Evaluation of dose to cardiac structures during breast irradiation

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Objective: Adjuvant radiotherapy for breast cancer can lead to late cardiac complications. The highest radiation doses are likely to be to the anterior portion of the heart, including the left anterior descending coronary artery (LAD). The purpose of this work was to assess the radiation doses delivered to the heart and the LAD in respiration-adapted radiotherapy of patients with left-sided breast cancer.

Methods: 24 patients referred for adjuvant radiotherapy after breast-conserving surgery for left-sided lymph node positive breast cancer were evaluated. The whole heart, the arch of the LAD and the whole LAD were contoured. The radiation doses to all three cardiac structures were evaluated.

Results: For 13 patients, the plans were acceptable based on the criteria set for all 3 contours. For seven patients, the volume of heart irradiated was well below the set clinical threshold whereas a high dose was still being delivered to the LAD. In 1 case, the dose to the LAD was low while 19% of the contoured heart volume received over 20 Gy. In five patients, the dose to the arch LAD was relatively low while the dose to the whole LAD was considerably higher.

Conclusion: This study indicates that it is necessary to assess the dose delivered to the whole heart as well as to the whole LAD when investigating the acceptability of a breast irradiation treatment. Assessing the dose to only one of these structures could lead to excessive heart irradiation and thereby increased risk of cardiac complications for breast cancer radiotherapy patients.

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Adjuvant radiotherapy applied after breast conserving surgery of breast cancer improves the rate of local control and overall survival [1]. However, this treatment implies irradiating some of the patient's ipsilateral lung and, for patients with left-sided cancer, also the heart, leading to the risk of long-term pulmonary and cardiac complications [1, 2].

The most recent update from the Early Breast Cancer Trialists' Collaborative Group indicates that radiation therapy was associated with excess mortality from heart disease [1]. Although many of the studies included in this review involved older treatment techniques, which probably delivered a higher dose to the heart than seen in modern radiotherapy clinics, the issue of cardiac morbidity and mortality after breast cancer treatment is still relevant, as demonstrated by recent publications on the topic [3–5].

In the last decade, there has been a strong focus on reducing the radiation dose to the heart in order to minimise the risk of side effects with the help of advanced imaging and treatment techniques. Modern CT-based three-dimensional (3D) conformal treatments are thought to have reduced the risk of heart damage [1]. The newest techniques include breathing-adapted radiotherapy, which takes advantage of the change in the patient's anatomy during the respiratory cycle: in this case, patients only

receive radiation when they are at deep inspiration, so as to inflate the lungs and "push" the heart out of the radiation field. Our research group as well as other groups have documented that this technique further reduces the radiation dose to the heart [6–10]. It is, however, still unclear what the mechanisms of cardiac radio-induced toxicity really are, and what dose levels are relevant. Moreover, the whole heart is often the only organ volume included in retrospective dose evaluation studies. However, the dose distribution in the heart is not homogeneous and the highest doses are likely to be delivered to the anterior heart, including the left anterior descending coronary artery (LAD). This is a concern since new studies suggest that arteries are particularly sensitive to radiation, and the LAD is one of the typical sites of origin for ischaemic heart disease [11].

In this context, it is appropriate to ensure that radiation treatments for breast cancer patients are designed to minimise the dose to cardiovascular structures while still ensuring a proper irradiation of the target volume (breast and associated lymph nodes). The purpose of the present work is to assess the radiation doses delivered to the heart and the LAD in respiratory-gated of left-sided high-risk breast cancer patients.

Methods and materials

24 patients referred for adjuvant radiotherapy after breast-conserving surgery for left-sided lymph node-positive breast cancer were evaluated (all women, age

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ranging from 36 to 76 years, median 58.5 years, at the time of treatment). Patients were treated to 48 Gy in 24 daily fractions (5 fractions a week). The target volume typically encompasses the remaining breast tissue after tumorectomy and, in cases with lymph node metastases, also the regional lymph node areas. In the present study, this implies the irradiation of the lymph nodes along the ipsilateral internal mammary vessels. The latter procedure is controversial and not performed in all countries [12]. It goes beyond the scope of this study to discuss the controversy, but we expect that the results of the study are applicable regardless of the irradiation technique and target volumes.

A relationship can generally be established between the volume of a healthy organ receiving high radiation doses and the probability of side effects. Increasing irradiation of the heart leads to increased risk of ischaemic heart disease [11], and it has been shown that patients with left-sided cancer had a higher risk of cardiac mortality than patients with right-sided cancer [13]. For a clinically relevant example, it has been suggested that if 5% of the heart receives 40 Gy, the risk of cardiac mortality exceeds 2% [14]. Consequently, in the adjuvant setting it is pivotal to minimise radiation to the heart since breast cancer survivors have a good prognosis for cancer-free survival and may live several decades after treatment. The Danish Breast Cancer Cooperative Group (www.dbcg.dk) recommends that the volume of heart receiving more than 40 Gy be kept below 5%, as well as the volume receiving more than 20 Gy be kept under 10%.

Keeping the dose to the organs at risk within the above constraints is not always achievable when delivering a high dose to the whole target volume, and sometimes a compromise must be reached. For example, since patients with left-sided breast cancer may present a considerable volume of heart in the irradiation field, otherwise indicated internal mammary node chain irradiation may have to be abandoned in this group in order to minimise the risk of radiation-induced ischaemic heart disease.

In our institution, breathing-adapted radiotherapy was introduced in 2003 and is now the standard treatment for patients with left-sided node-positive breast cancer. This technique is a highly technology-dependent treatment method, since all the steps of the treatment process (from treatment planning CT scanning of the patient to acquire anatomical information, to the treatment delivery in itself) have to be performed in synchronisation with the patient's breathing cycle. A complete description of the equipment used, as well as the clinical workflow, can be found in previous papers [7, 15, 16].

In clinical routine, CT images from the patient are exported to a treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA), where the radiation oncologist contoured the target volume: remaining breast, internal mammary nodes (IMNs), periclavicular and axillary lymph nodes, and the LAD in the CT volume. In our clinic, the arch of the LAD is routinely contoured by the radiation oncologist and is used as a surrogate for evaluation of heart irradiation. Additionally, in this study the whole heart and the whole LAD are retrospectively contoured for research purposes. It should be noted that contouring the LAD is difficult when contrast is not injected and should be performed by a radiologist or a radiation oncologist who received special training to perform this challenging task.

A three-field mono-isocentric 6 MV partial wide-tangent photon field technique is used with two tangential fields to cover the breast and IMN (Figure 1a) and an anterior field to cover the axillary and periclavicular lymph nodes (occasionally an additional fourth posterior field was needed to achieve the latter). Beam modifiers, such as wedges and multileaf collimators, are used to achieve dose uniformity throughout the target volume, and to shield critical normal tissue (see Figure 1b).

The prescription dose is 48 Gy to the target volume, given in 24 fractions. The criteria for the treatment are that the dose to the target volume should be between 90% and 110% of the prescription dose, while a maximum of 35% of the ipsilateral lung volume may receive 20 Gy or higher. The arch of the LAD is considered to receive an unacceptably high dose when any part of the contoured volume receives 20 Gy or more. The doses and volumes are evaluated using dose-volume histograms (DVHs), in which the cumulative doses to the organ volumes are graphed. An example of a typical DVH graph and a description of its interpretation are presented in Figure 2.

In this study, the whole heart and the whole LAD are retrospectively contoured on 24 patients for research purposes in addition to the arch of the LAD. The acceptability of the treatments delivered to this patient group is then analysed considering the dose delivered to (1) the whole heart, (2) the arch of the LAD and (3) the whole LAD. The whole LAD is considered to be receiving a high dose when over 10% of the contoured volume received 20 Gy or more.

Results and discussion

The results are presented in Figure 3 as DVHs of the three cardiac structures considered. The data for each patient are represented by a specific colour.

For 13 patients, the plans are acceptable based on the criteria set for all 3 contours (in 8 of these 13 patients the radiation dose to any cardiac structure is virtually 0). For the remaining 11 patients, however, there are disagreements on acceptability based on the respective contours.

For 9 patients, the volume of whole heart irradiated is well below the recommended thresholds (20 Gy to 10% and 40 Gy to 5% of the total volume), whereas a high dose is still being delivered to the whole LAD. In three cases, the dose to the arch LAD is very low, although a significant (but still within acceptability criteria) portion of the heart is included in the field. In one single case, a plan that was accepted on the basis of a low dose to the arch LAD retrospectively showed 20% of the contoured heart volume received over 20 Gy (Figure 3a). In three patients, the dose to the arch LAD is virtually zero whereas the dose to the whole LAD is considerably higher (up to 46% of the contoured volume received over 20 Gy).

Figure 3b,c illustrates the fact that the inferior portion of the LAD receives the highest dose. Irradiation of this area is arguably less likely to lead to cardiovascular complications than irradiation of the arch, as it supplies a smaller part of the myocardial tissue, but should still be considered at risk in view of the high doses.

In this group, the mean doses to cardiac structures are 2.9 ± 2.2 Gy for the heart and 17.8 ± 14 Gy for the whole

Figure 1. (a) Axial view of a CT-based breast radiation treatment plan. Two tangential beams (white arrows) are used to cover the breast tissue (in some cases, the treatment field will be extended to include lymph nodes). The area in red colour-wash represents the anatomy that will receive a dose of radiation of 20 Gy or more. (b) Projected view of a tangential radiation field onto a breast cancer patient anatomy. A multileaf collimator (displayed as blue lines) is used to exclude as much of the heart as possible from the radiation field without compromising dose to the breast. However, one can clearly see that the anterior heart (yellow) and a small portion of the left anterior descending coronary artery (LAD) (pink) are still included in the treated area.

LAD. Although the mean dose to the heart is on par with other reports in the literature [5, 17, 18], the dose to the LAD is higher. For example, Taylor et al [5] quote the mean doses received by Swedish women treated for left-sided breast cancer in the 1990s as 3.0 ± 0.5 Gy to the heart and 12.0 ± 2.3 Gy for the LAD (including 1 cm margin). These differences could be caused by differences in

Figure 2. Dose-volume histograms for a typical breast irradiation plan. For each dose level on the horizontal axis the per cent volume of each organ receiving that dose level or more is plotted. The dose delivered to several structures is assessed. The breast should be covered by 90–110% of the prescription dose (here 48 Gy). The dose to critical healthy organs should be limited. In this case, the left lung receives a dose of 20 Gy or more to 30% of its total volume. The volume of arch left anterior descending coronary artery (LAD) irradiated to 20 Gy is virtually zero (as illustrated by the dotted arrow). This fulfils the dose constraints described in the “methods” section. Hence, the plan was judged satisfactory for treatment.

treatment techniques or more likely in contouring strategy: in the present study, the irradiation technique uses wide tangential fields with deep-inspiration respiratory gating and the LAD is contoured without additional margin.

From Figure 3c, one can clearly distinguish 2 groups of patients: one where the dose delivered to the whole LAD volume lies well below 20% of the total dose, and another group where the LAD receives up to 40 Gy to a significant relative volume. It would be valuable to see how much the dose to the LAD can be reduced in this second group by additional optimisation of the treatment plan with this dose as an evaluation criterion. Another important parameter is the resulting cardiac risk to this patient group. The average probability for cardiac mortality (calculated using a relative seriality model [14] and based solely on the dose distribution to the heart) in these 24 patients is 0.6%. However, 3 patients have a probability of cardiac mortality between 1% and 2%, whereas for a single patient (who received 20 Gy to 20% of the heart volume) this probability is 5.7%. The results of this study suggest that at least in a subgroup of patients, some volume of the LAD receives a high (well over 10 Gy) radiation dose. No model describing the risk resulting from LAD irradiation is available, but it is possible that high doses to the LAD might be linked to an increased risk of cardiac complications which has not been taken into account in the current cardiac toxicity models.

These results also indicate that it is hard to find one single surrogate organ to estimate the dose received by cardiovascular structures. However, a very low (virtually zero) dose to the whole LAD seems to be associated with a very low dose to the heart. The reverse statement is not true. In view of these results, we propose that the whole LAD should be contoured as a risk organ along with the whole heart and used prospectively for plan

Figure 3. Dose–volume histograms for all patients for (a) the heart, (b) the arch of the left anterior descending coronary artery (LAD) and (c) the whole LAD. Each patient has a separate colour code. (a) The dose thresholds recommended by the Danish Breast Cancer Cooperative Group are illustrated as dotted black lines.

optimisation (the arch LAD does not seem to provide any additional information). If it is not possible to contour both structures owing to time constraints, the whole LAD should be preferred as an organ at risk.

Conclusion

In our experience it is not sufficient to calculate the dose to one surrogate organ as an estimate of the dose to all cardiac structures: we recommend that both the whole heart and the whole LAD be contoured and their respective dose burdens evaluated when investigating the acceptability of a breast irradiation treatment. As a result of this study, in our clinic, the practice will change from contouring only the arch of the LAD to using the entire visible part of the LAD as a risk organ.

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