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Treatment constraints for single dose external beam preoperative partial breast irradiation in early-stage breast cancer

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ABSTRACT

Background: Following breast-conserving surgery and post-operative 3D-conformal accelerated partial breast irradiation (APBI), suboptimal cosmetic results have been reported. Preoperative radiation delivery to the intact tumor enables better target visualization and treatment volume reduction. Single dose preoperative APBI has the potential to improve toxicity profiles, reduce treatment burden and enable in vivo exploration of breast cancer radiogenomics.
Purpose: Develop practical guidelines for single dose external beam preoperative APBI.
Methods: Recommended dose constraints were derived from pooled dosimetry estimates from 2 clinical trials. In an American dose escalation trial, a uniform 15, 18 or 21 Gy dose has previously been evaluated for non-lobular cT1N0 or low/intermediate grade DCIS <2 cm in prone position ($n = 32$). In the Netherlands, the feasibility of ablative APBI (20 Gy to GTV, 15 Gy to CTV) to non-lobular cT1N0 in supine position, is currently being explored ($n = 15$). The dosimetric adherence to the developed constraints was evaluated in new APBI plans with a 21 Gy uniform dose but an extended CTV margin ($n = 32$).
Results: Dosimetric data pooling enabled the development of practical guidelines for single dose preoperative APBI.
Conclusion: The developed guidelines will allow further explorations in the promising field of single dose preoperative external beam APBI for breast cancer treatment.

Introduction

Accelerated partial breast irradiation (APBI) has been explored as an alternative to whole breast irradiation (WBI) following breast-conserving surgery [1–9]. In selected patients with early-stage breast cancer and low-risk of local recurrence, APBI efficacy appears to be equivalent to WBI with respect to local control and survival rates [3,6–10].

Several randomized controlled trials have evaluated different approaches to deliver APBI following breast-conserving surgery, each with its own advantages and disadvantages. Interstitial multicatheter brachytherapy (IMB) is the technique with the longest clinical follow-up available and good clinical results when compared to WBI with equivalent efficacy, and comparable toxicity profiles [6,9]. However, due to the invasiveness of the technique, the required physician's expertise and brachytherapy equipment, IMB has not been widely implemented. Second, intra-operative radiotherapy (IORT) is an appealing technique due to the single treatment approach at the time of surgery but requires costly and cumbersome equipment. External beam APBI has the advantage of widespread equipment availability and expertise, but when compared to the previous techniques, larger treatment volumes have typically been utilized. As a result, an increase in soft tissue fibrosis and suboptimal cosmetic outcomes has been seen with 3-dimensional conformal external beam radiation therapy (3D-CRT) [4]. However, more dose conformal techniques such as intensity-modulated radiotherapy (IMRT), have the potential for superior toxicity and cosmetic outcome profiles when compared to WBI, suggesting that the results of external beam APBI could be improved upon [8].

In an effort to overcome the disadvantages and capitalize on the advantages of the previous APBI techniques, the concept of MRI-guided single dose external beam partial breast irradiation

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delivered prior to surgical resection has been developed [11–13]. The single dose concept of IORT using a non-invasive external beam technique can minimize the treatment duration and burden for patients, without the purchase of any supplementary radiotherapy equipment. In addition, the delivery of radiation (RT) preoperatively to the intact tumor allows more precise targeting when compared to post-surgery, resulting in significantly smaller treatment volumes and possibly less RT-induced toxicity [11,14]. Another advantage of preoperative APBI concerns the uniformity of treatment volume definition, with less interobserver variation in target volume delineation when compared to a postoperative approach [15]. MRI-guided preoperative target definition can further improve the tumor visualization (i.e. tumor spiculae) [16]. This could facilitate dose escalation, enabling an ablative, definitive treatment approach for early-stage breast cancer. Finally, preoperative APBI allows the direct evaluation of RT effects in breast tumors, aiming at the identification of radiation response predictors and biomarkers, which may help to guide personalized treatment for future patients [17].

Single dose external beam preoperative APBI has great potential in clinical practice to deliver a precise and uniform, minimally burdensome treatment with less associated toxicity, and opens a new window of opportunity in radiogenomics. Based on the clinical experience with this approach in two university medical centers, this manuscript introduces practical guidelines for the delivery of single dose external beam preoperative radiotherapy.

Methods

Study population

The current study includes data from 2 pre-existing studies and was approved by the Institutional Review Boards of the participating institutes.

In both trials, toxicity was prospectively evaluated at predefined, overlapping time points using the Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version_4.03).

At Duke University Medical Center, Durham, Unites States of America, a phase I dose escalation trial (ClinicalTrial.gov NCT00944528) was conducted between August 2010 and March 2013 in order to determine the maximum tolerated dose of single dose preoperative APBI in prone RT position. A total of 32 patients $\geq$55 years with cT_1N_0 invasive ductal carcinomas or DCIS $\leq$2.0 cm were included [12]. A lumpectomy was performed within 10 days following RT. The updated treatment toxicity at a median of 37 months follow-up is in line with the previous published results, with chronic grade 1–2 local fibrosis, dermatitis and breast pain being the most common toxicities. In all patients treated with single dose APBI only, good to excellent cosmetic outcomes were assessed by the treating physician.

At the University Medical Center Utrecht, The Netherlands, an ongoing trial evaluates the clinical feasibility of a radiosurgical approach for early-stage breast cancer (ClinicalTrial.gov NCT02316561). A lumpectomy is performed at 6 months following RT in the supine position, in order to evaluate the primary endpoint, the pathological response. The current study included the first 15 study patients $\geq$50 years with $cT_1N_{0(sn)}$ invasive ductal carcinoma. At time of analysis, eleven (of the planned 25) patients had a lumpectomy performed, and only grade 1–2 toxicity has been observed at a median follow-up of 7 months (Appendix Table A1).

Treatment planning

At Duke, IMRT was used to deliver 15 Gy, 18 Gy or 21 Gy to the gross tumor volume (GTV) and the clinical target volume (CTV) (Eclipse®version 10). At Utrecht, a single dose Volumetric Modulated Arc Therapy (VMAT) treatment was concomitantly prescribed to deliver two dose levels, 20 Gy to the GTV and 15 Gy to the CTV (Monaco®version 19). Study details have been previously published [12,13,18]. Table 1 and Fig. 1 illustrate treatment planning characteristics.

Guidelines development

Since the initial dosimetric parameters of interest differed between the institutions, a new protocol for treatment plan evaluation was reached in consensus. Using the original treatment plans, this protocol evaluated target volume coverage and dose to organs at risk (OAR) with respect to NSABP B39/RTOG 0413 and QUANTEC guidelines for target and normal tissue constraints, converted to a single-dose prescription [13,19]. Furthermore, in order to achieve a uniform evaluation between institutions the chest wall delineation was adjusted, and two different skin definitions were assessed (i.e. first 3 and 5 mm subcutaneous tissue).

Since no dose limiting toxicity has been encountered, no normal tissue complication probability curves were developed. Reasonable constraints were pragmatically defined based on descriptive statistics of the pooled dosimetric parameters in the clinical cohorts. Overall median, interquartile range (IQR) and 10th and 90th percentile doses were determined for target volume and OAR parameters. Optimal and acceptable dosimetry was defined as an OAR value that did not exceed the 75th (upper IQR) and 90th percentile of the pooled dosimetric parameter, respectively.

Dosimetric feasibility guidelines

To determine the feasibility of these new dose constraints for future studies, new treatment plans were performed for the patients in the dose escalation cohort ($n = 32$) using Eclipse®version 13.6. Given the variation in breast delineations, some ipsilateral and contralateral breast contours were adjusted, following consensus [20]. A uniform 21 Gy dose was prescribed to the intact tumor with a 2.0 cm margin in order to assess our guidelines using a larger CTV margin that more closely approximates existing post-operative external-beam APBI data. Due to the 0.5 cm CTV extension from the initial treatment plans, this would more often align the skin. Adequate target volume coverage was therefore defined as $\geq$95% of prescription dose to $\geq$98% of the CTV. Table 1 illustrates RT planning characteristics for this replanned cohort. The new plans were evaluated for adherence to the previously defined optimal or acceptable dosimetry from the clinical cohorts.

Results

Dosimetry across cohorts

The median GTV and CTV receiving $\geq$95% of the prescribed dose (PD) was $\geq$99% in all 3 cohorts. The median PTV receiving $\geq$95% of the PD was $\geq$97% in the clinical cohorts and 95% in the replanned cohort. Table 2 gives an overview of the treatment volumes. In the integrated boost cohort treatment volumes are larger compared to the dose escalation cohort, given the 0.5 cm additional CTV extension. When evaluating PTV overdosage in relation to the CTV PD in the integrated boost cohort, the median $V_{110\%}$ and $V_{105\%}$ was 29% and 43%, respectively. Table 3 illustrates the dosimetry across the various clinical cohorts. Higher mean ipsilateral breast and skin dosimetry are encountered with higher PD. Lower PD fall-off is observed in the integrated boost cohort.

Optimal or acceptable plan dosimetry

Optimal and acceptable dosimetry was defined from the clinical cohorts as a value up to the 75th percentile (i.e. upper IQR) and