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Phase III randomised trial

Hypofractionated whole breast irradiation for patients with large breasts: A randomized trial comparing prone and supine positions

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ABSTRACT

Background and purpose: Comparison of acute toxicity of whole-breast irradiation (WBI) in prone and supine positions.

Materials and methods: This non-blinded, randomized, prospective, mono-centric trial was undertaken between December 29, 2010, and December 12, 2012. One hundred patients with large breasts were randomized between supine multi beam (MB) and prone tangential field (TF) intensity modulated radiotherapy (IMRT). Dose–volume parameters were assessed for the breast, heart, left anterior descending coronary artery (LAD), ipsilateral lung and contralateral breast. The primary endpoint was acute moist skin desquamation. Secondary endpoints were dermatitis, edema, pruritus and pain.

Results: Prone treatment resulted in: improved dose coverage ($p < 0.001$); better homogeneity ($p < 0.001$); less volumes of over-dosage ($p = 0.001$); reduced acute skin desquamation ($p < 0.001$); a 3-fold decrease of moist desquamation $p = 0.04$ (chi-square), $p = 0.07$ (Fisher's exact test)); lower incidence of dermatitis ($p < 0.001$), edema ($p = 0.005$), pruritus ($p = 0.06$) and pain ($p = 0.06$); 2- to 4-fold reduction of grades 2–3 toxicity; lower ipsilateral lung ($p < 0.001$) and mean LAD ($p = 0.007$) dose; lower, though statistically non-significant heart and maximum LAD.

Conclusions: This study provides level I evidence for replacing the supine standard treatment by prone IMRT for whole-breast irradiation in patients with large breasts. A confirmatory trial in a multi-institutional setting is warranted.

Adjuvant radiotherapy (RT) after breast conserving surgery halves the recurrence risk and reduces breast cancer death by about one sixth [1,2]. Long-term epidemiological data showed that patients who received radiotherapy had an increased risk of death by cardiac events and increased risk to develop ipsilateral lung cancer and contralateral breast cancer [3–6]. Adverse effects that outweighed the benefits of radiotherapy on overall survival were observed in patients treated before the 1980's [7]. Survival benefit in more recently treated patients correlates with lower radiation doses to the heart, lung and contralateral breast achieved by newer radiation techniques. Recent data of Darby et al. [6] showed a linear relationship between mean heart dose and rates of ischemic heart disease starting within a few years and continuing decades after breast RT. The supine patient position is part of the standard setup for breast RT and is associated with non-negligible acute toxicity even when intensity modulated radiation therapy (IMRT) is used. Randomized controlled trials, comparing IMRT with non-IMRT, showed significant reduction of acute toxicity [8,9], but still up to 40% of the IMRT-treated patients developed acute and late skin toxicity or breast fibrosis leading to discomfort and altered body image. Causes include volumes of over-dosage [dose levels higher than the prescribed range, i.e. between 95% and 107% of the prescription dose (PD)] in the breast and in folds that shield skin tissue from the protective build-up effects (in unfolded skin the maximum dose lays about 1.5 cm beneath the skin/air interface for 6 MV photon beams); both occur especially in larger breasts. Prone breast irradiation exploits gravity to elongate the treated breast away from the heart and lung. Formenti et al. [10,11] demonstrated the clinical feasibility of this procedure resulting in further dose-reductions to heart and lungs, which have been confirmed by others [12–17]. As compared to supine, the prone position opens the infra-mammary fold, thereby restoring protective build-up, and reduces the radiological path-length i.e. the length of breast tissue traversed by tangential X-rays which helps reducing volumes of over-dosage.

With this rationale for prone breast RT we initiated a randomized controlled trial comparing prone with supine position for large breasted patients. The primary objective was to test the

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hypothesis of decreased incidence of acute moist desquamation with prone IMRT, compared to our best supine technique: non-opposed multi-beam (MB) IMRT. Secondary endpoints included the analysis of acute and late skin toxicity, breast fibrosis, cosmetic alterations, quality of life and dose-volume parameters. Dose-volume parameter analysis included volumes of over-dosage in the treated breast and radiation doses delivered to volumes of organs-at-risk (OARs: heart, left anterior descending coronary artery (LAD), contra-lateral breast and ipsilateral lung). We, hereby, report on the primary objective of the study and on dose-volume parameters of treated breast and OARs.

Patients and methods

The study was designed as a non-blinded, randomized, prospective, mono-centric trial comparing prone and supine setup in patients who receive hypo-fractionated IMRT after breast-sparing surgery. Under the hypothesis of a 40% rate of moist acute skin desquamation for supine-IMRT [8,9] and 10% for prone-IMRT, at least 42 patients in each arm were needed for $\alpha = 0.05$ and $\beta = 0.1$. The study was approved by the Ethics Committee of Ghent University Hospital (GUH) on June 10 2010 and registered under number 2009184 (http://www.clinicaltrials.gov/ct2/show/NCT00887523).

Patients

Between December 29, 2010 and October 25, 2012, 100 female adult patients with European cup size C or more were randomized to receive either supine or prone computed tomography (CT)-simulation, planning and treatment. Cup size was based on patients' bra size. If required, this was checked during clinical consultation by fitting bra models. All patients underwent breast-sparing surgery with a resection margin of $\geqslant$1 mm, were lymph node negative and were appointed for WBI according to the multidisciplinary breast cancer board of GUH. Patients with previous breast radiotherapy or the need of bilateral breast irradiation were excluded from this trial.

Randomization and masking

All patients received oral and written information and signed written informed consent. After obtaining the informed written consent, patients were randomly assigned in a 1:1 ratio by the biostatistics unit of Ghent University Hospital. Each enrolled patient was allocated independently from the study investigators and the treatment arm was revealed at the day of the simulation. The analysis is based on clinical data that were collected till December 12 2012.

Treatment techniques and plan evaluation

The prone tangential field (TF), 2 beam-IMRT technique was described by Veldeman et al. [14,15]. A 6 beam-IMRT technique with 3 medial and 3 lateral beams, non-opposing, was applied in supine position [18]. Fig. 1 shows prone positioning using the unilateral breast holder (U-BH) developed by Van de Velde (Schellebelle, Belgium) and the prone breast board constructed by Orfit Industries (Wijnegem, Belgium) used in this trial.

OARs and target volumes were delineated as previously described [14]. The groove between the left and right ventricles was used as landmark whenever visualization of the LAD was difficult. A planning target volume (PTV) was generated to account for anatomical changes and setup variability during treatment. A planning target volume for optimization (PTV_{optim}) was created by extracting the in-air part of the PTV and an additional 7 mm skin-zone of the PTV to exclude most of the build-up regions of photon beams.

A prescription dose (PD) of 40.05 Gy in 15 fractions was delivered to the whole breast [10,19]. A boost of 10 Gy in 4 fractions was given to the tumor bed in 75 patients (39 supine and 36 prone). The PTV_{optim} dose distribution was evaluated by the dose

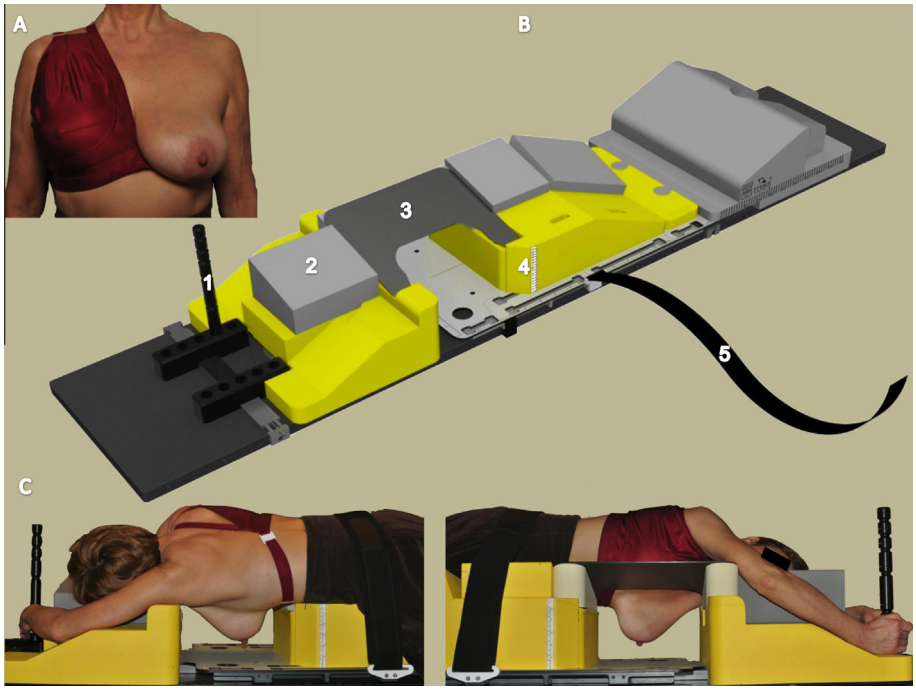

Fig. 1. Patient set-up devices for prone CT-simulation and treatment: (A) Unilateral breast holder to retract the contra-lateral breast away from the treated breast. (B) Prone breast board: 1: hand grip; 2: head rest; 3: carbon fiber wedge support of the contra-lateral breast; 4: numeric scale (at both sides of the caudal part) to adjust table height using the in-room laser system; 5: safety belt. (C) Ipsilateral (left panel) and contralateral (right panel) views of a patient positioned on the breast board.