Cardiotoxicity in breast cancer patients after radiotherapy – modern methods of minimizing the dose to the heart and dilemmas of choosing critical cardiac structures for monitoring dose distribution

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ABSTRACT

Radiotherapy in breast cancer patients is an important component of multidisciplinary treatment. It reduces the risk of local recurrence and mortality from breast cancer. However, it can lead to secondary effects due to the presence of the heart within the irradiation field. Adjuvant radiation therapy for breast cancer increases the risk of coronary artery disease, myocardial infarction and cardiovascular death. It is important to determine the optimal treatment to minimize cardiotoxicity. Modern radiotherapy techniques may reduce radiation-induced cardiac toxicity, but it is necessary to determine the most sensitive structures within the heart, tolerance doses, and methods for early detection and monitoring of adverse effects.

KEY WORDS: cardiotoxicity, radiotherapy, breast cancer

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INTRODUCTION

Use of radiotherapy in the thoracic region is associated with late cardiac radiation-induced complications. This is particularly true of patients treated with radiotherapy for left-sided breast cancer. Adverse effects of radiotherapy include exacerbations of coronary artery disease manifested by myocardial ischemia and infarction or even sudden cardiac death. Historically, patients with breast cancer treated with radiotherapy have been at a higher risk of cardiac death relative to radiation-naïve patients. The risk of coronary artery disease complications (such as myocardial infarction and resultant death) increases linearly with rising mean dose to the heart. Based on studies involving long-term follow-up periods, the risk of cardiovascular complications increases after 5 years from completion of radiotherapy and shows a steady upward trend [1]. Modern radiotherapy techniques help to significantly reduce both the mean dose and the high dose areas affecting the heart. However, in practice we do not know whether the important factor is the mean dose received by the entire heart or the pericardium alone, or the dose received by the coronary vessels or other potentially vulnerable anatomical structures. We are also not knowledgeable about the cardiac effect of small doses in a high volume, typically administered when using static and dynamic intensity-modulated radiotherapy techniques (IMRT). These issues remain unclear because modern technologies have been introduced relatively recently (dynamic IMRTs have been used in clinical practice for 5 years while static IMRTs for ca. 10 years) and not enough time has passed for us to be able to assess their potential cardiotoxicity. In practice, we are guided by dosimetry data (spatial distribution of dose over patient's organs) which are obtained after planning radiotherapy on the basis of digitally processed CT scans taken of the patient in a treatment position.

DISCUSSION

Yeboa and Evans discuss factors that need to be taken into consideration when planning and administering radiotherapy to breast cancer patients [2]. Modern heart-sparing techniques include use of heart shields, particularly for patients with clearly visible tumour bed, which however may result in insufficient irradiation of 2.8% of breast tissue on average [3]. On the other hand, no increase in local recurrence rate has been observed in patients on whom shields were used. Another factor is the proper position and immobilisation of the patient. To this end, it is recommended to use breast boards. They help to reduce the mean dose to the heart by 60% and the maximum dose by 30% relative to irradiation received by a patient lying flat on the treatment table [4]. When the patient is in a prone position, the heart volume present in the irradiation field decreases in 85% patients. The volume of heart present in the irradiation field is reduced by 87%, however the benefits are primarily experienced by patients with breast volume not smaller than 750 cm^3 [5]. Using the deep inspiration breath hold (DIBH) technique in radiotherapy helps to reduce the dose to the heart in patients with left-sided breast cancer. The volume of heart present in the irradiation field is reduced by up to 80% [6], the volume of heart included in the 50% isodose is reduced from 19% to 3% [7], while the volume of the left coronary artery within the 20 Gy isodose line is reduced by 5% on average [8]. When used on a selected group of patients in early stages of the disease, the accelerated partial breast irradiation (APBI) approach helps to reduce the mean dose to the heart by 84% relative to the whole-breast irradiation technique [9]. Hypofractionated radiation therapy (involving higher than standard fractionated doses, lower total dose and shorter total treatment time) in whole-breast irradiation achieves comparable outcomes and cosmetic effects to conventional radiotherapy and is more convenient to patients and treatment centres (more cost effective). To date, hypofractionated techniques have not shown a statistically significant effect on cardiovascular mortality. Thus, hypofractionated radiotherapy is considered an alternative to conventional radiotherapy [10]. Using modern radiotherapy techniques helps to plan and optimise doses more effectively. Static IMRT may offer advantages in terms of mean dose to the heart relative to dynamic IMRT. Proton therapy (with results being evaluated on the basis of early-phase clinical trials so far) helps to reduce the mean dose to the heart to 0.009 Gy relative to 1.6 Gy when using DIBH IMRT [11]. The mean dose received by the heart of patients who underwent proton beam irradiation of the left breast is 1 Gy. We should not expect the proton technique to become more accessible to breast cancer patients in the near future due to high cost and, so far, no findings from clinical trials about its efficacy and toxicity relative to widely used photon beam radiation.

The rules for monitoring cardiotoxicity of radiotherapy are another issue. To date, the most frequently used measure has been the mean dose to the heart. However, based on the hypothesis that radiotherapy exacerbates the sclerotic lesions in coronary arteries occurring with age and reduces vessel tolerance, it appears useful to estimate the dose administered to the main coronary vessels, particularly the anterior interventricular branch of left coronary artery (also: left anterior descending artery, LAD) which is typically found in the irradiation field. A 1 Gy increase in the mean dose to the heart translates into a 4.82 Gy increase in the dose to the LAD [12]. Thus, it seems reasonable to spare the LAD even though the tolerance dose is not known yet and the most efficient measure for preventing cardiovascular death has not been defined.

Based on a study involving 2,168 female patients treated with radiotherapy for breast cancer with mean dose to the heart of 4.9 Gy, Darby et al. [12] reported a 7.4% increase in cardiovascular complications (myocardial infarction, vessel revascularisation and death due to ischemic heart disease) for a 1 Gy increase. The higher rate was seen in both women with additional risk factors for a heart disease and women with no such additional factors. Total risk increased more in patients with cardiac risk factors (R = 6.67). Patients who have received radiation therapy on the left breast showed a higher rate of cardiovascular complications than patients whose right breast was irradiated. As part of the study, doses received by the heart and LAD were estimated. The mean dose to the heart was 6.6 Gy for patients with left-sided breast cancer and 2.9 Gy for patients with right-sided breast cancer. The risk of cardiovascular complications was 10% in patients whose mean dose to the heart was < 2 Gy, 30% for 2–4 Gy, 40% for 5–9 Gy and 116% for > 9 Gy.

Lee et al. [13] showed results from 12 years of following up 1,851 female patients who received adjuvant radiotherapy after mastectomy. The risk of acute coronary symptoms was significantly higher for patients who underwent radiation therapy, particularly in the case of hypertensive or diabetic patients, when compared with the control group. Patients with cardiac risk factors who received radiation therapy should receive intensive cardiac care subsequent radiation therapy.

Boekel et al. [14] published findings from a study on a group of 70,230 patients who underwent surgery due to breast cancer. They compared the risk of cardiovascular diseases in such patients relative to the entire population. In comparison to mastectomy alone and adjuvant radiotherapy following right-sided mastectomy, adjuvant radiotherapy following left-sided mastectomy was shown to increase cardiac risks, including risk of ischemic heart disease, heart valve disorder and congestive heart failure.

Taylor et al. [15] reviewed the mean doses of radiotherapy administered to the whole heart of patients irradiated due to left-sided breast cancer on the basis of 149 studies conducted in 28 countries. The mean dose for tangential fields (3D radiotherapy technique most frequently used in the last 20 years, not relying on IMRT) was 5.4 Gy across the entire group, 4.2 Gy in the group receiving regimens that did not include the internal mammary lymph nodes, 1.3 Gy in the breathing control group, 1.2 Gy in the lateral-decubitus position group and 0.5 Gy in the proton radiation therapy group. For IMRT, the mean dose was 5.6 Gy across the entire group and 8 Gy in the group receiving regimens that included the internal mammary lymph nodes. In case of patients treated with radiation therapy for right-sided breast cancer, the mean dose to the heart was 3.3 Gy.

McGale et al. [16] presented a study on 35,000 female patients treated with radiation therapy due to breast cancer which showed that patients after left-sided therapy were at a higher risk of cardiovascular complications including ischemic heart disease, pericarditis and valve heart disorder [17].

Tariq and Harrison [18] drew attention to the question whether the dose received by the whole heart or by the coronary arteries is more important. Post-radiotherapy angiography showed that patients who received the highest doses on the mid and distal LAD were at the highest risk of complications.

Nitsche et al. [19] discus cardiotoxicity from the radiotherapeutic point of view. At present, there seem to be no significant cardiovascular complications associated with adjuvant radiation therapy in breast cancer when employing modern techniques, including in combination with chemotherapy and immunotherapy. Radiation therapy seems to be safer than in the past, however patients must be followed-up to ensure there are no late complications.

Kingsley and Negi [20] demonstrated that while it is true that IMRT, DIBH and spiral tomotherapy (a variation of dynamic IMRT) may reduce cardiotoxicity, the most important factors that lead to reduction of the heart dose are both the selected radiotherapy technique and the skills and experience of radiation oncologists. Irradiation of the heart may result in severe pathological damage which is manifested by diffuse interstitial fibrosis, microcirculatory damage leading to ischemia and fibrosis, fibrous thickening of the pericardium, valvular fibrosis and severe atherosclerosis. These act as clinical symptoms of coronary artery disease, pericarditis, cardiomyopathy, valvular heart disease and conduction disturbances. Risk factors of cardiac diseases include total dose > 30–35 Gy, fractionated dose > 2 Gy, large volume of irradiated heart, young age at exposure to radiation, time elapsed since exposure, use of cardiotoxic chemotherapy or trastuzumab, co-morbidities such as diabetes, hypertension, dyslipidemia, obesity and smoking [21]. However, more recent studies suggest that doses below 20 Gy or even below 5 Gy may increase the risk of cardiovascular complications. Further studies are needed to assess the long-term effect of low doses of irradiation (0.5–5 Gy) on the heart. Conventional adjuvant radiotherapy using tangential fields involves administration of ca. 2 Gy on the heart and ca. 8 Gy on the LAD [22]. The differences result from the diverse curvature of the chest wall and the proximity of the heart and lungs to the irradiation field. IMRTs are recommended for patients treated with conventional irradiation techniques whose maximum heart distance (MHD, the distance between the anterior heart contour and the posterior field border of a tangential treatment beam) is small and the doses to the heart and LAD are high.

Jacob et al. [23] presented a report from a 2-year follow-up of 120 patients treated with adjuvant 3D CRT radiotherapy for breast cancer without chemotherapy. The patients were followed up using echocardiography, coronary computed tomography angiography and biomarkers. The absorbed dose was evaluated for the whole heart and its substructures, including in particular the coronary arteries, and the dose effect on the subclinical dysfunctions was assessed. To date, dose to the heart has been typically evaluated using dose-volume histograms (DVH). However, they provide no information about the high-dose areas observed in the apex and the anterior apical region of the heart. The study is expected to show in detail the distribution of radiation across the heart and coronary vessels for all patients based on CT angiographs, and its association with subclinical lesions seen in imaging, function tests and lab results. The study intends to optimize radiotherapy protocols, leading to individualised radiation therapy and higher therapeutic index for each patient. It may improve primary prevention as well as early detection and treatment of cardiotoxicity in patients receiving radiotherapy.

CONCLUSIONS

In summary, personalisation (recently a trendy term, not only in oncology) of radiotherapy, taking into account individual characteristics of each patient such as individual anatomy, pre-existing cardiac risk factors and the need to use systemic treatment, appears to be a reasonable way forward from a radiotherapy oncologist's point of view. Having regard to that, contemporary radiotherapy techniques enable selection of the most optimum irradiation planning and treatment methods, based on the technical capabilities and experience of each treatment centre. The key issue is to determine the most beneficial dose distribution in the heart region, reduce the dose to the heart as much as possible, and most importantly reduce the dose to the LAD. It is crucial to ask which technique is associated with lower risk of cardiovascular complications, whether conventional radiotherapy using tangential fields where higher doses of irradiation are administered to a smaller portion of the heart or the dynamic IMRT where lower dose is used on a larger portion of the heart with a possibility to reduce the dose to the left coronary artery. The tolerance dose for coronary arteries needs to be determined. Early detection and monitoring of cardiovascular complications relying on laboratory tests of cardiac biomarkers, angiography and echocardiography are also relevant. However, a full overview of late cardiovascular complications will only be obtained after many years of following up patients treated with modern radiotherapy techniques. And, last but not least, we cannot forget about pulmonary toxicity (particularly in elderly patients with decreased pulmonary reserve) and the risk of inducing secondary tumours in patients after radiotherapy and chemotherapy (in case of younger people before the age of 55–60). The data discussed in this paper, new technologies used in radiotherapy and continuously improving long-term outcomes in breast cancer treatment suggest that the issue of radiation-induced cardiovascular complications must be re-visited or even verified by prospective clinical trials given that the data available at present is largely outdated and historic.

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