Updated feasibility and reproducibility results of multi-institutional study of noninvasive breast tumor bed boost

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ABSTRACT

PURPOSE: To report updated feasibility and reproducibility results for high-dose-rate noninvasive breast brachytherapy (NIBB) for tumor bed boost with whole breast radiation therapy (WBRT) in the setting of expanded patient and treatment facility number.

METHODS AND MATERIALS: Fifteen independent community-based and academic centers reported 518 early-stage breast cancer patients from July 2007 to February 2015 on a privacy-encrypted online data registry. All patients’ treatment included lumpectomy followed by combination of WBRT and NIBB. NIBB was completed with commercially available (AccuBoost, Billerica, MA) mammography-based system using high-dose-rate 192Ir emissions along orthogonal axes. Harvard scale was used to grade cosmesis.

RESULTS: Total patient cohort had median followup of 12 months (1–75 months) with subset of 268 having available cosmesis. Greater than 2- and 3-year followup was 29% and 14%, respectively. Entire cohort had 97.4% excellent/good (E/G) breast cosmesis and freedom from recurrence of 97.6% at the final followup. WBRT timing with respect to NIBB delivery demonstrated no statistically significant difference in E/G cosmesis. Achieved E/G cosmesis rate was also not statistically significant (χ² p-value = 0.86) between academic and community institutions with 97.8% vs. 96.6%.

CONCLUSIONS: NIBB represents an alternative method for delivery of breast tumor cavity boost that has shown feasibility in a diverse group of both academic and community-based practices with reproducible early cosmesis and tumor control results. Recommendations are updated noting ideal timing of boost delivery likely to be before or early during WBRT given equal cosmesis and less documented treatment discomfort. © 2016 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: High dose rate; Noninvasive breast brachytherapy; Breast boost

Introduction

Treatment options for early-stage invasive breast cancer and noninvasive ductal carcinoma in situ (DCIS) currently include mastectomy or breast-conserving surgery (BCS) followed by adjuvant radiation (1–4). In BCS for invasive breast cancer, survival benefit has association with
reduction in in-breast recurrence as achieved by whole breast radiation therapy (WBRT) (5, 6). Tumor bed remains at highest risk for in-breast recurrence (7–9). To maximize in breast control, current practice is to deliver a tumor bed boost after WBRT as all studied subgroups of invasive ductal carcinoma demonstrated improvement. This boost is commonly extrapolated to other histologies such as invasive lobular carcinoma and DCIS (7–9).

Although breast tumor bed boost is considered standard for most patients, there is no standard delivery modality or setup technique. Tumor bed boost was designed historically based on clinical setup around visible external scar and delivered with electron-based treatment (8, 9). Other delivery modalities include invasive interstitial brachytherapy (8, 10), and recently, photon-based treatment delivery has been increasing (11). However, no modality will be effective if the target (i.e., tumor bed) is not identified correctly (12). Tumor bed identification is one of the greatest challenges in delivery of boost radiation therapy. Three-dimensional (3D) CT boost planning improves tumor cavity identification and allows optimization of tumor bed dosimetry coverage compared to clinically defining boost volume by placing a margin around the surgical scar (13, 14). Use of 3D-CT imaging has highlighted interobserver target contouring discrepancies suggesting additional improvements in target identification and physician delineation can be made (15, 16). Even with 3D planning, interfraction and intrafraction errors are not completely addressed by traditional delivery techniques (17–19). These errors are presented due to factors such as daily patient and breast setup variability, respiratory motion, and potential for tumor resection cavity volume changes over time (20–22).

Noninvasive breast brachytherapy (NIBB) is an alternative technique to deliver breast tumor bed boost that uniquely attempts to address the above challenges. NIBB incorporates pretreatment mammography-based imaging and reproducible breast compression (23–25). The initial feasibility, patient tolerance, and acute toxicity of NIBB in a small set of patients have been previously been reported by Hamid et al. (23). The current study provides longer median followup, larger patient number, and increased treatment site participation expanding evidence of technique feasibility and demonstrating reproducibility of NIBB in a diverse group of community and academic clinical practices.

Methods and materials

Patient population

Population consisted of 518 women with early-stage breast cancer between July 2007 and February 2015. All women completed BCS, WBRT, and tumor bed boost with NIBB. Additional patient characteristics are presented in Table 1. Patients were excluded from analysis if they had no followup data, not stated to have negative margins at time of treatment, or were not early stage (T1-T3N0-1 based on AJCC seventh edition) or noninvasive (Tis).

Treatment centers

All practices actively treating patients with NIBB as boost were contacted by e-mail, in person, and/or phone and invited to participate in online registry. Participating sites retrospectively logged patient, treatment, and outcome date in the online NIBB database. Fifteen independent community-based and academic centers volunteered to report retrospective data. Two centers were academic based, and 13 were community based. No financial incentive was provided for center or patient participation.

NIBB system and treatment

NIBB (AccuBoost, Billerica, MA) is a commercially available treatment device that uses mammography-based image-guided radiation therapy to deliver breast tumor
bed boost. Description of image guidance, positioning NIBB applicator, appropriate breast immobilization has been previously reported (23–25). Figure 1 demonstrates patient positioning and example of mammographic image that aids in identification of tumor cavity and brachytherapy applicator selection. In brief, after breast immobilization with compression, review of pretreatment mammographic imaging along with review of patient’s clinical and operative history, a tungsten alloy applicator is sized (range 4–8 cm diameter) at the treating physicians discretion (23–25) to cover breast tumor cavity (i.e., clinical target volume) with margin (i.e., planning target volume [PTV]). New NIBB users are advised to plan boost PTV in accordance with the same practice and procedures they had been using for other boost techniques such as electrons, photons, or catheter-based brachytherapy. An expansion of at least 1.0 cm beyond the excision bed as defined by surgical clips or postoperative scarring seen on mammographic images is endorsed, and where feasible, a 1.5-cm PTV margin expansion is recommended similar to the guidance used in defining the PTV for the GEC-ESTRO brachytherapy Accelerated Partial Breast Irradiation (25–29). Patients are not excluded if tumor cavity is in close proximity to skin requiring skin flash or if tumor cavity was close to chest wall (CW) as long as there was 1 cm or greater between CW and applicator edge. Skin flash is defined as any portion of applicator extending beyond the skin surface. If tumor cavity is close to the CW, a D-shaped applicator is recommended for treatment delivery.

HDR $^{192}$Ir photon emissions were delivered along orthogonal axes. All tumor bed boosts are delivered over several sessions (fractions) with exact number and fraction dose determined by individual treating physicians as shown in Tables 2 and 3. Based on institutional practice and each site’s treating physician, timing of NIBB is delivered before, after, or during EBRT. The timing choice is consistent for individual providers and institutions and chosen for logistical reasons at the discretion of individual centers. Sessions could be delivered with either the craniocaudal (CC) or mediolateral (ML) compression. Most common delivery scheme alternated CC and ML compression with each fraction.

Data collection and analysis

After approval from institutional review board, retrospective data were collected using a privacy-encrypted online data registry. Individual institutions were provided password-protected access to their own treatment information. When queried, the online data registry provided de-identified patient and treatment characteristics, and followup toxicity, tumor control, and subjective physician reported cosmesis data. The treatment characteristics data fields included need for re-excision, total dose/fraction of WBRT, total dose/fraction of boost, type and size of selection of applicator, quantitative degree of compression, and timing in relationship to delivery of WBRT. An additional field was qualitative measure of patient discomfort during each NIBB session which was entered into database as “yes or no” as documented by treating physician. Toxicity and cosmesis were evaluated after radiation therapy and graded according to the Common Toxicity Criteria (v3.0) and the Harvard scale, respectively. Basic statistical analysis was performed using Microsoft Office Excel (2010), and statistical analysis used SAS version 9.2 and R version 3.2.1. All categorical variables are summarized into proportions, and their association is investigated by means of
cross-classification table with $\chi^2$ test for association. Statistical significance of association is determined based on $p$-value threshold of 5%. Continuous treatment variables are tested for association by fitting a linear model and using F-test for statistical significance of the relevant coefficient.

### Results

#### Patient characteristics

Total cohort was 518 patients and had median followup of 12 months (1−75 months) with a subset of 268 patients having followup cosmesis data and median followup of 12 months. Greater than 1-year followup was reported on a subset of 163. The mean age was 60 years (range 19−87 years). The average tumor size was 1.5 cm (std ± 1.03 cm). Most common histology was invasive ductal carcinoma (63%), followed by DCIS (22%), and invasive lobular carcinoma (9%). Approximately 80 percent were estrogen-receptor positive, and 5% were Her2Neu amplified. Additional patient characteristics are summarized in Table 1.

#### Treatment characteristics

All patients completed BCS with 22% undergoing surgical re-excisions to achieve histologically negative margins. All patients were recorded in database as having negative margins upfront or after re-excision. Physicians reported tumor bed identification was assisted by intraoperatively or postoperatively placed clips and pretreatment NIBB mammographic tumor bed appearance in about 60% of patient, whereas remainder used mammographic changes alone. The most common number of WBRT fractions by decreasing frequency was 28 (43%), 25 (26%), 26 (23%), and 16 (8%). Hypofractionated regimens of either 16 or 15 fractions represented less than 10% of WBRT. Additional treatment characteristics are seen in Table 2. Of patients with reported cosmesis data, the boost was delivered before WBRT in 16%, during WBRT, but not on the same day as WBRT in 52%, and after WBRT in 30% of patients. Mean boost dose per fraction was 1.8 Gy (std ± 0.7) with mean total boost dose of 10.6 Gy (std ± 3.9). Most common applicator selected at physician discretion during CC compression was D-shape, 4.5 cm size. The mean CC compression was 5.7 (±1.2 cm). Most commonly used applicator during ML compression was circular and size 5 cm. The mean ML compression was 6.5 (±1.3 cm). Additional boost characteristics are seen in Table 3.

#### Pain

Overall low rates of physician documented patient pain were only 14% for CC and 6% ML compression. Of patient with reported pain during any boost treatment, the percentage by timing of WBRT was pre-WBRT 7%, intra-WBRT 19%, and post-WBRT 74%.

#### Early tumor control

Entire cohort (n = 268) with followup data had freedom from any recurrence of 98.4%. Crude freedom from locoregional recurrence within breast tissue treated with WBRT and NIBB was 99.2% (two ipsilateral breast recurrences...
at 30 and 36 months). There were two reported patients that developed metastatic disease at 21 and 42 months. Additionally, two patients were reported to have contralateral recurrences. At 24 months, actuarial recurrence rate is 1.2%, and at 36 months, recurrence rate is 5.8%.

**Early overall cosmesis**

Entire cohort (n = 268) had observed ipsilateral breast cosmesis (postsurgical and radiation) of excellent/good (E/G) in 97.4% at time of the final followup. Excellent was observed in 58% of patients (n = 156). There was only one reported poor cosmetic outcome reported. No subset analysis was found to have statistically significant difference in E/G cosmesis results. An analyzed subsets related to treatment center included center’s first five treated patients cosmesis vs. subsequent patients (p = 0.59). E/G cosmesis was observed as 97% in both high volume centers (greater than 15 total patients treated) and low volume centers (less than 15 total patients treated) (p = 1.0). Similar rates of E/G cosmesis were observed between academic (98%) vs. community (97%) centers (p = 0.86). No analyzed subset related to boost treatment delivered demonstrated statistical significance in cosmesis: CC applicator shape (circular 96% vs. natural D 99%, CC vs. natural D 96%, p = 0.95), and skin flash (yes 94% vs. no 98%, p = 0.66). The E/G cosmesis for timing of boost was 98% pre-WBRT, 97% intra-WBRT, and 99% post-WBRT (p-value = 0.73) (Fig. 2). Cosmesis rates remained stable when evaluated by patient followup length (Fig. 3). E/G cosmesis for cohort of patients with minimum of 1 year followup was 96.9% (total cohort with minimum 1 year, n = 163) and still no statistical difference by timing of boost treatment before (93%), during (95%), or after (97%) WBRT. Although academic centers more commonly reported more patients with >1-year followup (70%), there was no difference between E/G cosmetic rates 95% from academic centers vs. 96% from community centers. E/G cosmesis with minimum of 2-year followup was 96.2% (total cohort with minimum 2 year, n = 79).

**Discussion**

NIBB represents an alternative method for delivery of breast tumor bed boost that is feasible for a diverse group of breast cancer patients and radiation oncology treatment centers. Retrospectively recorded, early cosmesis as report at the final followup was E/G greater than 95% and only two reported ipsilateral recurrences. This publication’s larger subset of patients with minimum followup of 1 and 2 years showed no decline in reported cosmesis outcomes strengthening the initial publications hypothesis that cosmesis does not worsen over time and demonstrating reproducibility (23). No subsets demonstrated statistically significant differences in early cosmesis representing a change from previously reported improved cosmesis with skin flash and post-WBRT NIBB delivery (23). These differences are hypothesized to be related to improved statistical analysis with larger patient number within subsets and present publications combination of excellent and good cosmesis. E/G cosmesis was combined to help address known subjectivity of physician reporting and reduce retrospective reporting bias. Both current and initial publications showed physician recorded pain increased with delivery of boost after external beam. Because this report’s early cosmesis seems unaffected by timing of boost, authors now recommend delivery of boost before or early in course of WBRT to minimize patient discomfort.

Optimal technique for breast tumor cavity boost target delineation and treatment modality continues to evolve. Historical clinical scar-based delineation of the tumor bed target with electrons often inadequately covers the target (12, 30). CT-based planning improves dosimetric coverage and improves geographic miss in up to about 50% of patients when compared to scar-based tumor bed delineation (12–14). Even with CT-based tumor bed delineation, interobserver, intrafraction, and interfraction variability exists (31–35). A meta-analysis of intrafraction and interfraction variability during supine radiation treatment of the breast, the average intrafraction motion was 1.82 mm (range of maximum deviation 2.0–25.6 mm) in CC direction, and additionally, interfraction average motion was 2.60 mm (range of maximum deviation 3.6–22.9 mm) (31). Interfraction variability could be caused by seroma or other tumor bed volume changes and daily external breast contour changes due to patient and/or bolus positioning (31). Example of intrafraction motion includes variability of external breast contour due to respirations (19, 31). Image-guided radiation therapy after CT-based planning with KV or MV or ultrasound imaging with or without fiducials has had success in reducing interfraction variation, but each has limitations and does not address intrafraction motion (31–36). Ultrasound relies heavily on user experience, and nonmammography-based x-ray imaging has poor tumor cavity visualization particularly in the absence of fiducial markers (36). Interstitial brachytherapy for tumor bed boost reduces inter/intrafraction variability as radiation
applicators are within tumor cavity throughout duration of treatment; its limitation is the need for invasive procedure and requirement for technical expertise (37). NIBB attempts to address interfraction variability through pretreatment mammographic kV imaging and intrafraction variability with compression-based breast immobilization (37, 38). Mammography has good sensitivity and specificity in women with a personal history of breast cancer and is diagnostic modality of choice to follow women after BCS (39). Interobserver variability for NIBB is beyond the scope of this retrospective study.

Several challenges were associated with this multi-institutional retrospective review. Patient data were reported on a volunteer basis, and therefore, many data fields were inconsistently reported in the online database. To partially address this concern, only patient and treatment characteristics were reported for those participants that had recorded cosmesis and subset analysis was completed for patients with a minimum of 1 year followup. Due to retrospective reporting, authors are unable to distinguish cosmetic changes as surgical or radiation affect and reported E/G cosmesis cases implies the initial good surgical results. Additionally, pain reporting was based on retrospective chart review not a validated physician or patient score. In future, evaluation of NIBB validated pain reporting will be necessary as breast compression leading to discomfort is a potential limitation to technique use. Due to need to excluded patients with missing followup data, there is no way to completely eliminate reporting bias which could lead to false sense of efficacy. Study results show high rates of E/G comesis and low rates of recurrence, so statistical power for evaluation of subsets and actuarial recurrence is limited by low number of fair/poor cosmetic and recurrence events. Incomplete followup data were more common for community vs. academic centers which is another source of potential biases. Additionally, two centers closed and one was under new management limiting authors the ability to clarify data discrepancies. Despite these limitations, community and academic physician and site participation are felt to strengthen study by making NIBB feasibility more generalizable. Continued community center collaboration will be important for future publications.

Fig. 3. Cosmesis with extended followup demonstrating consistent reported cosmesis for patients with extended followup.
and participating centers will continue to be asked to provide complete reporting of requested fields within the online database. Future evaluations will attempt to request for more specific dosimetric information. Given diversity of treatment centers and lack of registry field to capture costs, accurate cost analysis is not possible within the scope of this study.

Conclusions

NIBB represents an alternative modality for delivery of breast tumor bed boost. This technique uniquely attempts to address intrafraction and interfraction errors through daily pretreatment kV imaging and breast compression-based immobilization. Updated reporting with longer followup and increased participants shows reproducible cosmetic and tumor outcomes consistent with the initial publication and strengthens hypothesis that cosmesis does not decline in patients with minimum of 1-year and 2-year followup. No statistical differences in E/G cosmesis seen between academic and community groups, high and low volume centers, or first five treated patient and entire center patient cohort. This expanded report suggests that ideal NIBB timing is before definitive irradiation or early in course of external beam given reduced patient-reported pain without cosmesis detriment.

References


