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Comparison of heart dose in early-stage left-sided breast cancers treated with intraoperative radiation therapy or whole-breast irradiation with deep inspiratory breath hold

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ABSTRACT

PURPOSE: To compare heart dose between patients treated with lumpectomy and either intraoperative radiation therapy (IORT) with CT-guided high-dose-rate brachytherapy (*precision* breast IORT [PB-IORT]) or whole-breast irradiation with deep inspiratory breath hold (WBI-DIBH) for early-stage left-sided breast cancers.

METHODS AND MATERIALS: We retrospectively identified the 17 patients with left-sided breast cancers treated with PB-IORT on a phase I clinical trial and 17 patients with left-sided tumors who had undergone lumpectomy and adjuvant WBI-DIBH. Dosimetric data were obtained. T-testing was performed and biologically effective doses (BEDs) were calculated using an α/β ratio of 2 Gy.

RESULTS: Mean heart dose was significantly lower with WBI-DIBH compared with PB-IORT (0.61 vs. 0.87 Gy, $p = 0.006$). Mean heart BED was lower with WBI-DIBH (0.62 vs. 1.3 Gy_2, $p = 0.0001$). Nominal maximum heart dose was higher with WBI-DIBH (11.37 vs. 4.81 Gy, $p = 0.004$). Maximum heart dose BED was similar between WBI-DIBH and IORT, 16.63 vs. 19.36 Gy ($p = 0.64$), respectively. No difference was found in mean left anterior descending artery dose: 2.18 Gy with WBI-DIBH and 1.89 Gy with IORT ($p = 0.446$). The maximum left anterior descending doses were 9.63 Gy and 3.62 Gy with WBI-DIBH and IORT, respectively ($p = 0.016$). Distance from the heart to the lumpectomy cavity was inversely associated with heart dose for PB-IORT, but not for WBI-IORT.

CONCLUSIONS: Heart doses were low in both groups. Expected increase in cardiac risk at these doses is minimal. It is unlikely that there will be a clinically significant difference in cardiac toxicity in patients treated with WBI-DIBH or PB-IORT. Further research is needed to evaluate the actual clinical impact of the observed cardiac doses delivered with these modalities.

Keywords: IORT; DIBH; Heart dose; Breast cancer

Introduction

Breast cancer is the most common nonskin malignancy diagnosed in women in the United States (1). There are numerous treatment options available for early-stage breast cancer, including mastectomy or breast-conserving surgery. Breast-conserving surgery is typically followed by radiation therapy, including whole-breast irradiation (WBI) therapy or accelerated partial breast irradiation (APBI). Breast-conserving surgery followed by adjuvant WBI has been shown to have equivalent survival compared with mastectomy (2). APBI can be delivered as intraoperative radiation therapy (IORT), fractionated brachytherapy, or external beam radiation therapy. APBI is considered an appropriate alternative to conventional WBI therapy in select patients per the NCCN Guidelines (3).

Potential for radiation-related cardiac toxicity may influence treatment selection in patients with breast cancer. Prior studies have shown a correlation between increased cardiac dose and cardiac events. A 7.4% increase in major cardiac events per Gy of mean heart dose was reported by

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Darby *et al.* (4).Such findings have led to the investigation of cardiac sparing radiation therapy techniques.

One of the most common cardiac sparing radiation techniques is deep inspiratory breath hold, which is used during WBI treatments (WBI-DIBH). DIBH is a technique in which the patient is instructed to take and hold deep breaths; the patient is only treated with external beam radiation therapy during the breath hold. This process is repeated multiple times until the planned dose of radiation is delivered. The distance between the heart and the chest wall is increased during the breath hold, leading to decreased heart dose with the use of DIBH compared with free-breathing techniques (5). Indeed, DIBH has been shown to decrease heart dose in patients treated with WBI (5).

IORT is another technique with the potential to decrease cardiac doses. It also has the advantages of reduced treatment and transportation time and potential to spare normal tissues from receiving significant doses of radiation. In appropriately selected patients, prior studies have shown IORT to be noninferior to WBI in regard to local control, using predefined noninferiority criteria. Although the TARGIT-A trial did show a statistically significant difference in local control favoring WBI by 2%, this was within the prespecified noninferiority criteria of 2.5% (6, 7). A meta-analysis of multiple studies supported a survival benefit with IORT compared with WBI, hypothetically attributable to increased WBI toxicity (8). This difference in survival was partially attributed to differences in cardiac mortality, with the TARGIT-A trial reporting a decreased number of cardiac deaths in patients treated with IORT compared with WBI (2 vs. 8 cardiac deaths) (6). This improvement in survival has been met with substantial criticism, particularly, because of the short latency from treatment to cardiac death, leading some to speculate that the correlation with treatment modality is spurious (9). Furthermore, this survival benefit has been disputed in another meta-analysis, by the Cochrane Review, which found no overall survival benefit and a slightly worse local recurrence-free survival with partial breast irradiation (HR 1.62) (10). Although a phantom study has suggested low heart doses in IORT patients, which would support a theoretical improvement in cardiac events (11), prior clinical studies have lacked CT planning to directly support improved cardiac toxicity dosimetrically.

At the University of Virginia, we developed a unique form of IORT, which uses CT-guided HDR brachytherapy (*precision* breast IORT [PB-IORT]). A phase I study was completed, which demonstrated the safety and feasibility of PB-IORT (12). A phase II study, designed to determine the long-term efficacy of PB-IORT, is underway. The purpose of this present study is to compare heart dose between patients treated with lumpectomy and either PB-IORT or WBI-DIBH for early-stage left-sided breast cancers at our institution. These are the first studies published using CT-guided IORT in the breast setting and will, therefore, allow for comparison of doses to normal structures between PB-IORT and WBI-DIBH treatment plans.

Methods and materials

Twenty-eight patients were enrolled and treated in a phase I study that was designed to evaluate the safety and feasibility of PB-IORT between December 2013 and April 2015 (12). Inclusion criteria for this trial included patients aged 50 years and older with tumor size less than or equal to 3 cm, node-negative disease, and either invasive or ductal carcinoma *in situ*, who opted for breast-conserving surgery. All 17 PB-IORT patients had negative surgical margins. PB-IORT was performed either at the time of lumpectomy or within 30 days of lumpectomy. Patients were excluded if they had bilateral breast cancer, positive nodes, multifocal disease, treatment with neoadjuvant therapy, or prior ipsilateral breast radiation therapy. The PB-IORT technique has been discussed in detail previously. In summary, it consists of lumpectomy, placement of a multicatheter brachytherapy balloon into the lumpectomy cavity (Contura multi-lumen; Hologic, Inc, Bedford, MA), CT acquisition using an in-room CT-on-rails, immediate treatment planning, and delivery of 12.5 Gy in a single fraction, followed by balloon removal and surgical closure, all performed under anesthesia (12). The prescription dose of 12.5 Gy to 1 cm from the balloon surface was selected because it delivers a surface dose of approximately 20 Gy, consistent with the surface dose used in the TARGIT-A trial, which had previously been shown to be well tolerated (6, 13). Of the 28 patients treated on the phase I study, 17 had left-sided breast cancers. These 17 left-sided patients constitute the PB-IORT group in this study.

We retrospectively identified a group of patients with left-sided breast cancers treated during a similar time period who would have met the aforementioned phase I IORT trial criteria and were treated with whole-breast irradiation using deep inspiratory breath hold (WBI-DIBH) for cardiac sparing. At our institution, patients treated with WBI-DIBH are simulated in the supine position with their arms up using a Vac-Lok and slant board for custom immobilization with the isocenter placed at mid-breast, at the lung/chest wall interface. Motion management is performed using an infrared tracker placed above the patient's xiphoid process (Varian RPM). Patients are instructed to take a deep breath and hold it at the time of their CT acquisition and during treatment. All ipsilateral breast tissue and the lumpectomy cavity with margin (if boosting) are contoured as targets. Opposed tangents with nondivergent medial borders are placed, multileaf collimation is performed on the medial border to reduce heart and lung doses, and field-in-field techniques are used to achieve tissue homogeneity. The decision to boost was made on an individualized basis; typical indications for boost at our institution were margins <2 mm, age <60 years, or high-grade disease. Boost