decades (Guarneri and Conte 2004; Kanapuru et al. 2012). Therefore, a larger number of women are at risk of presenting late effects of oncologic treatments, particularly after breast irradiation. To select methods of cardiac avoidance, the pathophysiology, clinical

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manifestations, and dose correlations of late cardiac toxicity must be understood. As part of this, several studies have demonstrated that cardiac risk conferred by breast irradiation, such as coronary artery disease (CAD) or cardiomyopathies, potentially reduces survival (Hooning et al. 2006; Lee et al. 2013). The increase in coronary events related to the heart mean dose (7.4% Gy) occurring within 5 years of radiation treatment and regardless of prior cardiovascular risk factors (Darby et al. 2013). As expected, evidence suggested that the cardiac avoidance in breast RT can provide a real decrease in clinical manifestations of cardiac toxicity (Darby et al. 2013; Clarke et al. 2005). However, guidelines and techniques for evaluating heart substructure doses have not been standardized. First, the methodology for calculating cardiac dose in the majority of studies included the average anatomy and not the cardiac substructure segmentation. With this regard, some experiences have provided valuable delineation of chambers, heart, and great vessels for left-sided breast cancer (Francolini et al. 2019; Feng et al. 2011). Thus, many authors have recently put more emphasis on the opening questions about cardiac toxicity, threshold dose to the heart, and cardiovascular risks associated with RT (Yeboa and Evans 2016; Shah et al. 2014; Zhu et al. 2018). Nevertheless, recent development in RT techniques can represent the key to achieve the goal of minimizing dose to the heart.

In this paper, we provide a wide narrative overview of the main contemporary RT techniques to minimize dose at the heart substructure in breast cancer patients often presenting long-life expectancies with a particular focus on deep inspiration breath-hold (DIBH) approaches.

Materials and methods: evidence acquisition

Key references were obtained from a PubMed query (through June 30, 2020), using the combination of the following keywords: “breast cancer radiotherapy AND DIBH”, “breast cancer radiotherapy AND DIBH AND cardiotoxicity”, “breast cancer radiotherapy AND cardiotoxicity”. Selection criteria included English language publications in humans, with no limits for the year of publication. Hand searching included meeting proceedings of the European SocieTy for Radiotherapy & Oncology (ESTRO), European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO). The website clinicaltrials.gov was also searched. Reference lists of the identified studies were explored and cross references were allowed. Data extraction was performed independently by two researchers (G.C.I. and V.S.) and disagreements were resolved on a case by case basis with a discussion with a third party (I.D.).

Radiation-induced heart disease in breast radiotherapy

The cardiac risk conferred by breast irradiation may result in late radiation-induced cardiac alterations, including heart diseases (Rong et al. 2014). Commonly, long-term cardiac toxicity of RT manifests itself as arrhythmias, pericarditis, congestive heart or ischemic heart disease, and valvular damage. There are several common pathways involved in the development of radiation-induced heart diseases (RIHD) such as microvascular injury, inflammation, and fibrosis. Radiation treatments contribute to small vessels' microangiopathy and macroangiopathy of the coronary artery leading to coronary artery disease, damage of the AV node and conduction system, accelerated atherosclerosis, and myocardial fibrosis (Duma et al. 2014; Ong et al. 2013; Taylor et al. 2009a; Correa et al. 2007). While medium and large size vessels are characterized by collagen deposition and endothelial cell proliferation, in small- to medium-size vessels, the foam cells and lipid-laden macrophages accumulate in the intima. Due to fibrosis, the pathomechanism of the aforementioned events is endothelial dysfunction and subsequent microvascular damage: endothelial cell radiation and oxidative damage cause the release of pro-inflammatory cytokines, fibroblast growth factor, platelet-derived growth factor and TGF-beta (Haubner et al. 2013; Maity et al. 1997; Darby et al. 2010). The cellular processes leading to endothelial dysfunction after irradiation create a disparity between atheroprotective and atherogenic factors and enhance the risk of coronary artery disease commonly related to age. Due to inflammatory and prothrombotic events, the microvascular injury to the myocardium may lead to cell death and replacement of myocardial tissue with fibrosis. As part of this, the wall motion, ventricular activity, and cardiac perfusion may be altered. The deposit of fibrin and replacement of pericardial fat with a collage are responsible for acute and late pericardial injury from radiation causing the pericardial disease. The microvascular damage leading to fibrotic alterations to valves and cardiac myocyte conduction damage are the major responsible for the development of arrhythmias and valvular disease (Taunk et al. 2015). The pathomechanisms of acute and late alterations in cardiac tissue and the corresponding clinical implications are well documented (Hardenbergh et al. 2001; Veinot and Edwards 1996). However, the correlation between heart damage and dose radiation exposure remains challenging and the low-dose contribution is not completely clarified

(Darby et al. 2010). Although myocardial fibrosis is often asymptomatic and the diagnosis is incidentally on echocardiography (Heidenreich et al. 2003), ventricular dysfunction is rare but can clinically manifest itself. The risk of ventricular or coronary artery alterations increases if anthracycline chemotherapy is performed and the radiation doses to large volumes of the heart are high (> 30 Gy). Darby et al.'s series confirmed that radiation-induced heart disease occurred within a year or two of exposure at a dose above 30 Gy increasing with a higher dose, younger age of radiation exposure, and the cardiovascular risk factors in medical history. To our knowledge, a mean dose to the heart of 3 Gy during breast RT would increase the risk of death from cardiac cause from 1.9 to 2.4% and, particularly, the risk of an acute coronary event from 4.5 to 5.4%. Similarly, exposure to a mean cardiac dose of 10 Gy would increase the risk of death from ischemic heart disease, and the risk of having an acute coronary event were 3.4% and 7.7% respectively (Darby et al. 2013). Historically, long-term follow-up trials in breast cancer focused the efforts on well characterizing the effect of irradiation on heart disease (Cuzick et al. 1987). In this regard, Cuzick et al. designed a meta-analysis of randomized trials to evaluate the RT consequences on long-term survival in women suggesting the decrease of survival beyond 10 years. Additionally, comparing the women randomized to surgery plus RT vs surgery alone, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses assessed that mortality from cardiac events, particularly due to coronary artery disease, was increased by 27% after adjuvant RT (Clarke et al. 2005). Furthermore, the update of the EBCTCG data from patients followed for up to 20 years confirmed the correlation between mortality from cardiac disease with heart doses. This increase was higher in randomized studies with larger mean heart doses and the risk of death from cardiac disease increases by 3% per Gy (95% CI, 2–5%; $2P < 0.00001$) (Clarke 2008). In the Correa et al. (Correa et al. 2007) series, breast cancer patients had a 10-year risk of developing coronary artery disease of 7%, regardless of the tumor laterality. After a median follow-up time of 12 years, 82 left- and right-sided cancer women performed cardiac stress testing. The alterations in stress tests were 59% and 8% ($P = 0.001$) in left versus right side-irradiated patients, respectively, and 70% of stress tests abnormalities affecting the left anterior descending artery territory, suggesting the correlation between left-sided breast irradiation and the increased risk of late radiation-associated coronary disease (Correa et al. 2007). Finally, the left side-irradiated patients should have a careful follow-up and may benefit from modern cardiac-sparing techniques during breast RT.

Advances in cardiac sparing techniques in breast radiotherapy

Over the last decades, the development of modern RT approaches has contributed to an important decrease of the heart doses during breast RT, potentially minimizing the radiation-related heart disease. In the conventional breast irradiation technique, the standard of care for whole breast irradiation (WBI) consisted of parallel-opposed tangential photon fields, which provided acceptable coverage of the breast and reduced the dose to the adjacent organs at risk (Al-Rahbi et al. 2013). However, this technique implicated remarkable dose inhomogeneity within the irradiated volume contributing to poor cosmetic outcomes, especially for women with large breast volume. To obtain dose homogeneity in the target volume, the field-in-field (FIF) technique could provide optimal results as reported by Al-Rahbi et al. (2013). The FIF-forward planned-intensity-modulated radiotherapy (FiF-FP-IMRT) findings were similar to the three-dimensional conformal radiotherapy (3D-CRT technique) in terms of breast coverage (95% of the prescribed dose to > 95% of the breast PTV), the PTV mean dose and the hot spot regions. However, in the inverse planned-intensity-modulated radiotherapy (IP-IMRT) plans, the mean maximum doses were more than 110% of the prescribed dose. These results suggested that FiF-FP-IMRT was in a simple and efficient planning technique for breast irradiation reducing the size of the hot spot and required less planning time (Al-Rahbi et al. 2013). Increasingly, IMRT and volumetric modulated arc therapy (VMAT) have been involved in left-sided breast irradiation to allow acceptable target coverage and minimize the high dose to heart and lung (Xie et al. 2020). Among the different cardiac-sparing techniques for breast cancer patients (particularly those with left-sided lesions), the IMRT has reported significant improvement in breast dose homogeneity as well as a decrease in heart dose (Li et al. 2000; Sakka et al. 2017). Increasingly, IMRT has been used for the treatment of the whole breast improving cardiac dosimetry compared with 3D-CRT tangential approach in terms of mean cardiac dose, maximum cardiac dose and volume receiving a high dose (Beckham et al. 2007; Selvaraj et al. 2007; Rudat et al. 2011). On the other hand, VMAT developed in 2007 can allow optimal dose conformity and distributions, provide acceptable target volume coverage and spare OAR, changing the gantry rotation speed, the shape of field and dose rate during treatment delivery. VMAT may also reduce individual radiation treatment time and may be combined with breathing-adapted RT to obtain a significant reduction in the heart and lung dose compared to free breathing (FB) (Rana 2013; Swamy et al. 2014). Breathing-adapted RT

is another reliable strategy in breast cancer patients to minimize heart doses, allowing the possibility to be combined with other techniques including IMRT and VMAT. Comparing the DIBH and FB position for each IMRT and VMAT plan, Sakka et al. found that DIBH technique significantly minimized the dose of the heart and left anterior descending coronary artery (LADCA) (Sakka et al. 2017). To our knowledge, the breath hold for breast cancer is one of the most well-investigated cardiac-sparing strategies and approaches used in clinical practice. Therefore, we purpose to outline the principal aspects of breathing-adapted treatments focusing our efforts on the overview of deep inspiratory breath hold (DIBH)-based RT.

Deep inspiratory breath-hold gating

Technological advances in modern breast RT have introduced numerous strategies of cardiac avoidance including heart blocking, modalities of patient positioning, and the timing of RT with the breathing cycle (Yeboa and Evans 2016). The management of the respiratory cycle in breast cancer RT has been investigated for two decades. During inspiration, the heart moves away from the chest wall minimizing the exposition of cardiac volumes to radiation and the moderate-deep inspiration breath hold gives the optimal cardiac dislocation (Chen et al. 1997; Lu et al. 2000; Sixel et al. 2001; Remouchamps et al. 2003). On the other hand, the compensation for movement effects and particularly for intrafraction breathing-related motion remains challenging. Due to this approximation, the use of generous margins is usually needed with a resulting increase in OAR exposure to radiation. As part of this, DIBH gating may be advantageous not only for more common indications, such as stereotactic body radiotherapy (SBRT) of the lung, liver, and upper abdominal site of disease, but also for normofractionated schedules in mediastinal lymphomas, lung, and breast cancer treatments (Boda-Heggemann et al. 2016). To our knowledge, different methods for establishing deep inspiration breath hold (DIBH) are documented. DIBH can be performed by voluntary breath-hold or feedback approaches and airway blocking based on computer-controlled tools. First, to obtain a cardiac dose reduction in breast cancer RT, a voluntary breath-hold technique without additional devices can be used. This approach is not completely unchecked thanks to additional light field verification monitoring the patient's breath hold (Pedersen et al. 2004; Bartlett et al. 2014; Prabhakar et al. 2007). Although several studies have confirmed the dosimetric benefits and the reliable precision of this approach, voluntary breath hold is not the most common method adopted to date (Pedersen et al. 2004; Bartlett et al. 2013, 2014; Prabhakar et al. 2007; Osman et al. 2014). Computer-controlled methods allowed generating a static geometrical situation of the patient body during the planning CT. The inspiration volume was performed by a spirometer and the patient was guided by a "target zone" projected on a screen during the respiratory cycle (Linthout et al. 2009). Using a device known as active breathing control (ABC) (Wong et al. 1999) (e.g., ABC from Elekta, Stockholm, Sweden), the patients can hold their breath to maintain respiratory volume. However, to obtain optimal feedback, good compliance of the patient remains mandatory. Thus, an indirect method for breath-hold gating such as optical surface tracking may fit for the majority of patients. Due to visible light on the patient, the system was able to verify breathing-related motions and subsequently tumor position (Pallotta et al. 2012). Daily surface monitoring allows optimal inter- and intrafraction setup and provides superiority compared with spirometer-based systems in terms of better repositioning, particularly for left breast cancer RT (Pallotta et al. 2012; Tanguturi et al. 2015; Tang et al. 2014). With regard to dosimetric and clinical cardiac outcomes of DIBH, the decrease of lower heart doses preserving optimal target volume coverage was well documented (Korreman et al. 2005; Hjelstuen et al. 2012; Schönecker et al. 2016). Although data on the effects of DIBH on cardiac outcomes and mortality are still limited, several dosimetric evaluations have confirmed the advantages of DIBH regarding cardiac avoidance. As part of this, Korreman et al. showed a decrease in cardiac mortality compared with free-breathing techniques in left-sided patients and a reduction of the heart V50 for left-sided cancers about 80–90% (Korreman et al. 2005). In recent years, numerous reports about methods and efficacy of DIBH have been designed as summarized in Table 1 (Osman et al. 2014; Tanguturi et al. 2015; Bolukbasi et al. 2014; Comsa et al. 2014; Verhoeven et al. 2014; Eldredge-Hindy et al. 2015; Joo et al. 2015; Mulliez et al. 2015; Rochet et al. 2015; Wiant et al. 2015; Yeung et al. 2015; Walston et al. 2017; Lawler and Leech 2017; Kunheri et al. 2017; Mohamad et al. 2017; Vuong et al. 2019; Dell'Oro et al. 2019). Particularly, an extensive systematic meta-analysis comparing DIBH versus the free-breathing population in left side breast cancer patients has been performed. From this evaluation, the DIBH group significantly led to lower doses to heart ($P < 0.01$) and LADCA ($P < 0.01$) with similar results in heart dose (Dmean, Dmax, V20, and V30) and LADCA dose (Dmean, Dmax) subgroups. Specifically, using DIBH a reduction of 25–67 and 20–73% in mean heart doses and mean left anterior descending artery doses was documented after the comparison of free breathing with DIBH breast cancer RT (Hong et al. 2018). The benefit of DIBH as a cardiac-sparing technique was confirmed by several data from patients undergoing 3D and IMRT treatments (Smyth et al. 2015). Due to the anatomical proximity of the heart to the target, the left-sided breast tumor remains one of the principal factors for offering DIBH to patients. To date, numerous dosimetric evaluations show that right-sided

Table 1 Dosimetric results from studies comparing free breathing and DIBH gating for breast cancer radiotherapy

Study	Year	Patients (*n*)	DIBH methods	Target volumes	Results
Bolukbasi et al. (2014)	2014	10	vDIBH	Breast	mLADd: 1.7 (FB) vs 0.8 (DIBH), reduction of 53% (IMRT) mHd: 1.7 (FB) vs 0.7 (DIBH), reduction of 59% (IMRT)
Comsa et al. (2014)	2014	50	ABC	Breast, chest wall, SCV, A LN	mHd: 3.1 (FB) vs 1.2 (DIBH), reduction of 61% (breast); 4.5 (FB) vs 2.1 (DIBH), reduction of 53% (Breast,Chest wall and LN)
Osman et al. (2014)	2014	13	vDIBH	Breast, chest wall, SCV, A LN, IMC LN	mHd: 5.8 (FB) vs 4.1 (DIBH), reduction of 29%
Verhoeven et al. (2014)	2014	17	vDIBH	Breast	mLADd: 30.9 (FB) vs 22.4 (DIBH), reduction of 28%; mHd: 3,5 (FB) vs 1.6 (DIBH), reduction of 54%
Eldredge-Hindy et al. (2015)	2015	86	ABC	Breast, chest wall, SCV, A LN, IMC LN	mHd: 2.7 (FB) vs 0.9 (DIBH), reduction of 67%
Joo et al. (2015)	2015	32	vDIBH	Breast, chest wall, SCV, A LN	mLADd: 40.8 (FB)vs 23.7 (DIBH), reduction of 42%; mHd: 7.2 (FB) vs 2.8 (DIBH), reduction of 61%
Mulliez et al. (2015)	2015	12	vDIBH	Breast	mLADd: 17.6 (FB) vs 10.9 (DIBH), reduction of 38% mHd: 4.0 (FB) vs 2.2 (DIBH) reduction of 45%
Rochet et al. (2015)	2015	35	vDIBH	Breast, chest wall, SCV, A LN, IMC LN	mLADd: 14.9 (FB) vs 4.0 (DIBH), reduction of 73%; mHd: 2.5 (FB) vs 0.9 (DIBH), reduction of 64%
Tanguturi et al. (2015)	2015	146	vDIBH	Breast, chest wall, SCV, A LN, IMC LN	mHd: 2.6 (FB) vs 1.4 (DIBH), reduction of 50%
Wiant et al. (2015)	2015	25	vDIBH	Breast	mHd: 3.0 (FB) vs 1.4 (DIBH), reduction of 53%
Yeung et al. (2015)	2015	20	vDIBH	Breast, chest wall, SCV, A LN, IMC LN	mLADd: 13.6 (FB) vs 4.1 (DIBH), reduction of 70%; mHd: 2.6 (FB) vs 1.3 (DIBH), reduction of 50%
Walston et al. (2017)	2017	15	vDIBH	Breast, chest wall, SCV, A LN, IMC LN	mHd: 1.3 (FB) vs 0.9 (DIBH), reduction of 31% (breast); 5.1 (FB) vs 3.6 (DIBH), reduction of 29% (Chest wall and LN)
Lawler and Leech (2017)	2017	28	vDIBH	Breast, chest wall, SCV	mLADd: 10.9 (FB) vs 5.2 (DIBH), reduction of 52%; mHd: 1.8 (FB) vs 1.2 (DIBH), reduction of 33%
Kunheri et al. (2017)	2017	45	ABC	Breast	mLADd: 13.2 (FB) vs 6.1 (DIBH), reduction of 54%; mHd: 3.1 (FB) vs 1.6 (DIBH), reduction of 52%
Mohamad et al. (2017)	2017	22	ABC	Breast, chest wall, SCV, A LN, IMC LN	mLADd: 21.3 (FB) vs 9.4 (DIBH), reduction of 56%; mHd: 5.8 (FB) vs 2.2 (DIBH), reduction of 62%
Vuong et al. (2019)	2018	29	vDIBH	Breast, Chest wall, SCV	mHd: 2.12 (FB) vs 1.01 (DIBH), reduction of 51,9%
Dell'Oro et al. (2019)	2019	20	vDIBH, ABC	Breast, chest wall, SCV, IMN LN	mHd: 2.7 (FB) vs 1.4 (DIBH), reduction of 48,1%

mHd mean heart dose (Gy), *mLADd* mean LAD dose (Gy), *LAD* left anterior descending artery, *SCV* supraclavicular, *ALN* axillary lymph nodes; *IMC LN* internal mammary chain lymph nodes, *DIBH* deep inspiration breath-hold, *FB* free breathing, *vDIBH* voluntary DIBH, *ABC* active breathing control

breast cancer patients may also benefit from DIBH, in terms of decrease of heart dose (Dell'Oro et al. 2019) with particular regard to women receiving nodal irradiation to the internal mammary chain (IMC) (Yeung et al. 2015). Thus, data suggest that IMC irradiation may also be an additional selection factor for DIBH gating in breast cancer RT.

Finally, an ulterior patient-specific factor is the maximum heart distance in the radiation field (distance between the posterior border of the tangent field and the anterior cardiac edge). Deep inspiration breath hold can minimize heart dose compared to free breathing by optimizing the distance between heart and the chest wall, specifically in left-sided breast cancer patients (Vuong et al. 2019). These anatomical variations correlated with the mean heart dose in several analyses (Taylor et al. 2009b; Kong et al. 2002) highlighting the relevant correlation between longer parasagittal cardiac contact distance and higher heart doses (Rochet et al. 2015).

Conclusions

Cardiovascular side effects may negatively burden the benefit of RT in thoracic malignancies. In this regard, it is noteworthy to underline that the high ratio of cured patients highlights the problem of late complications. Currently, technological improvements in RT delivery techniques have significantly decreased the side effects of thoracic RT. At the same time, improvements in our understanding of the biologic underpinnings of these side effects and the influence of dosimetric variables have made treatment safer and efficacious. As part of this, DIBH is an important strategy for cardiac sparing compared to free breathing especially in left-sided breast cancer patients. Despite the growing interest in dosimetric measures and clinical cardiac outcomes of DIBH, the main limitation of the previous studies is the retrospective nature and the small sample size. Further prospective evaluations on a larger number of patients aimed to optimize patient selection and to enhance DIBH techniques are needed. Additionally, further dosimetric evaluations are expected to identify patients at higher risk of late radiation-induced toxicities, thus tailoring multimodality approaches on the single patient.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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