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Original article

Long-term risks of secondary cancer for various whole and partial breast irradiation techniques

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ABSTRACT

Introduction: For early stage breast cancer patients, non-breast cancer mortality including secondary cancers and cardiac events can overshadow the benefit of adjuvant radiotherapy. This study evaluates the excess risk of secondary cancer for various breast radiotherapy techniques including accelerated partial breast irradiation (APBI).

Methods: Secondary cancers Lifetime Attributable Risks (LAR) were calculated using a modified BEIR-VII formalism to account for the specific survival of breast cancer patients. Those survivals were extracted from the SEER database. Doses scattered to various organs were measured into a Rando phantom with custom-made breast phantoms. Treatments delivered typical doses of brachytherapy APBI (34 Gy in 10 fractions), external beam APBI (38.5 Gy in 10 fractions) using 3D-conformal, Cyberknife stereotactic (CK), or VMAT, as well as whole breast irradiation (WBI) delivering 42.5 Gy in 16 fractions.

Results: WBI resulted in the highest total LAR, with 4.3% excess risk of secondary cancer for a patient treated at age 50 years. Lung cancers accounted for 75–97% of secondary malignancies. For a typical early stage patient irradiated at 50, the excess risks of secondary lung cancer were 1.1% for multicatheter HDR, between 2.2% and 2.5% for 3D-CRT or CK, 3.5% for VMAT APBI, and 3.8% for WBI.

Conclusions: APBI reduces the risk of secondary cancer 2–4 fold compared to WBI. These techniques are well suited for long-living early stage breast cancer patients. HDR brachytherapy and 3D-conformal APBI achieve mean lung doses between 1 and 1.5 Gy, which could serve as reference.

Today breast cancer is frequently diagnosed at an early stage and has an excellent prognosis. SEER data show that 60% of the patients are diagnosed at a localized stage, without extension to the regional nodes, and the 5-year cancer specific survival for those patients is 98.9% [1]. Standard treatment includes limited surgery followed by whole breast irradiation (WBI). Long-term follow-up of large randomized trials comparing lumpectomy with or without adjuvant radiotherapy has shown that the benefit of radiotherapy is eclipsed by non-breast cancer mortality [2,3]. The most common causes of non-breast cancer mortality include major cardiac events and secondary cancers [4–6]. To reduce cardiac toxicity, the radiation oncology community has massively adopted preventive measures like breath-hold [7,8]. The issue of secondary cancer has not yet led to changes regarding the breast irradiation technique.

Accelerated partial breast irradiation (APBI) has been recently proposed for selected patients with favorable characteristics, and results of the few randomized trials suggest non-inferiority in local control compared to WBI [9–12]. Introducing new irradiation techniques may result in differences in the amount of dose to the whole body and thus to differences in the risk of radiation-induced secondary cancer [6,13]. Scarce comparisons of secondary cancer risks for different techniques have been published [14–16]. They focused either exclusively on whole breast radiotherapy techniques or evaluated the scatter dose theoretically using Monte Carlo simulation. Currently there is no thorough comparison between whole breast radiotherapy and APBI.

The aim of this study is to evaluate the risk of secondary cancer of whole breast radiotherapy and several APBI techniques, using a modified BEIR VII formalism accounting for the specific survival of a breast cancer population, and experimentally measure the scatter dose to various organs for these breast radiotherapy techniques.

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Materials and methods

Calculation of lifetime attributable risks (LARs)

LARs were calculated using the BEIR VII formalism [17]. This model includes empirical and *in vitro* data to calculate secondary cancer risks for specific organs depending on sex, age at exposure and attained age. For the esophagus, we used the organ specific parameters from the study by Berrington de Gonzalez [18]. We selected age at exposure of 40 years and older, since this age corresponds to the lower threshold of the "cautionary group" of the ASTRO guidelines and the "intermediate-risk group" of the GEC-ESTRO guidelines [19–21]. We used the probability of survival for the general population from the U.S. Decennial Life Tables for 1999–2001 [22]. We corrected the probability of survival for breast cancer patients using the probability of survival after localized breast cancer from the SEER database [23]. The SEER database provides survival data up to 40 years after diagnosis. For the period after this, we extrapolated the linear trend in the survival probability. We used the baseline cancer risks for the general population from the SEER database [24]. To put the risks into perspective, we calculated the lifetime Relative Risk (RR) of secondary cancer per organ.

Radiotherapy planning and phantom treatments

Measurements of the scatter dose for various breast radiotherapy techniques were performed using a Rando-Alderson phantom (Radiology Support Devices, Inc., Long Beach, CA, USA) with custom-made tissue equivalent breast phantoms adapted from Ruschin et al. [25]. Five surgical clips were inserted in the upper outer quadrant of the right breast at typical places found on patients treated in our institutions, and creating a virtual seroma of about 3 cm in diameter.

Planning CT-scans of the realistic breast phantom were made according to our institutional protocol. The whole breast clinical target volume (CTV) was delineated up to the chest wall and excluded the first 5 mm below the surface. The whole breast CTV expanded by a 5 mm margin and limited 5 mm under the surface corresponded to the PTV for WBI. The tumor bed was delineated using the surgical clips. It was expanded with a margin of 15 mm to create the CTV for the APBI treatments following the NSABP B-39/RTOG 0413 protocol [26]. The planning target volume (PTV) margin was 10 mm for the external beam APBI techniques and zero mm for the HDR techniques [26].

Whole breast radiotherapy used a hypofractionated regimen of 42.5 Gy in 16 fractions mixing 6 and 10 MV tangent beams. Beam angles were optimized to limit the contralateral breast and lung dose. Dynamic wedges were used to improve the dose distribution and the treatment was delivered using an Elekta Synergy S linear accelerator.

The technique described by Baglan et al. was used to plan the 3D-conformal (3D-CRT) APBI treatment [27]. The prescribed dose was 38.5 Gy in 10 fractions. The plan fulfilled the dose constraints of the NSABP B-39/RTOG 0413 protocol [26]. VMAT APBI was delivered using a single 6 MV arc ranging from 190° to 20°. The plan was optimized for breast conformality, minimizing the heart and lung dose according to the NSABP B-39/RTOG 0413 constraints [26]. The prescribed dose was 38.5 Gy in 10 fractions. Cyberknife plans were created in Multiplan version 5.3.0 (Accuray Inc., Sunnyvale, USA) with an inverse plan optimization. Plans used either the Iris (CK-Iris) or the MLC (CK-MLC) collimators. Beams were not allowed to enter through the contralateral breast or heart. The prescribed dose, margins and dose constraints applied were identical to the other external beam APBI techniques.

For HDR multicatheter APBI, 8 catheters were inserted in the breast phantom in 2 planes using a free hand implantation technique. A post-implant CT-scan was acquired, and the images were transferred to the Oncentra brachytherapy dose planning system version 4.5.1 (Elekta). The prescribed dose was 34 Gy in 10 fractions. Dwell times were optimized to ensure that coverage and dose homogeneity were optimized following the constraints of the NSABP B-39 protocol [26]. To mimic a balloon for HDR balloon-based APBI, a single catheter was inserted in the breast phantom. On the planning CT-scan, a sphere of 3.5 cm diameter was delineated around the catheter to represent the balloon. A dose of 34 Gy in 10 fractions was delivered to a point 1 cm away from the balloon surface. The plan also satisfied the constraints from the NSABP B-39/RTOG 0413 protocol for balloon-based HDR [26]. Both HDR APBI techniques were delivered using a 192-Ir Flexitron Remote Afterloading system (Elekta).

Dose measurement

Dose was measured in the lungs, contralateral breast, thyroid, esophagus, colon, ovaries and the uterus. Those organs were chosen because of elevated risks of radiation-induced cancers reported in these organs [5,28–30]. Doses were measured using 34 ThermoLuminescent dosimeters (TLDs) distributed uniformly over the organs and Gafchromic film for the lungs (Ashland Advanced Materials, Bridgewater, USA). The LiF 700 powder TLDs were read out using the Pitman 654 TLD-reader and annealed with the Pitman 622/B annealing facility using a standard of 400 °C for 1.5 h and 80 °C for 16 h, with subsequent natural cooling down to room temperature. TLDs were calibrated for doses of 1 cGy to 10 Gy. Gafchromic EBT3 films were used next to TLDs to measure the scatter dose in the lungs in the presence of steep dose gradients. The films were analyzed after 24 h storage in the dark at room temperature using the dose-density curve for each batch of films.

For each technique a single dose of 10–12 Gy was delivered to the PTV, to ensure that the TLDs and films received a dose within its accuracy range. Measured doses were rescaled to the total dose that would be delivered per technique. Mean organ doses were calculated weighing the dose from each TLD or film for the percentage of the organ it represented. Each measurement was repeated 3 times.

Results

The mean organ doses per technique are shown in Table 1. The lungs had the highest mean doses, ranging from 50 to 200 cGy depending on the breast radiotherapy technique. The mean doses to the other organs varied a lot, but they generally remained well below 70 cGy. The only exception was the esophagus which received more than 100 cGy with the 3D-CRT APBI. The mean doses to the ovaries and uterus were very low, ranging from 1 to 8 cGy. Comparing the various techniques, whole breast radiotherapy delivered the highest doses overall. Conversely, all APBI techniques resulted in lower doses to the lungs and contralateral breast. The two Cyberknife techniques showed a slightly higher dose to the abdominal organs compared to other APBI techniques, which is due to the non-coplanar technique.

Table 2 shows the LARs for the individual organs and the total LARs per technique for ages at exposure of 40, 50, 60 and 80 years using the BEIR VII formalism. The results are presented graphically in Fig. 1 for age at exposure of 50 years, which corresponds to the ASTRO "suitable group" and the GEC-ESTRO "low-risk group" [19–21]. As the secondary cancer risks are proportional to the mean organ doses, the comparison of the various techniques in terms of LAR yields the same findings as the comparison of the various

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