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review

Pericardial disease after breast cancer radiotherapy

Tanja Marinko

Institute of Oncology Ljubljana, Department of Radiotherapy, Ljubljana, Slovenia

Radiol Oncol 2019; 53(1): 1-5.

Received 5 May 2018
Accepted 12 May 2018

Correspondence to: Tanja Marinko, M.D., Ph.D., Institute of Oncology Ljubljana, Zaloška cesta 2, SI-1000 Ljubljana, Slovenia.
Phone: +386 1 5879 515; Fax: +386 1 5879 400; E-mail: tmarinko@onko-i.si

Disclosure: No potential conflicts of interest were disclosed.

Background. Breast cancer is the second most common cancer worldwide. Thanks to the modern oncological treatments, disease specific survival has improved throughout the last decades. The number of breast cancer survivors has been increasing, and more and more attention has been paid to the breast cancer treatment side effects. Whereas there are many data regarding ischemic heart disease after radiotherapy for breast cancer, there is not much data in the literature about the incidence and clinical meaning of pericardial disease after breast cancer radiotherapy.

Conclusions. Although radiation-induced pericarditis is the earliest form of radiation-induced cardiovascular disease after irradiation of the heart, it seems that in clinical practice, especially by using modern radiotherapy treatment techniques, it is underdiagnosed because patients are mostly asymptomatic. In some cases, especially in its late form and after multimodal systemic oncological treatment in combination with radiotherapy, it could be presented in severe form and life threatening. Treatment modalities for radiation-induced pericardial diseases are the same as in the non-irradiated population, but in the irradiated patients, surgery may be difficult.

Key words: pericardial disease; cardiotoxicity; cardio- oncology; breast cancer; radiotherapy

Introduction

Nowadays, breast cancer is a highly curable disease. Thanks to the modern oncological treatments, patients with early breast cancer live many years, decades after the treatment. For many of them life expectancy some years post treatment is the same as for the general population.[1] Consequences of the oncological treatment may have a very important influence on the quality of the subsequent life. Therefore, all the efforts must be oriented towards treatment benefits as well as in minimizing treatment's side effects.

Radiation therapy is an important part of treatment for early breast cancer with a significant impact on survival of breast cancer patients.[2] Besides its treatment effect, it also has side effects. Among them, one of the most important is cardiotoxicity. This is of special concern, because in its severe form it is life-threatening, instead of breast cancer itself.

Radiotherapy of the breast cancer, especially of the left breast, almost always involves some incidental irradiation of the heart. It can result in a range of cardiotoxic effects including coronary artery disease, cardiomyopathy, pericardial disease, valvular dysfunction and conduction abnormalities.[3] Radiation induced heart disease generally occurs with a latent period of 10 to 15 or even more years.[4] It can be intensified with chemotherapy and other systemic oncological treatments, but its occurrence also depends on patient's habits (smoking, diet) and simultaneous, especially cardiovascular diseases.[3,5,6] In addition to radiotherapy, breast cancer therapy may include anthracyclines and therapies targeting human epidermal growth factor receptor 2 (HER2) that may have important cardiotoxic effects (Khouri 2012, Taskforce).[3,7] Radiation-induced heart disease is of special concern, especially in younger patients as they survive longer.[8]

Radiation-induced pericardial disease is one of the most common and also the earliest manifesta-

tion of radiation-induced heart disease to occur following irradiation of the heart.[9] It could be presented as acute pericarditis, pericardial effusion, delayed thickening and constrictive pericarditis. It is classically associated with mediastinal irradiation.[10]

There is not much data in the literature about the incidence of pericardial disease after breast cancer radiotherapy. In 2011, McGale *et al*. published a large study about the incidence of heart disease in 35.000 women treated with radiotherapy for breast cancer between 1976 and 2006 in Denmark and Sweden.[5] In this, clinical and national registers based study, they reported that incidence for pericarditis was 1.61 (95% CI 1.06–2.43) higher if the patient had been irradiated for left breast cancer compared to the patient irradiated for right breast cancer. Altogether, among 35.000 breast cancer patients, they found 96 patients with subsequent, clinically or on autopsy proven pericardial disease. Interestingly, the incidence of pericarditis for left breast cancer patients comparing to the right breast cancer patients was changing through the years passed from the treatment: in the first four years after the treatment it was 1.68 (0.96–2.96), from 5–9 years 1.92 (0.89–4.13), and after 10 years it was 0.95 (0.33–2.73). The weakness of these data is a small number of cases and a broad 95% confidence intervals, but nevertheless, these data are in accordance with the fact that most radiation-induced pericarditis resolve over the years post radiotherapy.

In a recently published study, analyzing early cardiotoxicity after adjuvant concomitant treatment with radiotherapy and trastuzumab in breast cancer patients, treated between 2005 and 2010 and evaluated with transthoracic echocardiography, 10 (5.7%) out of 175 patients had pericardial effusion after a median observation time of 4.7 years.[11] In this study, left breast cancer patients had significant more pericardial effusions than right breast cancer patients (9 [11%] *vs*. 1 [1%]; p = 0.007). The thickness of pericardial effusion, measured at transthoracic echocardiography, was > 1 cm in 1 patient with left breast cancer, all the rest were < 1cm wide.

The recently published study, with retrospective analysis of 63 patients who underwent pericardiectomy for constrictive pericarditis, which is the most severe form of radiation induced pericardial disease, between 1997 and 2012, showed a significant decrease in overall survival associated with postradiation etiology (p = 0.05). The number of irradiated patients in this study was very small (n = 3; 8.3%), but also other studies report similar data.[12]

A golden standard in the evaluation of cardiotoxicity in cancer patients is standard transthoracic two-dimensional echocardiography.[13] It provides useful morphologic and hemodynamic information. A standard part of the echocardiographic exam are measurements of heart chambers and great vessels dimensions, estimation of ventricular systolic and diastolic function, assessment of ventricular wall contraction abnormalities, valvular anatomy and function and diagnosis of pericardial disease. In obese patients or in patients after chest irradiation, the quality of measurements can be poor due to suboptimal chest echotranslucency. In these settings tissue Doppler imaging (TDI) offers additional information.[13] Computed tomography is particularly helpful in identifying calcification.[3] In the evaluation of constrictive pericarditis, also magnetic resonance imaging and right-sided catheterization is used.[14]

Pathophysiology

The pathophysiologic pathway responsible for most manifestations of cardiotoxicity appears to involve damage to blood vessels. The generation of reactive oxygen species, caused by radiation, disrupt DNA strands. Secondary inflammatory changes then lead to fibrosis.[15]

Acute pericarditis is caused by radiation-induced inflammation of the pericard. Pericard becomes porous, resulting in a neutrophilic infiltrate and collection of a high-protein exudate (exudative pericarditis).[16] Changes of pericard in acute stage may later lead to fibrosis of the pericard, impairing the venous drainage of extracellular fluid.[17] Inefficient drainage results in the accumulation and formation of pericardial effusions, which are mostly fibrinous exudates.[18] Pericardial fat is replacing by collagen. Early and acute or delayed and chronic pericarditis should be regarded from a histopathological standpoint as two distinct disease entities.[9]

The histopathologic picture of the radiation-induced pericardial disease, the dose-independent latency time, and the reversibility indicate that radiation-induced pericarditis is an acute radiation response of an actively proliferating cell population. Mesothelial cells are the most likely candidates for target cells, but systematic cell kinetic studies have not been performed.[6]

Clinical meaning and therapy

Acute pericarditis is a rare short-term complication of radiotherapy and develops during or days

to weeks after irradiation.[14,15] It can be revealed by asymptomatic pericardial effusion or symptomatic pericarditis. Patients may present with chest pain, they may have a fever, pericardial rub, electrocardiogram abnormalities (ST-T changes) and mild elevations in cardiac markers within days to weeks of therapy, near the timing of radiotherapy.[18] Acute pericarditis usually resolves by itself, spontaneous clearance of effusion may occur. Half of the patients do not require any active intervention.[15] Nevertheless, if treatment of pericarditis is needed, it is usually supportive with non-steroidal anti-inflammatory drugs (NSAID) and colchicine.[3,14,19] As a second-line agent, steroids may be prescribed. In resistant cases, interleukin 1β receptor antagonist is also an option.[15,20,21] In the case of large pericardial effusion, especially if the patient is hemodynamically compromised, pericardiocentesis is indicated. According to the literature, 20% of patients may proceed to have chronic pericarditis.[15]

Pericardial effusions may appear weeks, months or even years after irradiation with the mean latency for development of approximately one year.[8,14] Patients may be asymptomatic or develop progressive shortness of breath. Effusions that are hemodynamically insignificant require close monitoring, but those, who are symptomatic or in the case of tamponade, require urgent drainage of fluid.[20]

Constrictive pericarditis is usually the most severe form of pericarditis and commonly occurs with a latent period of 10 or more years post-radiation exposure as congestive heart failure.[18] It can lead to disabling symptoms and severe heart failure with the poor quality of life. Surgical pericardiectomy is the cornerstone of management.[12] In a recently published case report, in a 57-year-old breast cancer patient with late onset radiation-induced constrictive pericarditis and cardiomyopathy 22 years after radiotherapy for left breast cancer, even heart transplant operation was necessary and successfully done.[22]

Effect of radiation dose and techniques of treatment planning and delivery

Radiation-induced cardiotoxicity is related to both the irradiated volume of the heart and the radiation dose delivered to that volume. It seems that there is no safe dose that could be delivered to the heart with no increased risk of cardiovascular disease.[23]

The so-called »tolerance dose« of the pericard is described in the literature as a mean heart dose of greater than 36 or 40 Gy, or a > 50 Gy dose administered to > 30% of the heart.[6,8,24] The radiation effect on the pericard is highly dose-dependent, with the incidence of pericarditis increasing from < 5% to > 50% as the total dose to the heart is increased from 40 to 50 Gy.[25]

According to the data from the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review, published in 2010, which based on the previous report from Emami and colleagues published in 1991, the relations between the irradiated volume of the critical structure, threshold and outcome for pericarditis are as follows[25,26]:

- Mean heart dose < 26 Gy ..... < 15% probability for pericarditis
- Heart V30 < 46% ..... < 15% probability for pericarditis

Currently, all predictions for pericarditis probability are based on dose delivered to the heart. In the literature, there is no specific recommendations for dose restrictions that would base on the dose delivered to the pericard, as seems to be more accurate. Namely, in classical left breast irradiation with tangential fields, the pericard is the closest cardiac substructure that lies behind the irradiated target and, because of the steep gradient fall of the dose behind the targets, it probably receives a higher dose that the rest of the heart. In the current breast contouring recommendations and atlases, the whole heart is included, but it is likely that also cardiac substructures are important as we begin to understand the impact of radiotherapy on cardiac function.[27-29] At the moment, in the literature, there are at least two heart atlases, with instructions for countouring heart substructures. No one has detailed instructions for contouring of the pericard, although the second one, published in 2017, enables contouring of 15 cardiac segments.[29,30]

However, do we need to pay special attention on the contouring of the pericard as a specific structure, similarly as we contour coronary artery? According to the incidence of the treatment required, radiation-induced pericardial disease, it seems, that there is maybe no reason for that. But for the definite answer, it needs to be evaluated in a clinical study.

Dose, delivered to the heart during radiotherapy for breast cancer, largely depends on the treatment technique used. With the modern radiotherapy techniques, it is possible to spare the heart much more from radiation, than it was possible in the past by using older techniques.[31] Unlike 2D radiotherapy, 3D radiotherapy allows defining

the dose delivered to any point to the heart. If radiotherapy is delivered in a breath hold, which allows the heart to move down and posterior to the treatment volume, the sparing effect to the heart is even greater.[32] In a study comparing free breathing (FB) with voluntary deep inspiration breath hold (V-DIBH) resulted in a significant reduction of mean cardiac dose from 6.1 +/- 2.5 to 3.2 +/- 1.4 Gy ($p < 0.001$), maximum cardiac dose from 51.1 +/- 1.4 to 48.5 +/- 6.8 Gy ($p = 0.005$) and cardiac V25Gy from 8.5 +/- 4.2 to 3.2 +/- 2.5% ($p < 0.001$). There is no specific data for the dose to the pericard.

With an increasing awareness of potential cardiotoxicity of radiotherapy, new studies with proton therapy have emerged. Stick *et al.* in their study did an estimation of cardiac toxicity after comprehensive nodal photon versus proton therapy for breast cancer. In their report, they concluded that modern photon therapy yields a limited risk of cardiac toxicity in most patients, but proton therapy could reduce the predicted risk of cardiac toxicity by up to 2.9%.[33] A systematic review of the literature with the aim to evaluate proton therapy in locally advanced breast cancer, done by Kammerer *et al*., showed that proton therapy often decreased mean heart dose by a factor of 2 or 3. As an example for mean heart dose, they listed 1 Gy with proton therapy *versus* 3 Gy with conventional 3D, and 6 Gy for intensity-modulated radiotherapy (IMRT).[34] There is again no specific data for pericard.

Future directions

Good news is that the very recently published, registry-based study, reporting long-term heart-specific mortality among 347.476 breast cancer patients treated with radiotherapy or chemotherapy between 2000 and 2011, found that heart-specific mortality among breast cancer survivors was not increased compared with the general population.[35] According to the available literature, the absolute risk for pericardial disease associated with breast cancer radiotherapy is small and appears to be outweighed by the benefits of the treatment.

Nowadays, awareness about potential harm to the heart during radiotherapy is much higher than in the past, and efforts to deliver the prescribed radiation dose to the treatment target with the minimum possible dose delivered to the heart, are a part of a daily treatment planning routine in the majority of radiotherapy departments. But there is still a lot of room for improvement. The challenge for the future is in answering the question of the tolerance dose and the roll of each heart substructure in the etiology of radiation-induced heart disease.

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