Published in final edited form as:

J Radiat Oncol. 2014 December ; 3(4): 371–378. doi:10.1007/s13566-014-0153-8.

A PHASE II TRIAL OF BALLOON-CATHETER PARTIAL BREAST BRACHYTHERAPY OPTIMIZATION IN THE TREATMENT OF STAGE 0, I AND IIA BREAST CARCINOMA

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Abstract

Objective(s)—(a) To prospectively determine if multidwell position dose delivery can decrease skin dose and resultant toxicity over single dwell balloon-catheter partial breast irradiation, and (b) to evaluate whether specific skin parameters could be safely used instead of skin-balloon distance alone for predicting toxicity and treatment eligibility.

Methods—A single-arm phase II study using a Simon two-stage design was performed on 28 women with stage 0-II breast cancer. All patients were treated with multiple dwell position balloon-catheter brachytherapy. The primary endpoint was grade 2 skin toxicity. Initial entry required a balloon-skin distance 7 mm. Based on the toxicity in the first 16 patients, additional

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Ethical Standards Statement

Institutional review board approval was obtained prior to opening this phase II trial, and therefore all research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients before being included in the study.

Conflicts of Interest Notification

Sameer K Nath MD

Declares no conflicts of interest related to this project.

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patients were treated irrespective of skin-balloon distance as long as the Dmax to 1 mm skin thickness was < 130%.

Results—Compared to the phantom single dwell plans, multidwell planning yielded superior PTV coverage as per median V90, V95 and V100, but had slightly worse V150, V200 and DHI. Dmax to skin was decreased by multidwell planning at multiple skin thicknesses. The most common acute toxicity was grade 1 erythema (57%), and only two patients (7%) developed acute grade 2 toxicity (erythema). Late grade 1 fibrosis was seen in 32%. No patients experienced grade 3, 4, or 5 toxicity.

Conclusions—Multidwell position planning for balloon-catheter brachytherapy results in lower skin doses with equal to superior PTV coverage and an overall low rate of initial skin toxicity. Our data suggest that limiting the Dmax to < 130% to 1 mm thick skin is achievable and results in minimal toxicity.

Keywords

breast cancer; accelerated partial breast irradiation; MammoSite; skin toxicity; brachytherapy

Introduction

Breast conservation therapy (BCT) is a widely-accepted treatment option in the management of early stage breast cancer that allows for preservation of breast tissue without a compromise in oncologic outcomes. Large randomized controlled trials, now with 20 years of follow-up, have demonstrated equivalent long-term overall and disease-specific survival between BCT and mastectomy [1,2]. Furthermore, a recent meta-analysis of 10,801 patients from 17 randomized controlled trials of adjuvant radiation or no radiation following breast conserving surgery has demonstrated that radiation reduces the risk of ipsilateral breast cancer recurrence by one-half and reduces the breast cancer death rate by a sixth [3].

The optimal volume of breast tissue to irradiate post-lumpectomy has not been clearly established and is the subject of ongoing phase III trials. Clinical and pathologic data suggest that the benefit of whole breast irradiation derives from eradication of microscopic disease immediately surrounding the lumpectomy cavity [1,4]. It has therefore been questioned whether it is necessary for all women to receive treatment to the entire breast. In addition, receiving daily treatments for as long as 6–7 weeks as part of conventional whole breast irradiation is inconvenient for many women with breast cancer and is, in part, the reason why a substantial proportion of women do not receive radiotherapy after lumpectomy, particularly those who do not live in close proximity to a radiotherapy facility.

Based on the above considerations, accelerated partial breast irradiation (APBI) has become an increasingly popular alternative to conventional whole breast irradiation. The rationale behind APBI is that by targeting the breast tissue at highest risk of residual microscopic cancer cells and sparing a substantial proportion of normal breast tissue, larger fractions of radiation can be given, allowing the adjuvant radiotherapy course to be completed in a much shorter period of time. There are a variety of techniques currently in use for delivering APBI, including multicatheter-based interstitial brachytherapy, single-lumen balloon

catheter brachytherapy, multilumen balloon catheter brachytherapy, external 3-D conformal radiotherapy, and intra-operative radiotherapy. Multiplanar, multicatheter-based interstitial brachytherapy is the APBI technique with the most mature data supporting its use [5], however its availability in the United States is limited to select centers with expertise.

MammoSite® brachytherapy (MammoSite® Radiation Therapy System, Hologic Inc., New Bedford, MA) is a commonly used technique for APBI that was developed as a method to simplify the delivery and planning of APBI. After the 2002 Food and Drug administration approval of the MammoSite® device, the number of brachytherapy cases in the United States increased nearly 10-fold between 2002 and 2007 [6]. MammoSite® was originally designed to house a radioactive source in a single centrally-located position, referred to as “single-dwell position” technique. The prescription dose of 34 Gy was then delivered to a point 1 cm from the balloon surface in 3.4 Gy fractions, given twice daily.

The initial clinical experience with MammoSite® using single-dwell position planning was associated with excellent tumor control, as well as an 83% rate of good to excellent cosmesis in patients with > 5 years of follow-up [7,8]. However, while side effects were generally acceptable and self-limiting, mild-to-moderate skin toxicity was very common, including a rate of 57% with erythema without desquamation, 13% dry desquamation and 6% moist desquamation. In a European study of MammoSite®, 88% developed erythema, 54% hyperpigmentation, 42% seroma formation, and 8% telangiectasias (with 1 year follow-up) [9]. Finally, in the recent updates of the American Society of Breast Surgeons (ASBS) MammoSite® registry trial of 1440 patients from 97 institutions, 90.6% had good-to-excellent cosmesis at 5-years, 16.4% developed fibrosis, 13% developed symptomatic seromas, 9.5% developed infections, and 2.3% developed fat necrosis [10,11]. Although not explicitly stated in these studies, Proxima (former manufacturer of MammoSite®) estimated a 50% rate of grade 2 or higher combined acute and late toxicity with their initial technique [personal communication].

Owing to limitations in planning at the advent of MammoSite® use, specific volume-based dosimetric parameters for skin tolerance were not used [12]. The skin-balloon distance was thus used as a surrogate for skin dose with recommendations to keep the skin-balloon distance 5 mm. However, in early studies, a skin spacing of < 7 mm was found to be associated with an inferior cosmetic outcome [13,7]. This led to the recommendation of a skin distance of 7 mm. In addition, many catheters had to be explanted prior to treatment owing to a balloon-skin distance < 5mm (43 patients in the ASBS registry) [13]. Of note, the only factor associated with good/excellent cosmetic outcome in the ASBS registry trial was increasing skin-to-balloon distance as a continuous variable [10]. Although balloon-skin distance may correlate with toxicity/cosmesis, it is a crude approximation of skin dose, as dose depends on dwell positioning and exposure time [12]. In the ongoing NSABP B-39/ RTOG 0413 phase III randomized trial comparing PBI and conventional whole breast irradiation, dosimetric criteria for appropriate treatment include a minimum skin-balloon distance of 7 mm, or if the skin distance is 5–7 mm a plan can be deemed acceptable if the maximum point dose to the skin is < 145% of the prescription dose. This latter constraint corresponds to the skin dose from an average balloon diameter placed at a distance of 5 mm

from the skin [12]. Thus, optimal dose-volume parameters for skin tolerance during MammoSite® brachytherapy are not well-defined.

In an effort to evaluate the potential dosimetric advantages of multidwell position technique and to further address the need for dose-volume parameters to predict skin toxicity, we opened a single-arm phase II clinical trial with two major objectives: (1) to prospectively determine if a multiple dwell position dose delivery method could decrease skin dose and subsequent toxicity over historically reported rates of skin toxicity with single dwell position planning while achieving similar or superior PTV coverage, and (2) to evaluate if specific skin parameters could be identified and used to determine patient eligibility instead of skin-balloon distance alone. To these authors' knowledge, this is the only prospective trial on determining optimal skin-dose parameters for single-lumen MammoSite® reported to date.

Methods

Patient eligibility

Institutional review board approval was obtained prior to opening this trial, and therefore all research has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients before being included in the study. Women 50 years of age or older with stage 0, I, or IIA breast cancer with tumor size less than or equal to 3 cm and no nodal involvement were eligible for enrollment at a single academic institution. DCIS, invasive ductal carcinoma, and invasive lobular carcinoma histologies were allowed. Patients with invasive cancer were required to have a negative axillary lymph node dissection or negative sentinel lymph node evaluation. The tumor had to be clinically unifocal and encompassed by one lumpectomy with negative surgical margins greater than 2 mm. Patients with collagen vascular disease, previous radiation to the ipsilateral breast or thorax, or prior malignancy within the previous 2 years (excluding non-melanoma skin cancer, in situ melanomatic skin cancer or in-situ carcinoma of the cervix or colon) were considered ineligible. Following lumpectomy, there could not be any known unresected residual carcinoma or suspicious microcalcifications. A negative pregnancy test was required for women of childbearing age. No longer than 5 weeks was allowed between the last breast surgical procedure and initiation of MammoSite® brachytherapy. Neoadjuvant chemotherapy prior to surgery was not allowed.

Treatment technique

Following placement of the MammoSite® catheter, a treatment planning CT scan was performed with the patient in the supine position. Treatment planning was performed using Eclipse Brachytherapy Planning software (Varian Medical Systems Inc., Palo Alto, CA). All patients were treated with a multidwell position technique. Dwell times were determined such that coverage of the PTV_eval (defined below) and sparing of critical normal tissues were optimized. The clinical tumor volume (CTV) was the breast tissue within 10 mm of the balloon surface and did not include the volume of the balloon. The planning target volume (PTV) was set equal to the CTV. The PTV_eval was the final target volume and included the PTV limited to 5 mm from the skin surface and not extending into the chest wall and

pectoralis muscles. The volume of trapped air and fluid within the PTV_eval was also contoured and measured.

Four parameters were used for determining appropriateness for treatment: tissue-balloon conformance, balloon symmetry, minimal balloon surface-skin distance, and dose to skin and normal breast tissue. The tissue-balloon conformance was used to account for target breast tissue displaced by trapped air and fluid. The percentage of PTV_eval comprised of the trapped air/fluid was subtracted from the PTV_eval when determining coverage such that $(\%PTV_eval \text{ receiving } 100\% \text{ of the prescription dose}) - [(volume \text{ trapped air}/volume \text{ PTV_eval}) \times 100]$ was greater than or equal to 90%. Balloon symmetry was accounted for such that the physical geometry of the balloon did not deviate > 2 mm from the expected dimensions. Initially, a strict minimum of 7 mm balloon surface to skin distance was required. Normal breast tissue dose volume parameters were used to limit normal tissue damage as follows: the volume of tissue receiving 150% of the prescription dose was limited to < 50 cc and the volume of tissue receiving 200% of the prescription dose was limited to < 10 cc.

Treatment was initiated within 5 days of placement of the MammoSite® catheter. High dose rate Ir-192 was used to deliver a total of 34 Gy prescribed to approximately 1 cm from the balloon surface such that dosimetric requirements as described above were satisfied. Two fractions of 3.4 Gy were given per day, separated by at least 6 hours. A total of 10 fractions were delivered over a period of 5–10 days.

Toxicity evaluation

Patients were evaluated for toxicity by an attending physician prior to treatment, on the last day of brachytherapy, and at 4 weeks, 3 months, 6 months, and 1 year post-treatment. For the first 90 days post-treatment the Radiation Therapy Oncology Group (RTOG) acute toxicity scale was used and thereafter the RTOG/EORTC late toxicity scale was used.

Single dwell position comparison

For each multidwell plan, the percent volume of PTV_eval receiving 90% (V90), 95% (V95), 100% (V100), 150% (V150), and 200% (V200) of the prescription dose was recorded. The dose homogeneity index (DHI) was also calculated using the formula $(V100 - V150)/V100$. For the purpose of dosimetric comparison to our multidwell plans, two single dwell plans were generated for each patient. The first single dwell plan was matched such that the PTV_eval V95 was equivalent to the V95 for the multidwell plan. The second single dwell plan was matched for skin dose (using a 1 mm definition of skin) to the multidwell plan. The same dosimetric data was collected for these hypothetical plans as outlined above for the multidwell plans.

Skin dosimetry

In order to better understand the relationship between skin dose-volume parameters and skin toxicity, a variety of data was collected for each multidwell plan. Three superficial tissue volumes with thicknesses of 1 mm, 2 mm, and 3 mm from the body surface were segmented to model the skin. Maximum skin point doses were recorded for each plan using the 1 mm, 2

mm, and 3 mm definition of skin thickness. In addition, the minimum dose received by 0.078 cc skin (for 1 mm definition), 0.157 cc skin (for 2 mm definition), or 0.235 cc skin and 0.942 cc skin (for 3 mm definition) was recorded. These volumes correspond to the volumes of a 1 mm circular piece of skin with a diameter of 1 cm, a 2 mm thick piece of skin with a diameter of 1 cm, and a 3 mm piece of skin with a diameter of 1 and 2 cm, respectively. In addition, the same parameters were recorded for the phantom single dwell plans for the purpose of dosimetric comparison.

Statistical considerations

This was a phase II study that followed a Simon two-stage design [5] with the primary endpoint being acute/late grade 2 or higher skin toxicity at one year. Secondary endpoints included PTV_eval coverage and skin dose-volume parameters. After the first 16 patients were treated, skin dose data were analyzed to develop parameters that predicted for skin toxicity. Subsequent patients with balloon-skin surface distance < 7 mm were allowed to enroll if the skin dose parameter limits found in the first cohort to be associated with no more than grade 1 toxicity were met. In order to compare the multidwell plan to the single dwell plans, the Friedman test was used for non-parametric distributions (V90, V95, V100, V150, V200, and DHI), and a paired t-test was used for normally distributed data (skin dose parameters).

Results

Patient characteristics

Twenty-eight women in total were enrolled and had been treated on this trial at the time of analysis (12 additional patients accrued after the initial phase of 16 patients). Patient and tumor characteristics are listed in Table 1.

Treatment characteristics

Implant characteristics of all patients are listed in Table 2. The median skin to balloon distance was 12.5 mm. One patient had skin to balloon distance less than 7 mm and was enrolled during the second phase of the trial. The median volume of the PTV_eval was 88.1 cc and the median balloon volume was 45.4 cc. The median volume of residual air at the resection site was 1.1 cc.

Initial phase

For the initial phase of the trial, 16 patients were accrued in order to determine that the multiple dwell procedure was safe and associated with a low rate of toxicity, as well as to gather dosimetric information for evaluation of parameters predictive of skin toxicity. Preliminary analysis of dosimetric parameters suggested that multi-dwell planning was equivalent or superior to single dwell planning in terms of PTV coverage and lower skin dose. Interim evaluation revealed one patient with grade 2 or higher toxicity. This was grade 2 transient erythema in a patient who had a skin-balloon distance of 20 mm and a Dmax < 100% at all skin depths, but was the oldest patient enrolled on the trial, at age 87. Otherwise, two patients had a minimum skin distance of exactly 7 mm, and the associated maximum skin dose to 1 mm thickness of skin was 128%. Using a more conservative measure of 3 mm

of skin thickness, the maximum point dose to skin was 144% (less than the 145% recommended by NSABP B-39/RTOG 0413). It was therefore established that the multiple dwell position technique was dosimetrically and clinically safe. Based on this data, criteria for accrual of additional patients were created such that the balloon-skin distance could be less than 7 mm if the maximum dose to 1 mm thick skin tissue was $< 130\%$.

Target Coverage

The recorded dose-volume parameters for the PTV_eval using multidwell and phantom single dwell plans are listed in Table 3. When compared to the single dwell position plan matched for skin dose, the multidwell position plan PTV_eval had a significantly higher median V90, V95, V100, V150, and V200. The median DHI was 0.6 for the multidwell position plan, 0.5 for the single dwell position plan matched to V95, and 0.7 for the single dwell position plan matched to skin dose.

Skin Dosimetry

The recorded skin doses using the multidwell and phantom single dwell plans are shown in Table 4. Compared to the single dwell position plan matched for V95 coverage, the multidwell position plan had lower maximum doses regardless of whether 1, 2, or 3 mm of skin thickness was evaluated or whether a point dose or volume dose was evaluated.

Toxicity

Of the 28 women in this study, 26 (93%) had already completed their 1-year follow-up visits, and the remaining two patients completed their 6-month appointments. Four patients had no acute or late toxicities. There have been 2 patients (7%) who developed grade 2 toxicity (both transient erythema), and no patients have experienced grade 3, 4, or 5 toxicity (Table 5). The majority of toxicities were acute. As mentioned above, one patient with grade 2 erythema had a $D_{max} < 100\%$ at all skin depths, but was the most elderly patient enrolled on our trial at age 87. The second patient who experienced grade 2 erythema had balloon-skin separation of 8 mm, and a D_{max} to 1 mm of skin of 123%. Telangiectasias were mild (grade 1) and uncommon, occurring in two patients (7%).

Discussion

We conducted a single-arm phase II trial of MammoSite® breast brachytherapy in order to compare multidwell planning to standard single dwell position dose delivery, as well as to better define skin dosimetric parameters to predict skin toxicity and eligibility for treatment. Our data support the use of multiple dwell position MammoSite® brachytherapy rather than a single dwell position dose delivery method based on the superior target coverage and dose shaping allowing for minimization of the skin in the high dose region. Most importantly, our data indicates that relevant skin dose parameters can be used to predict skin toxicity and are likely superior to skin distance as has been used historically. Further data is needed to confirm the relevant dose-volume parameters, but it appears that it is likely safe to treat patients irrespective of balloon-skin distance as long as the maximum point dose to 1 mm skin thickness is $< 130\%$.

When matched for skin dose, multidwell position plans provided better coverage of the PTV_eval as evidenced by the significantly higher V90, V95, and V100. Most likely, the multiple dwell positions are better able to account for the anisotropy of the Ir-192 source which results in a “bowing in” of dose along the source axis and can result in under-dosing of this area if a single dwell position is used. The multi-dwell position plan did also result in a higher V150 and V200, as well as a lower DHI, potentially putting patients at higher risk for fat necrosis or fibrosis, although this was not observed in this study. Furthermore, the multidwell position plans also showed improved minimization of skin dose when compared to single dwell plans matched for PTV_eval coverage (V95). We attribute this to greater ability to shape dose to match the contour of the breast with multi-dwell planning, thereby minimizing the amount of skin in the high dose region.

Overall, the toxicity has been minimal using our approach. Two patients developed grade 2 erythema, and all other toxicities have been grade 1. This compares favorably to original studies of MammoSite® using single dwell position planning [7,13]. Multidwell position has been shown in retrospective studies to be correlated with decreased skin toxicity. Cuttino *et al* reviewed data on 483 patients treated with MammoSite® at a single institution [14]. In this report, 79% of patients received single dwell position dose delivery method, and the remaining 21% of patients were treated with multidwell planning. Overall cosmesis was excellent to good in 91% of patients. However, 12% of patients experienced a significant acute skin reaction (defined as dry or moist desquamation) and 14% developed significant subcutaneous toxicity (defined as visually apparent or requiring surgical intervention). The authors found that multiple dwell position dose delivery was significantly associated with a lower risk of hyperpigmentation and trended towards significance for a lower risk of acute skin reaction.

The NSABP B-39/RTOG 0413 trial mandated a maximum skin dose of 145% or less. Our data suggest that limiting the maximum point dose to < 130% to 1 mm thick skin is achievable with multi-dwell positioning and results in minimal toxicity. Since making this change to enrollment criteria, one woman was enrolled with a skin to balloon distance of less than 7 mm. The patient had a skin to balloon distance of 5 mm and a maximum point dose to 1 mm skin of 126.3%. She has been followed for 12 months and has thus far experienced only grade 1 erythema and grade 1 fibrosis.

Other groups have suggested that even more rigorous skin dose constraints might be achievable and result in lower toxicity. Arthur *et al* have reported on the ability of multi-lumen balloon breast brachytherapy to reduce skin dose to < 125% in greater than 90% of patients, allowing for treatment of patients with skin thickness of < 5 mm [15]. Cuttino *et al* reviewed toxicity data for 96 women treated with multicatheter interstitial brachytherapy or MammoSite® brachytherapy at their institution and found on multivariate analysis that a skin dose to > 120% was associated with an increased risk of late toxicity, such as telangiectasias and breast fibrosis [12]. In a recent report from the University of Pittsburgh, Vargo *et al.* retrospectively analyzed 157 patients treated with APBI using single-lumen MammoSite®. Telangiectasia development was found to correlate with skin dose >100% as the strongest predictive factor, as well as skin dose >120% and >145% [16].

Major limitations of our study include a small sample size and limited follow-up. Turesson has shown that telangiectasias may progressively develop over 5–10 years post-treatment, and the rate of progression is dose-dependent [17]. As such, the toxicity profiles may change with a longer duration of observation. In contrast, the strengths of our study include a prospective design with rigorous follow-up to ensure capture of all clinical events, prospective grading of toxicity and consistency of treatment delivery. In addition, our study provides useful prospective data on skin toxicity and dosimetric parameters, and to these authors' knowledge this is the only prospective trial focusing on identifying optimal skin-dosimetric parameters for single-lumen MammoSite® to date. Although newer APBI techniques have evolved (i.e. multi-lumen dose delivery methods) since the initiation of this trial, our data can be extrapolated to other techniques to provide guidance on optimal skin dose tolerances during patient selection and treatment planning. Furthermore, multi-lumen devices are still not readily available at all centers, and thus prospective data on optimal skin dosimetric parameters is valuable for institutions still employing single-lumen modalities.

Conclusion

Preliminary trials with MammoSite® brachytherapy using “single dwell position” technique reported high rates of acute skin toxicity, and many catheters were removed without treatment due to skin distance < 5 mm. Our trial aimed to determine whether a multidwell position technique can improve skin dose and resultant toxicity, as well as to prospectively determine dose-volume parameters to predict for skin toxicity and treatment eligibility. Our results show an overall low rate of initial skin toxicity associated with APBI and suggest that limiting the Dmax to < 130% to 1 mm thick skin is achievable and results in minimal toxicity. This parameter may serve as an appropriate surrogate for skin-balloon distance.

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TABLE 1**PATIENT AND TUMOR CHARACTERISTICS**

# Patients	28
Age- years, median (range)	64 (51–87)
Tumor Stage- # (%)	
Tis	4 (14%)
T1mi	1 (4%)
T1a	2 (7%)
T1b	10 (36%)
T1c	11 (39%)
Size of invasive component- cm, median (range)	1.0 (0.1–2.0)
Size of in situ component (all patients)- cm, median (range)	0.8 (0–2.8)
Size of in situ component (DCIS patients)- cm, median (range)	0.8 (0.3–2.2)
Grade- # (%)	
1	11 (39%)
2	14 (50%)
3	3 (11%)
ER status- # (%)	
Positive	28 (100%)
Negative	0 (0%)
PR status,-# (%)	
Positive	24 (86%)
Negative	4 (14%)
HER2/neu status (invasive disease only)- # (%)	
Positive	0 (0%)
Negative	24 (100%)
LVSI- # (%)	
Yes	0 (0%)
No	28 (100%)
Histology- # (%)	
DCIS	4 (14%)
Invasive ductal carcinoma	19 (67%)
Invasive lobular carcinoma	3 (11%)
Invasive tubulolobular carcinoma	1 (4%)
Invasive cribriform carcinoma	1 (4%)
Lymph node evaluation (invasive disease only)- # (%)	
Sentinel lymph node	24 (100%)

Axillary lymph node dissection	0 (0%)
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DCIS = ductal carcinoma in situ; cm = centimeters; ER = estrogen receptor; PR = progesterone receptor; LVSI = lymphovascular space invasion

TABLE 2**IMPLANT CHARACTERISTICS**

Patient #	V_{PTV_eval} (cc)	V_{balloon} (cc)	Skin-balloon distance (mm)
1	96.6	47.9	15.3
2	94.7	58.5	12.0
3	90.4	55.4	11.5
4	79.9	51.5	8.0
5	87.5	41.6	25.1
6	70.8	37.0	8.0
7	100.3	48.3	25.0
8	79.2	45.6	7.0
9	87.6	36.6	10.0
10	77.1	40.1	20.0
11	92.2	62.0	11.0
12	71.6	34.6	7.0
13	87.0	42.2	19.5
14	113.0	62.9	14.0
15	78.5	34.3	8.3
16	71.7	37.6	9.4
17	79.7	36.6	14.0
18	130.0	79.6	20.0
19	111.7	89.3	7.0
20	94.3	61.3	8.0
21	75.3	45.2	5.0
22	97.4	45.7	14.0
23	88.5	41.0	13.0
24	111.1	58.0	26.0
25	116.7	61.2	24.5
26	89.6	38.7	28.7
27	85.1	35.5	27.5
28	86.3	42.8	7.5
Median	88.1	45.4	12.5

V_{PTV_eval}(cc) = volume of PTV_eval in cubic centimeters; V_{balloon} (cc) = volume of balloon in cubic centimeters; mm = millimeters

TABLE 3**PTV_EVAL DOSE-VOLUME PARAMETERS**

	Multidwell position plan (median, SD)	Single dwell position plan-matching skin dose (median, SD)	Friedman Coefficient	P value
V90%	100.0 (1.4)	96.9 (7.9)	24.14	< 0.001
V95%	99.1 (2.7)	93.2 (9.8)	20.57	< 0.001
V100%	96.1 (3.9)	87.7 (11.1)	22.57	< 0.001
V150%	39.1 (5.1)	28.7 (10.8)	14.28	< 0.001
V200%	10.2(6.1)	3.8 (5.4)	14.28	< 0.001
Dose Homogeneity Index	0.6 (0.05)	0.7 (0.09)	8.03	0.0046

V90% = volume of PTV receiving 90% of the prescription dose; V95% = volume of PTV receiving 95% of the prescription dose; V100% = volume of PTV receiving 100% of the prescription dose; V150% = volume of PTV receiving 150% of the prescription dose; V200% = volume of PTV receiving 200% of the prescription dose; SD = standard deviation

TABLE 4**SKIN DOSE**

		Multidwell position plan (median, SD)	Single dwell position plan- matching V95 (median, SD)	P value
1 mm thick skin	Dmax %	96.9 (25.5)	110.4 (31.2)	< 0.001
	D _{0.078} %	88.4 (22.9)	93.7 (28.0)	< 0.001
2 mm thick skin	Dmax %	100.0 (26.7)	113.4(32.1)	0.0014
	D _{0.157} %	91.5 (23.6)	98.6 (33.9)	< 0.001
3 mm thick skin	Dmax %	106.2 (29.1)	120.2 (35.8)	< 0.001
	D _{0.235} %	96.6 (26.3)	108.3 (31.0)	< 0.001
	D _{0.942} %	88.6 (24.1)	99.4 (27.7)	< 0.001

mm = millimeters; SD = standard deviation; V95 = volume receiving 95% of the prescription dose; Dmax = maximal dose; D_{0.078} % = the minimum dose received by 0.078 cc skin; D_{0.157} % = the minimum dose received by 0.157 cc skin; D_{0.235} % = the minimum dose received by 0.235 cc skin; D_{0.942} % = the minimum dose received by 0.942 cc skin

TABLE 5

TOXICITY

Toxicity Grade	I	II	III	IV	V
Acute ^a					
Nausea	1				
Dizziness	1				
Tingling	2				
Fatigue	8				
Skin tightness	1				
Erythema	16	2			
Tenderness/pain	4				
Edema	3				
Seroma	1				
Gastroenteritis	1				
Hyperpigmentation	1				
Wound drainage	1				
Late ^b					
Tenderness/pain	4				
Fibrosis	9				
Hyperpigmentation	6				
Edema	1				
Seroma	1				
Alopecia	1				
Telangiectasias	2				

^a defined as events occurring less than or equal to 90 days from radiation treatment;

^b defined as events occurring greater than 90 days from radiation treatment