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REVIEW

New and Modern Radiotherapy Techniques to Prevent Radiation-induced Cardiotoxicity

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SUMMARY

Significant advances in technology have allowed radiation therapy to be administered in a way that minimizes cardiac dose and the risk of late cardiovascular complications while providing tumor control. Various treatment methods can be used to reduce the heart dose in the treatment of breast cancer and thoracic tumors with radiation. Deep inspiration breath hold technique, application of radiotherapy in the prone position, accelerated partial breast irradiation are frequently used methods in the treatment of breast cancer. Intensity-modulated radiotherapy and proton therapy have been shown to reduce the cardiac dose in many diseases such as breast cancer, lung cancer, esophageal cancer, mesothelioma, bilateral lung irradiation, lymphoma, and craniospinal irradiation. The best cardioprotective technique should be used by evaluating patient characteristics (age, comorbid diseases, and patient's anatomy) and technical possibilities.

Keywords: Deep inspiration breath hold, intensity modulated radiation therapy, proton therapy, radiation induced cardiotoxicity.

Introduction

In cancer treatment, side effects become more important as tumor control success and survival increase. Optimum protection of normal tissues at risk while maintaining tumor control is a radiation oncologist's top priority. One of the most important organs in radiotherapy applied to the thoracic region is the heart. The heart can be protected from side effects with increased awareness to avoid cardiotoxicity, tissue contouring, and treatment planning using three-dimensional (3D) imaging, appropriate systemic treatment selection, and other strategies.

While 2D techniques were used to apply radiation therapy in the past, today it is possible to evaluate targets and organs at risk in 3D with modern planning using computed tomography (CT).[1] Advanced radiation therapy planning techniques, proton-charged particle therapy, the use of modern imaging methods in RT planning, and the use of image-guided radiotherapy may provide the opportunity to create more compatible treatment plans and reduce cardiac dose.[2]

Heart doses can be reduced by using deep inspiration breath-hold technique (DIBH), prone patient positioning, accelerated partial breast irradiation, intensity-modulated radiotherapy (IMRT), proton therapy. These techniques and treatment modalities will be discussed in the following section.

Deep Inspiration Breath-hold Technique

The goal of this technique is to deliver radiation at a certain stage of the respiratory cycle while the breast and chest wall are as far away from the heart as possible.[3,4] When patients take a deep breath, the heart moves down, middle, and back. Treating patients with left breast cancer with this technique has been shown

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to reduce the radiation exposure of the heart during radiotherapy.[5,6]

In addition, the DIBH technique may also be effective in patients with right-sided breast cancer. It has been shown to reduce the liver doses as well as the heart and lung doses in these patients. The two most used breath-hold methods: the spirometry-based active respiratory coordinator system (Elekta, Stockholm, Sweden); and a video-based real-time position management system (Varian Medical Systems, Palo Alto, CA). Left-sided breast cancer, indication for internal mammaria node radiotherapy, and cardiac anatomy very close to the chest wall can be counted as patient selection criteria for DIBH.[7]

Some studies have looked at combining breath-hold techniques and the use of IMRT, and have found greater reductions in cardiac dose when both are used.[8] In a study comparing 3D conformal radiotherapy using the DIBH technique and IMRT plans in free breathing, significant reductions were found in all cardiac dose measurements with DIBH and 3D-conformal radiation therapy (CRT).[9] A CT-based study has shown that in almost half of the patients the heart can be completely removed from the treatment site.[10] Deep inspiration breast hold technique can also be combined with IMRT and 3D-CRT (Fig. 1).

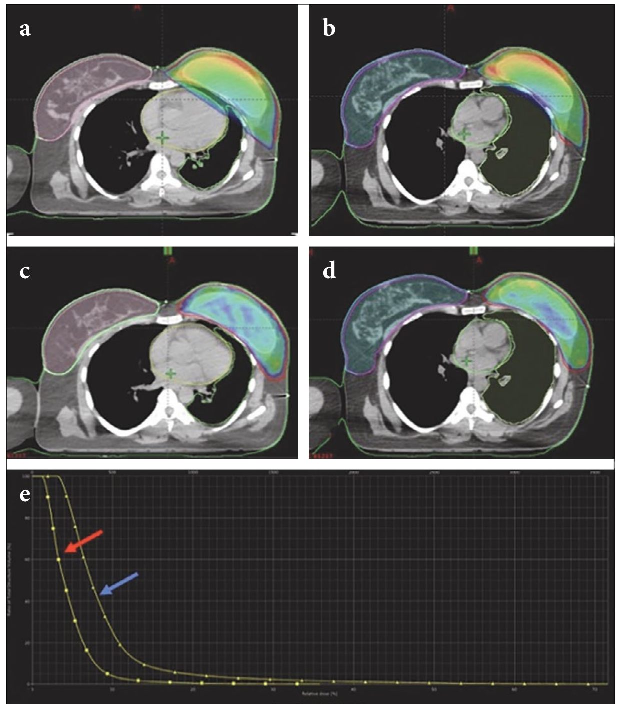

Fig. 1. Dose distribution of 45Gy in 25 fractions planned using FinF technique in a patient with left breast cancer in a and b (Picture a with free breath, Picture b with deep inspiration breath-hold technique); Dose distribution of 45Gy in 25 fractions planned using volumetric modulated arc radiotherapy (VMAT) technique in a patient with left breast cancer in c and d (Picture c with free breath, picture d with deep inspiration breath-hold technique); Dose volume histogram of the patient whose 25 fractinations of 45Gy were planned using VMAT technique in e (compared with free breath [blue arrow], it is seen that heart doses decreased with deep inspiration breath-hold technique [red arrow]).

Prone Position

Patients undergoing radiation therapy are typically treated in the supine position; however, prone positioning may be beneficial in patients with large, pendulous breasts, reducing the overall cardiac dose by allowing the breast to drop away from the chest wall and heart.[11,12]

In a study of 200 breast cancer patients simulated with both prone and supine positioning, it was found that prone positioning reduced cardiac volume in the field in 85% of patients. The reduction in cardiac volumes was 87% (8.8-1.3 cm^3). All women had reductions in heart volume, although the benefit was not statistically significant in women with a breast volume <750 cm^3. The greatest benefit was found in patients with large breast volume.[13]

However, there are conflicting data regarding the practical value of the prone positioning technique. A recent study showed that this technique reduced cardiac doses in 19 of 30 patients, but increased cardiac dose in 8 of 30 patients.[14] Similarly, in a planning study involving 18 patients, no significant heart-protective difference was found between the use of IMRT and the prone and supine positions.[15] Prone techniques can also be combined with IMRT and accelerated partial breast ırradiation (APBI). In the case of breast irradiation alone, treatment in the prone or lateral position may be an excellent alternative for patients with large or pendulous breasts.[16] However, the reliable application of this technique requires experience.

APBI

APBI is a technique in which only the lumpectomy cavity is treated with a margin in women at low risk of recurrence for breast cancer. While APBI is only suitable for a select group of breast cancer patients, it can significantly reduce the dose delivered to nearby structures, including the heart.

APBI can be administered via external beam radiation or brachytherapy catheters inserted into the lumpectomy cavity. Brachytherapy APBI studies have shown that the mean cardiac dose is between 1.65 and 2.45 Gy and the mean V5 is between 1% and 59.2%.[17] One study achieved a mean maximum cardiac dose of around 2.2 Gy with both Mammosite and Clearpath brachytherapy catheters, but patients in this study had lesions closer to the skin than to the chest wall.[18] External beam studies have shown that mean cardiac doses are 1.2Gy and V5 is 1%. RTOG 0413 detected a mean V5 value of 1.1% with external partial breast irradiation in left-sided patients.[19]

A study evaluating volumetric modulated arc radiotherapy (VMAT) achieved an APBI plan with a mean cardiac dose of 0.72 Gy.[20] Compared to a 3DCRT APBI plan, the IMRT, VMAT APBI plans were able to significantly reduce mean heart V5 from 3% to 1.1% and 1.7%, respectively.[21]

Intensity-modulated Radiation Therapy

High doses are limited to the heart in patients with left-sided breast cancer treated with IMRT, as has been demonstrated in many sites treated with intensity-modulated radiation therapy.[22,23] Different techniques such as prospective planned IMRT, reverse planned IMRT, and modulated arc therapies have been studied.

Studies have shown that IMRT reduces the dose specifically for the coronary arteries and left ventricle compared to conventional therapy.[24] Additional improvements in IMRT planning allow reductions not only in mean cardiac dose but also in the anterior myocardial region and left ventricular dose (areas at highest risk of cardiac morbidity from radiotherapy).[25]

Multiple IMRT techniques have been developed, each showing significant improvement in cardiac dose measurements compared to 3D-CRT (both when treating the entire breast alone and when regional lymph nodes are included). For whole breast IMRT, the field--in-field technique was found to be the most cardiac dose saver of the techniques used.[26,27] IMRT can also be used together with breathing techniques, prone technique, and APBI.

Kalapurakal et al.[28] evaluated cardiac protective whole-lung irradiation (WLI) using IMRT. They compared the doses received by the heart in the anterior-posterior 3D-CRT and IMRT WLI plans. Median 15 Gy of radiotherapy was applied. Compared with standard AP WLI, a statistically significant reduction in radiation doses to the whole heart, atria, ventricles, and coronary vessels was achieved with cardiac protective IMRT.

In the secondary analysis of the RTOG 0617 study, patients with lung cancer treated with IMRT had a lower heart dose than those treated with conventional 3D-CRT. The value of V40 was also inversely proportional to OS (V40 6.8% vs. 11.4%; $p<0.01$).[29]

Appropriate toxicity profiles have been reported for helical tomotherapy, IMRT, VMAT, and recently adjuvant radiotherapy with proton techniques in the treatment of mesothelioma.[30-33] Typical mean heart-Dmean doses 18.8-24.8 Gy (VMAT), It is in the range of 18.5-32.9 Gy (IMRT) and 21.5-24.8 Gy (HT), and lower heart-Dmean doses are obtained in right hemithorax radiotherapy.[34] More recently, intensity-modulated proton therapy (IMPT) has been shown to be clinically safe and feasible, with increased contralateral lung, heart, esophagus, liver, and ipsilateral kidney protection compared to IMRT or VMAT photon techniques.[33,35] Clinical and comparative planning studies have demonstrated clinically acceptable proton plans with simultaneous reduction of heart-Dmean, heart-V40, and V45 dosimetric parameters by 49-76%, 36-75%, and 53-69%, respectively.[35,36]

There are some studies comparing dosimetric isodose plans using modern irradiation techniques in esophageal cancer. Chen et al.[37] compared IMRT, tomotherapy, and 3D-CRT techniques and found that the heart (V30 and V45) was better preserved in IMRT and tomotherapy, but the lung V10 was more acceptable in 3D-CRT. Choi et al.[38] compared with 3D-CRT in V20, V30, and V40 parameters, using IMRT and VMAT recorded better cardiac protection. On the other hand, Wu et al.[39] compared the isodose plans of VMAT, IMRT, and 3D-CRT and suggested that 3D-CRT is a convenient and cost-effective option for radiotherapy of mid-thoracic esophageal cancer, although they found better protection of the heart.

Proton Therapy

Proton beam radiotherapy represents a technique that allows dose reduction to structures beyond the target volume, depending on the properties of the proton particle. The rapid dose reduction beyond the Bragg peak allows for a potential reduction in dose to critical adjacent structures and a reduction in acute and late toxicities.

Numerous dose comparisons have confirmed that compared to most modern photon technologies,

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such as stereotactic body radiation therapy, VMAT, and IMRT, proton therapy results in integral dose reduction in normal tissues exposed to unnecessary radiation. Epidemiologically common tumors including head-and-neck malignancies, gastrointestinal and thoracic malignancies, and breast cancer were investigated.[40]

Although primarily used for pediatric cancers, skull base tumors, and re-irradiation, there are some studies suggesting a role in reducing cardiac dose with PBT for breast cancer. Initial dosimetric studies evaluating single-site PBT found no difference in mean breast dose with protons compared with conventional photon or IMRT therapy but found a reduction in maximum cardiac dose.[41] IMPT has been shown to further reduce cardiac dose (lower V5Gy and V22.5Gy) compared to 3D-CRT and IMRT.[42,43] A phase III RADCOMP study comparing photon therapy versus proton radiation therapy after partial mastectomy with lymph node involvement is ongoing.[43]

Proton beam craniospinal irradiation (CSI) offers lower predicted risks of healthy tissue complications compared to photon beam CSI techniques. Because of the Bragg-peak, the output dose to the OAR is significantly reduced in the administration of proton radiotherapy therapy. Estimated complication rate risk reduction was shown by Ho et al.[44] In a small study of 17 pediatric patients, field-in-field photon CSI and passively scattered proton planes were compared. The RR (proton/photon) ratio for cardiac mortality ranged from 0.12 to 0.24. They succeeded in reducing the heart-Dmean value from 10.4±2.2 Gy in photon planes to 0.2±0.2 Gy in proton planes.[45]

Ling et al.[46] compared in 10 esophageal cancer patients proton therapy, IMRT, and 3DCRT in CT data. This study found no benefit of IMRT compared to 3D-CRT, but proton therapy was beneficial at lower cardiac doses compared to both IMRT and 3D-CRT. Similarly, the dosimetric study of Shiraishi et al.[47] reported that proton therapy was associated with significantly lower radiation exposure to the entire heart and cardiac infrastructures compared to IMRT. Prayongrat et al.[48] published clinical data of IMPT in 19 patients with esophageal cancer. They recorded only two grade 2 toxicities (pericardial effusion and atrial fibrillation) with a mean follow-up of 17 months.

Hirano et al.[49] compared proton therapy, IMRT, and 3D-CRT plans in CT data of 27 esophageal cancer patients treated with proton therapy. Proton therapy as a heart and lung protector achieved a better dose distribution compared to IMRT and 3D-CRT. Clinically, grade 2 late pericardial effusion developed in four patients (15%) after proton therapy.

Conclusion

There are different treatment techniques that can be used to prevent cardiotoxicity. With the breath hold technique, the cardiac volume in the field decreases; mean, maximum and other cardiac dose parameters decrease; left anterior descending dose decreases, the probability of cardiac mortality decreases. With treatment in the prone position, intra-field cardiac volume is reduced in 75-85% of patients with left-sided breast cancer; mean cardiac dose decreases. Especially at high doses, V20, V30 (10-50%) and maximum dose decreases are observed with the application of intensity-modulated radiotherapy. In addition, the doses of the left ventricle and left anterior descending artery are reduced. A reduction in maximum cardiac doses is detected with proton therapy compared to 3D-CRT and IMRT. The cardiac mean dose can be reduced to around 1 Gy and many cardiac dose parameters are reduced. Which of these techniques will be used is selected depending on the diagnosis of the disease, patient characteristics, and the technical equipment of the centers. Keeping the cardiac dose low in breast and thorax irradiations should be one of the primary goals.

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