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ORIGINAL ARTICLE

Myocardial damage on SPECT imaging among patients treated with radiotherapy for left-sided breast cancer: Systematic review with meta-analysis and narrative synthesis

Stella Pak[1], Ahmed A. Hawash[2], Juan Linares[1], Damian Valencia[1], Andrew Kilgore[2], Victor Valencia[3], John-Philip Markovic[1]

[1]Department of Medicine, Kettering Medical Center, Department of Medicine, Kettering, OH, USA; [2]Department of Medicine, Wright State University Boonshoft School of Medicine, Dayton, OH, USA; [3]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Summary

Purpose: *With advancements in radiation oncology techniques, the use of radiation therapy (RT) as a treatment modality for cancer has been steadily increasing. Incidental radiation exposure to surrounding tissue during breast cancer treatment has been known to cause myocardial damage, the extent of which can be detected with single-photon emission computed tomography (SPECT) perfusion studies. We undertook a systematic review and meta-analysis to investigate the impact of RT on myocardial perfusion.*

Methods: *A systematic review of the literature was conducted to identify 17 studies, of which 4 were included in this meta-analysis and 13 were included in the narrative synthesis.*

Results: *The incidence of post-radiation cardiac perfusion defects on SPECT was significantly higher in patients who received RT for left-sided breast cancer compared to those who had RT for right-sided breast cancer (OR=3.10, 95% CI 1.35-7.08, p=0.007).*

Conclusion: *In patients who undergo RT for left-sided breast cancer, the incidence of post-radiation cardiac perfusion defects on SPECT is higher compared to patients who undergo RT for right-sided breast cancer.*

Key words: *breast cancer, ischemic heart disease, radiation-induced heart disease, radiation therapy, SPECT*

Introduction

In 2016, the American Cancer Society and the National Cancer Institute estimated that there are approximately 3.56 million breast cancer survivors. In many instances, RT has become a standard of care in the management of breast cancer [1]. Evidence has shown that breast-conserving surgery followed by RT is an equivalent treatment to mastectomy with regards to overall survival in patients with early-stage breast cancer [2]. With this information available, about two thirds of patients with invasive breast cancer undergo RT as part of their treatment regimen [3]. The utilization rate of RT is on the rise as RT reduces both recurrence and mortality rates of breast cancer in addition to being associated with a better quality of life in comparison to mastectomy [4,5]. With its increased use, a spotlight has been shed on RT and its adverse effects, such as lymphedema, cutaneous reactions, rib fractures and cardiotoxicity [6]. RT-induced heart disease (RIHD) has been recognized since the 1960s and is a term that encompasses the structural changes produced by irradiation of cardiac tissue as well as the clinical manifestations of such changes [7,8].

Correspondence to: Stella Pak, MD. Kettering Medical Center, Department of Medicine, 3535 Southern Blvd., Kettering, OH 45429, USA.
Tel and Fax: +1 937 395 8063 and +1 937 395 8399, E-mail: stellapak.research@gmail.com
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Clinical manifestations of RIHD do not typically reveal themselves until years after radiation exposure. The clinical spectrum of RIHD includes, but is not limited to, delayed acute pericarditis, delayed pericardial effusion, diffuse myocardial fibrosis, coronary artery disease (CAD), conduction defects and valvular defects [9]. The most severe manifestation of RIHD is myocardial fibrosis, although it is far less common than pericardial defects. It usually presents with severe signs and symptoms of restrictive heart disease leading to heart failure, and typically after large doses of radiation exposure to the whole, or at least the majority, of the heart-as previously described in the treatment of Hodgkin's lymphoma [10].

Radiation exposure of cardiac tissue has been linked to a plethora of cardiovascular diseases: congestive heart failure, valvular stenosis, conduction abnormality, CAD, and constrictive pericarditis [11]. Radiation-induced CAD is particularly worrisome as it can result in sudden cardiac death or myocardial infarction many decades after the time of radiation exposure. The pathophysiology underlying this late complication of RT remains largely unknown. However, it has been postulated that oxidative stress, vascular inflammation, and accelerated cellular senescence precipitated by radiation exposure are key players in the formation of atherosclerotic plaque [12].

Many pioneering studies are underway to explore the somewhat novel association between cardiac exposure to RT and cardiac perfusion defects. SPECT is a widely used diagnostic tool for detection of cardiac perfusion defects. Due to its wide availability and capacity to differentiate reversible perfusion defects from irreversible perfusion defects, SPECT is a commonly utilized diagnostic modality in various type of studies [13]. Herein, we conducted a systematic review of the literature with meta-analysis and narrative synthesis to summarize the current body of knowledge on cardiac perfusion defects caused by RT among breast cancer survivors. Understanding the impact of RT on cardiac tissue may contribute to the development of evidence-based guidelines regarding cardiovascular and preventive care of this patient population. Evidence-based guidelines might help determine the need of cardiovascular risk assessment of patients prior to initiation of RT as well as benefit of cardiovascular risk-based RT regimen modification. Furthermore, the ability of SPECT to detect reversibility of the perfusion defect is valuable in understanding the pathophysiology of RT-induced CAD, as reversible defects are suggestive of chronic vasculopathies of inflammatory etiology and endothelial dysfunction. Irreversible perfusion defects, in contrast, would indicate myocardial fibrosis or degeneration.

Appendix 1. List of search terms used in database searching

Database	*Search Term*
MEDLINE	"Radiation Therapy"[TIAB] or "Radiotherapy"[TIAB]) and "SPECT"[TIAB] and Breast Cancer"[TIAB]
CINAHL	AB breast cancer and AB SPECT
Web of Science	TITLE: (breast cancer) and TITLE: (SPECT) and TOPIC: (radiation) Refining filter: Document types: (Article)

CINAHL: Cumulative index of nursing and allied health. TI: title, AB: abstract.

Appendix 2. Random effects: Univariate regression analysis of multiple variables

Variables	*Regression coefficient (R^1)*	*Coefficient of determination (R^2)*	*p value*
Age	0.1660	0.027559	0.694421
Follow-up period	-0.5202	0.27060804	0.186303
Radiation dose	0.6554	0.42954916	0.077685
First year of study	0.4195	0.17598025	0.300845
Last year of study	0.4915	0.24157225	0.216097
Smoking	-0.6451	0.41615401	0.16658
Hypertension	0.3997	0.15976009	0.432378
Diabetes mellitus, I or II	0.3899	0.15202201	0.444787
Hyperlipidemia	0.4973	0.24730729	0.315543

Methods

Systematic review

The systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols (PRISMA-P) guideline. To minimize the risk of relevant study omission, initial searches were performed using three different databases: PubMed, Web of Science, and CINAHL. Database queries were performed from December 13th, 2017 to December 23rd, 2017. We searched the databases using the search terms listed in Appendix 1.

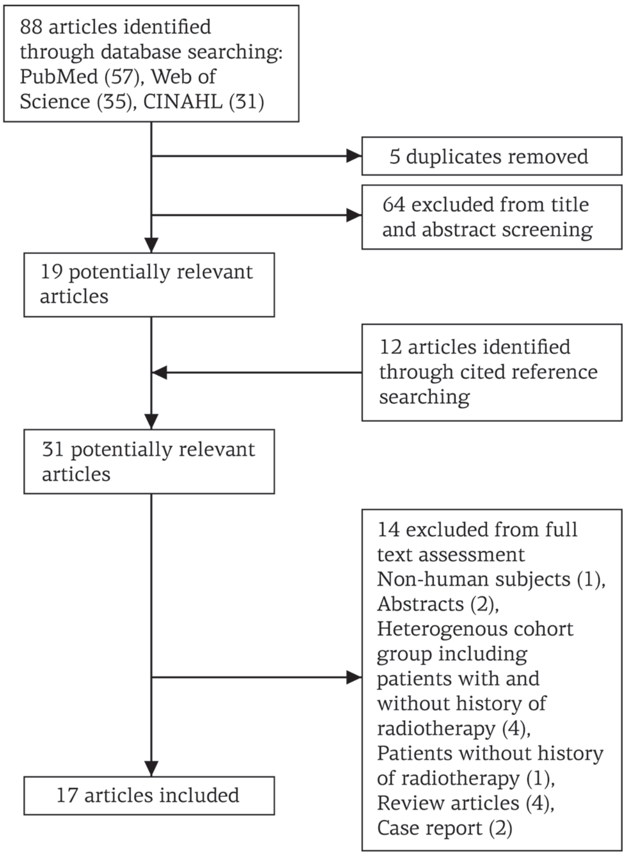

Figure 1. Flow chart of the systematic literature review process on radiation-induced heart disease. Two reviewers independently performed study selection using inclusion and exclusion criteria.

To be included in our systematic review and meta-analysis, studies had to meet specific inclusion criteria: (1) patients had to have received RT for breast cancer; (2) cardiac perfusion studies was performed using SPECT; (3) availability of the full text of the study in English. Exclusion criteria included the following: (1) a heterogeneous patient group; (2) patients without a history of RT; (3) the use of non-human subjects; (4) case studies; (5) review articles; (6) abstracts; and (7) editorials.

Two reviewers independently screened all titles and abstracts, then rated each included study using the systematic review tool Covidence (Covidence, Victoria, Australia). Disagreement between the two reviewers was resolved with discussion between them, or with a third reviewer.

Quality appraisal

The Newcastle-Ottawa quality assessment scale for case-control studies was utilized for quality appraisal of the included studies. Quality appraisal was independently conducted by two independent reviewers. Disagreement between the two reviewers was resolved with discussion between them, or with a third reviewer.

Data extraction

Quality appraisal was independently conducted by two independent reviewers. Disagreement between the two reviewers was resolved with discussion between them, or with a third reviewer included.

Meta-analysis and statistics

A random-effect meta-analysis was performed on four different case-control studies. Heterogeneity was determined using the I^2 value. The funnel plot method was utilized to assess potential publication bias. All statistical tests were two-sided and a p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using Review Manager 5.3 (The Nordic Cochrane Centre, 2014) and R programming (R foundation; Vienna, Austria). A total of 121 patients with left-sided RT and 92 patients with right-sided RT were included in this meta-analysis.

Study or Subgroup	Left-Sided Events	Left-Sided Total	Right-Sided Events	Right-Sided Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Gustavsson	4	34	2	33	17.4%	2.07 [0.35, 12.13]	1999
Seddon	17	24	2	12	17.7%	12.14 [2.10, 70.22]	2002
Sioka	15	28	8	18	30.9%	1.44 [0.44, 4.74]	2011
Eftekhari	15	35	6	36	34.0%	3.75 [1.24, 11.30]	2015
Total (95% CI)		**121**		**99**	**100.0%**	**3.10 [1.35, 7.08]**	
Total events	51		18				

Heterogeneity: Tau² = 0.21; Chi² = 4.23, df = 3 (P = 0.24); I² = 29%
Test for overall effect: Z = 2.68 (P = 0.007)

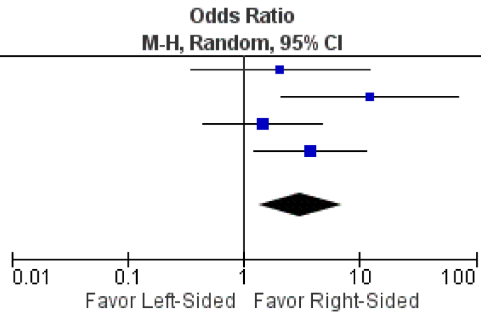

Figure 2. Forest plot illustrating the individual and combined effect sizes for studies comparing the effect of radiation therapy on myocardial perfusion in patients who received radiation therapy for left-sided breast cancer compared to those who had RT for right-sided breast (odds ratio=3.10, 95% confidence interval 1.35-7.08, p value=0.007). Referenced studies: Gustavsson [14], Seddon [15], Sioka [16], Eftekhari [31].

Narrative synthesis

A narrative synthesis was conducted to analyze the 13 studies that were not included in the meta-analysis due to different study design. These 13 studies were grouped into two categories. One category included those studies that employed breath holding techniques and the other category included those studies that did not employ breath holding techniques.

Results

Systematic review

A total of 88 articles from the initial search were screened and 5 duplicate records were removed. Using exclusion criteria, 64 articles were excluded through title and abstract screening. Twelve additional studies were found through cited reference searching. The full text of 31 articles was critically appraised. Only 17 articles that fully met the inclusion criteria were included in our review. Appendix 1 shows the summary of 17 articles included in this review. Four articles were case-control studies comparing the rate of perfusion abnormalities in patients who received RT on the left side of the chest compared to the right side [14-17]. These 4 studies were included in our meta-analysis, and their baseline characteristics are described in Table 1. Thirteen other articles had different compositions of case and control groups or were single cohort group observations [18-30]. These 13 articles were included in the narrative review section. The selection process is illustrated in Figure 1.

Meta-analysis

A total of 4 studies were included in the meta-analysis. As shown in Figure 2, women with history of RT for left-sided breast cancer were about

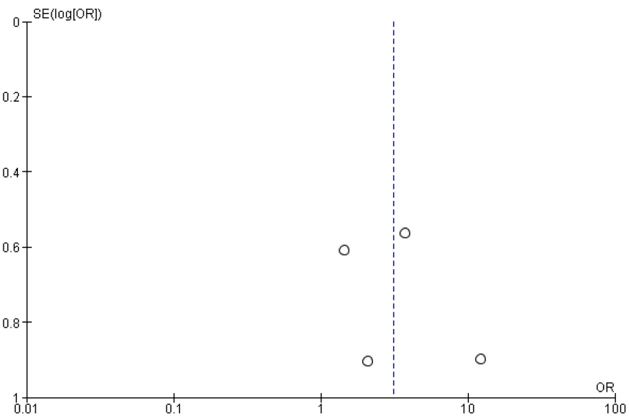

Figure 3. Funnel plot of included studies in the meta-analysis demonstrates no significant asymmetry. The absence of significant asymmetry appearance on the funnel plot indicates a low risk for publication bias.

Table 1. Baseline characteristics of studies included in meta-analysis

Studies	*Number of patients*	*Age*	*Follow-up (months)*	*Radiation dose (Gy)*	*Start and end year*	*Anthracycline-based therapy (%)*	*Hormone-based therapy (%)*	*Smoking (%)*	*Hypertension (%)*	*Diabetes mellitus (%)*	*Hyperlipidemia (%)*	*Total perfusion abnormality (%)*	*Reversible perfusion defect (%)*	*NOS*
Gustavsson, 1999	34(L), 33(R)	59(L), 57(R)	156	43	1978-1983	NA	NA	23.52(L), 39.39(R)	11.7(L), 15.15(R)	0	11.76(L), 12.12(R)	11.765(L), 0.0606(R)	0	9
Seddon, 2002	24(L), 12(R)	62.5	79.8(L), 99.6(R)	50	1993-1995	20.83(L), 33.3(R)	83.3(L), 66.66 (R)	25(L), 41.66(R)	16.66(L), 25 (R)	0(L), 8.33(R)	12.5(L), 0(R)	70.8(L), 16.7(R)	41(L), 16.7(R)	8
Sioka, 2011	28(L), 18(R)	59.93(L), 57.5(R)	35(L), 41(R)	60	1998-2010	39.3(L), 27.8(R)	NA	7.1(L), 14.3(R)	50(L), 21.4(R)	25(L), 14.3(R)	35.7(L), 32.1(R)	53.57(L), 44.44(R)	53.57(L), 44.44(R)	6
Eftekhari, 2015	35(L), 36(R)	44.8(L), 45.8(R)	6	48	2010-2012	100	NA	NA	NA	NA	NA	42.9(L), 16.7(R)	28.6(L), 8.3(R)	8

NA: not available; NOS: Newcastle-Ottawa Score

Table 2. Characteristics of studies on individuals who received radiation for left-sided breast cancer

Studies	*Number of patients*	*Age*	*Follow-up (months)*	*Radiation dose (Gy)*	*Start and end year*	*Anthracycline-based therapy (%)*	*Hormone-based therapy (%)*	*Smoking (%)*	*Hypertension (%)*	*Diabetes mellitus (%)*	*Hyperlipidemia (%)*	*Total perfusion abnormality (%)*	*reversible perfusion defect (%)*	*NOS*
Prosnitz, 2007	44	55	36	46-50	1998-2006	47.72	86.36	36.36	47.72	4.54	13.63	68	NA	9/10
Gyenes, 1994	20	65.1	220.8	45	1971-1976	0	0	30	30	5	NA	25	15	9/10
Cowen, 1998	19	59	100.8	60	1987-1983	0	0	0	0	0	0	0	0	9/10
Hojris, 2000	10	63	94.8	50	1982-1990	0	50	20	10	0	20	44.4	33.33	8/10
Gyenes, 1996	12	57	13	46-50	1993-1994	25	67.16	33	25	NA	25	50	0	7/10
Gyenes, 1997	12	57	13	46-50	1993-1994	25	58.83	NA	NA	NA	NA	50	0	7/10
Marks, 2005	114	57	6-24	62-68	1998-2001	NA	NA	35.96	27.19	8.77	14.91	27-42	NA	8/10
Yu, 2003	83	54	16	46-52	1998-2001	60.24	0	NA	NA	NA	NA	37	NA	6/10
Hardenbergh, 2001	20	54	6	46-50	1995-2000	50	0	NA	NA	NA	NA	60	NA	7/10
Lind, 2003	69	53	6-18	46-50	NA	59.42	82.59	23.21	33.3	6.15	20	15.94	NA	7/10
Zellars, 2014	29	58.7	6	46-48	2006-2010	NA	69	NA	NA	NA	NA	NA	NA	8/10
Chung, 2013	32	50	12	50-52.2	2006-2010	96.87	0	53.12	18.75	0	18.75	0	NA	7/10

NA: not available; NOS: Newcastle-Ottawa Score

Table 3. Characteristics of studies on individuals who received radiation with active breath hold for left-sided breast cancer

Studies	*Number of patients*	*Age*	*Follow-up (months)*	*Radiation dose (Gy)*	*Start and end year*	*Anthracycline-based therapy (%)*	*Hormone-based therapy (%)*	*Smoking (%)*	*Hypertension (%)*	*Diabetes mellitus (%)*	*Hyperlipidemia (%)*	*Total perfusion abnormality (%)*	*Reversible perfusion defect (%)*	*NOS*
Zagar, 2017	20	56	6	46-50	NA	35	0	0	45	10	30	0	0	8/10
Zellars, 2014	28	52.8	6	46-48	2006-2010	NA	67	NA	NA	NA	NA	NA	NA	8/10

NA: not available; NOS: Newcastle-Ottawa Score

3.1 times more likely to develop a perfusion defect abnormality compared to those who had RT for right-sided breast cancer (OR=3.10, 95% CI 1.35-7.08, p=0.007). A mild degree of heterogeneity (I^2=29%) was detected. The funnel plot (Figure 3) for the studies did not show any significant publication bias. As shown in Appendix 2, smoking (R^2= 0.41615401) and radiation dose (R^2= 0.42954916) showed moderate positive correlation, but the other variables did not demonstrate any significant correlation with incidence of cardiac perfusion defects. The univariate regression analysis of these variables failed to identify any statistically significant associations with the incidence of cardiac perfusion defects.

Narrative synthesis

A narrative synthesis was conducted to analyze the 13 studies that were not included in the meta-analysis due to different study designs. Table 2 illustrates the baseline characteristics of the 12 studies that did not use active breath holding technique. Table 3 shows the baseline characteristics of two studies whose participants used active breathing technique.

Discussion

RIHD is characterized by diffuse interstitial fibrosis typically limited to the myocardium of the left ventricle. The extent and severity of left ventricular fibrosis is highly variable but clearly related to radiotherapy intensity. Diffuse fibrosis is the aftermath of damaged microcirculation of the myocardium, with subsequent ischemia [31]; this suggests that cardiomyocytes are never directly damaged by radiation. Fibrosis is more frequently seen in the anterior and lateral walls of the left ventricle than the posterior wall. Fibrosis of the atria is rarely identified. The characteristic scarring of a past myocardial infarction (MI) via coronary artery occlusion is not seen in RIHD.

Diffuse myocardial fibrosis and arterial lumen narrowing are well-known patho-histological features of RIHD [32]. This study demonstrates that endothelial cells of the capillaries are of greatest radiobiological importance. Progressive endothelial damage occurs in the myocardial capillaries, which can lead to endothelial damage after only a single dose of radiation. It appears that this destruction of the myocardial capillaries is followed by compensatory proliferation of unaffected endothelial cells [31,33].

Delayed lesions can be seen in irradiated small and medium-sized arteries including coronary arteries. The lesions can be seen as soon as 3-6 months post-radiation. Histologic evaluation of these lesions includes fibrotic and foamy cell plaques in the intima and throughout the full thickness of the muscular wall [34]. Most frequently, the pathogenic process begins as intimal fibrosis followed by transmural necrosis with subsequent healing.

Evidence has shown that patients who have had the mediastinum irradiated (for Hodgkin's lymphoma or breast cancer) have a relative risk (RR) between 2.6 and 3.8 for the development of CAD. The RR is much higher if irradiated before 20 years of age [35-38]. The morphology, clinical manifestations and treatment of RI-CAD are no different than those of CAD by atherosclerosis [39,40]. A retrospective population-based study by Darby et al. analyzed 2168 patients from Nordic cancer registries. They found the relative risk for ischemic heart disease increased by 7.4% for every 1 Gy increase in the mean heart dose [41].

In response to a growing body of evidence supporting the association between RT and breast cancer, deep inspiration breath-hold (DIBH) and positional techniques have been developed to minimize the impact of radiation on myocardial tissues. The DIBH, which involves the patient inspiring deeply and holding the breath during the delivery of a radiation dose, can decrease the radiation dose delivered to the heart. The two most common methods for applying DIBH are the spirometry-based active breathing coordinator (ABC) and video-based real-time position management (RPM). Currently, comparative studies between techniques are sparse, thus the method of choice is mostly center-based. These techniques lower the radiation dose to the heart without compromising coverage to breast or chest wall tissue [42-44]. Studies have demonstrated mean heart dose reductions in radiation ranging from 26.2% [45] to as high as 75.0% [46] using the techniques mentioned. Therapy administration protocols like the DIBH also allow for the use of additional techniques such as wide-angled tangents which allow for good radiation coverage of the internal mammary chain while delivering a reduced dose of radiation to cardiac tissue.

One major issue with DIBH techniques is patient compliance. DIBH requires the patient to actively breathe and hold. Although high compliance rates have been reported, one must take into account the differences in the ability of patients to consistently and repetitively hold breaths, especially if there are comorbidities that prevent patients from comfortably doing so [47].

It seems that it would be quite beneficial for RT candidates to undergo pre-treatment SPECT screening for cardiac disease, although several concerns must be addressed. Given the high cost of SPECT analysis, it is uncertain whether it would be cost-effective to screen all breast cancer patients who are candidates for RT. This is unlikely to be a minimal healthcare cost to any health system considering that approximately 3.56 million breast cancer survivors were living in 2016 [1]. Other questions arise, such as whether (1) all breast cancer RT candidates should be screened by SPECT or only those that are high-risk for cardiac complications; (2) an age limit for SPECT screening should be imposed given that RIHD typically takes over a decade to develop; (3) the relatively low risk of RIHD would change the RT regimen administered by the radiation-oncologist. Tolerance doses are already in place and recognized by radiation-oncology societies, so it is unknown whether SPECT screening would change the approach to treatment. These are all issues that need to be explored before routine SPECT screening is implemented for breast cancer patients receiving RT.

Limitations

The limitations of our study stem from the poor specificity of SPECT, lack of large-scale studies, and a mild degree of heterogeneity. SPECT has limited specificity (85%) and sensitivity (92%) [48], and this technical limitation may have affected the data. Obtaining individual patient data from all studies was not feasible due to low response rates from corresponding authors of the studies. As a result, our study was performed using the aggregate data reported rather than individual participant data. We could not evaluate the impact of confounding factors other than those reported in the studies.

Conclusion

A conclusion that can be drawn from this study is that RT is a significant risk factor for myocardial damage and perfusion defects. Active screening and modification of traditional cardiovascular risk factors, such as obesity, smoking, or recreational drug use, may benefit cancer survivors with a history of RT. Radiotherapy techniques such as DIBH can be implemented to reduce radiation related myocardial damage. Breast cancer patients may benefit from SPECT screening prior to and during RT for monitoring of myocardial damage and risk factors. Many questions are still left unanswered and further studies on SPECT monitoring for myocardial damage and radiotherapy are warranted.

Conflict of interests

The authors declare no conflict of interests.

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