Original article

On the feasibility of treating to a 1.5 cm PTV with a commercial single-entry hybrid applicator in APBI breast brachytherapy

Kent A. Gifford, PhD[1], Christopher L. Nelson, PhD[1], Steven M. Kirsner, MS[1], Kelly D. Kisling, MS[1], Matthew T. Ballo, MD[2], Elizabeth S. Bloom, MD[2]

[1]Department of Radiation Physics, The University of Texas M.D. Anderson Cancer Center, [2]Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, USA

Abstract

Purpose: To evaluate and determine whether 30 patients previously treated with the SAVI™ device could have been treated to a PTV_EVAL created with a 1.5 cm expansion. This determination was based upon dosimetric parameters derived from current recommendations and dose-response data.

Material and methods: Thirty patients were retrospectively planned with PTV_EVALs generated with a 1.5 cm expansion (PTV_EVAL_1.5). Plans were evaluated based on PTV_EVAL_1.5 coverage (V90, V95, V100), skin and rib maximum doses (0.1 cc maximum dose as a percentage of prescription dose), as well as V150 and V200 for the PTV_EVAL_1.5. The treatment planning goal was to deliver ≥ 90% of the prescribed dose to ≥ 90% of the PTV_EVAL_1.5. Skin and rib maximum doses were to be ≤ 125% of the prescription dose and preferably ≤ 100% of the prescription dose. V150 and V200 were not allowed to exceed 52.5 cc and 21 cc, respectively. Plans not meeting the above criteria were re-computed with a 1.25 cm expanded PTV_EVAL and re-evaluated.

Results: Based on the above dose constraints, 30% (9/30) of the patients evaluated could have been treated with a 1.5 cm PTV_EVAL. The breakdown of cases successfully achieving the above dose constraints by applicator was: 0/4 (0%) 6-1, 6/15 (40%) 8-1, and 3/11 (27%) 10-1. For these PTV_EVAL_1.5 plans, median V90% was 90.3%, whereas the maximum skin and rib doses were all less than 115.2% and 117.6%, respectively. The median V150 and V200 volumes were 39.2 cc and 19.3, respectively. The treated PTV_EVAL_1.5 was greater in volume than the PTV_EVAL by 41.7 cc, and 60 cc for the 8-1, and 10-1 applicators, respectively. All remaining plans (17) successfully met the above dose constraints to be treated with a 1.25 cm PTV_EVAL (PTV_EVAL_1.25). For the PTV_EVAL_1.25 plans, V90% was 93.7%, and the maximum skin and rib doses were all less than 109.2% and 102.5%, respectively. The median V150 and V200 volumes were 41.2 cc and 19.3, respectively. The treated PTV_EVAL_1.25 was greater in volume than the PTV_EVAL by 16 cc, 24.9 cc, and 33.5 cc for the 6-1, 8-1 and 10-1 applicators, respectively.

Conclusions: It is dosimetrically possible to treat beyond the currently advised 1.0 cm expanded PTV_EVAL. Most patients should be able to be treated with a 1.25 cm PTV_EVAL and a select group with a 1.5 cm PTV_EVAL. Applicator size appears to determine the ability to expand to a 1.5 cm PTV_EVAL, as smaller devices were not as propitious in this regard. Further studies may identify additional patient groups that would benefit from this approach.

J Contemp Brachyther 2012; 4, 1: 29-33
DOI: 10.5114/jcb.2012.27949

Key words: APBI, breast brachytherapy, PTV_EVAL, SAVI.

Purpose

Accelerated partial breast irradiation (APBI) offers several benefits over conventional radiation techniques in the adjuvant treatment of early stage breast cancer for women undergoing breast-conserving surgery. From a patient perspective, APBI is more convenient and less time consuming than the standard 6 weeks conventional whole breast irradiation. These factors are even more pronounced for patients residing long distances from the treatment center [1]. APBI has been delivered via interstitial multi-catheter brachytherapy as well as with single-entry single lumen applicators and single-entry hybrid brachytherapy applicators. Examples of these devices are the Mammosite® (Hologic, Inc., Bedford, MA) single lumen applicator, the Mammosite® multi-lumen applicator, the Contura® (SenoRx, Inc., Irvine, CA) multi-lumen applicator [2] and the SAVI™ (Cianna Medical, Aliso Viejo, CA) multi-lumen applicator [2].

Typical PTV expansions from the cavity are 1.5-2.0 cm for an interstitial implant and 1.0 cm for the single-entry single lumen and single-entry hybrid devices. The 1.0 cm treat-

Address for correspondence: Kent A. Gifford, PhD, MD, Department of Radiation Physics, The University of Texas M.D. Anderson Cancer Center, Anderson Physician's Network, 7505 S. Main Suite 500, Houston, TX 77030, USA, phone: (713) 563-2596; fax: (713) 563-6949, ✉ e-mail: kagifford@mdanderson.org

Received: 12.12.2011
Accepted: 04.02.2012
Published: 31.03.2012

ment distance is in part supported by the studies of Imamura and Ohtake *et al.* [3, 4]. Imamura *et al.* [3] examined 324 invasive ductal breast carcinoma cases divided into three age groups and assessed disease extension as well as proliferative activity of the tumor. Their study found that the maximum distance of ductal spread from the edge of the invasive focus was 8.32 mm for the 40-64 age group and 5.28 mm for patients 65 years and older. Ohtake *et al*. [4] studied specimens from 20 patient quadrantectomies and found the maximum intraductal disease extension from the edge of the primary tumor to be 7.7 mm for patients 50 years and older. Indeed, the guidelines for selecting APBI brachytherapy candidates echo these findings. The American Society of Breast Surgeons (ASBS) guidelines [5] indicate that patients with invasive ductal carcinoma or ductal carcinoma in-situ, age greater than or equal to 45, tumor size less than or equal to 3 cm, node negative and with negative surgical margins are the potential candidates for APBI brachytherapy. The American Brachytherapy guidelines (ABS) [6] are more conservative than those of the ASBS in that the patient must be 50 years or older and only invasive ductal carcinomas are considered.

The Strut Adjust Volume Implant® or SAVI™ is fashioned in 4 different configurations: a mini 6-1 (total of 7 catheters), a standard 6-1 (7 catheters), an 8-1 (9 catheters) and a 10-1 (11 catheters). It is a single-entry hybrid catheter and is the only device on the market that provides 7 or more catheters. This device was designed to be a single-entry alternative for interstitial breast brachytherapy where 10-30 catheters are inserted into the breast tissue for treatment. As is typical for single-entry APBI breast devices, the PTV is the cavity expanded by 1.0 cm avoiding the pectoralis muscle and 2-5 mm from the skin surface.

The aforementioned clinicopathological studies present limited data and it is possible that cancer cells may reside at distances larger than 7-8 mm, quoted by Imamura *et al.* [3] and Ohtake *et al*. [4]. In fact, Vicini *et al.* [7] found residual carcinoma extending from 1.0 to 1.5 cm in 10% of the re-excision specimens in their study. Balloon based devices, in some patient cases may be able to treat to a larger expansion (> 10 mm) due to tissue compression [8]. The SAVI™ will not be able to compress tissue appreciably due to the strut based design. It is for this reason that we examined using expansions beyond the typical 1.0 cm to generate the PTV for patients treated with the SAVI™ device.

Material and methods

Patient selection and treatment

Thirty patients treated with the SAVI™ applicator were selected from our clinical database retrospectively. These thirty SAVI™ patient cases constituted the entirety of our currently treated SAVI™ patients. Each of these patients was enrolled in an investigational review board approved clinical protocol. This protocol was written to assess early and late sequelae from accelerated partial breast brachytherapy treatments. All patients were treated to 34 Gy in 10 fractions (BID), separated by 6 hours or greater, in less than 10 elapsed days on a Nucletron MicroSelectron v3 remote afterloader (Nucletron B.V., Veenendaal, the Netherlands).

Patient simulation

Patients were placed supine in a Vac-Loc (MedTec, Orange City, IA) immobilization cradle with both arms abducted above their head. Laser marks were placed on the patient to ensure inter-fraction setup reproducibility. The SAVI™ stylettes were removed from the catheters and 6F transfer tubes (Nucletron B.V., TH Veenendaal, the Netherlands) were then attached to each catheter at one end and the source position simulator on the other end. The source simulator (Nucletron B.V., TH Veenendaal, the Netherlands) was advanced to the end of each of the catheters of the SAVI™device to measure the indexer lengths. These measurements were entered into the treatment planning computer. All patients were scanned using a Lightspeed RT4 CT scanner (General Electric Healthcare Systems, Milwaukee, WI) at 120 kVp, 300 mA with a slice thickness of 1.25 mm. The patients were scanned to include the entire breast with a 2 cm margin superiorly and inferiorly. Upon completion of the scan, AP and lateral scout images were reviewed to determine the maximum expansion of the device. The minimum cavity to rib distance, minimum cavity to skin distance, and volume of the cavity were all measured and recorded. All CT images were then sent to the Nucletron Oncentra Masterplan version 3.3 (Nucletron B.V., TH Veenendaal, the Netherlands) treatment planning system for planning. The cavity was defined as the region delineated by the outermost extension of the struts of the SAVI™ device in contact with the patient.

Treatment planning – contouring

Contours of the organs at risk (OAR) and the target were generated using the tools available in the Nucletron Oncentra (Nucletron B.V., TH Veenendaal, the Netherlands) treatment planning system. The skin, ribs, and pectoralis major muscle were all contoured as OARs. The skin was generated by contracting the external surface of the patient by 2 mm to create a rind of tissue extending from the skin surface to 2 mm in depth. This 2 mm rind was then limited to the superior (left or right) quadrant of the body of the patient depending on which side the device was implanted. This was performed since it was felt that the skin should not be represented as simply a surface, but rather as extending in a finite distance within the tissue [9]. In addition, throughout the treatment, the minimum distance from the periphery of the APBI device to the skin surface can decrease as postoperative swelling decreases. The 2 mm rind of skin yields a more accurate representation of the dose delivered to the skin. We chose only the involved quadrant of skin, since including the entire skin contour would bias our DVHs, due to a large volume of skin receiving a relatively small dose. Each rib was contoured as a separate organ and after the final treatment plan was completed, the rib receiving the maximum dose was chosen as the organ for analysis. The final OAR that was contoured was the pectoralis major muscle. Next, the cavity was contoured. The planning target volume (PTV_OPT) that was used for optimization of the plans was generated by expanding the cavity 1 cm in an isotropic manner and limiting it from the pectoralis muscle, ribs and 2 mm from the superficial skin surface. Subsequently, the planning target volume used to evaluate

dose coverage (PTV_EVAL) was generated. This was accomplished by subtracting the cavity region of interest from the PTV_OPT region of interest to obtain a shell that expanded 1 cm around the cavity, but was limited by the pectoralis muscle, the ribs and 2 mm from the skin surface. The PTV_EVAL was edited to include any invaginated tissue between the struts. The PTV_EVAL was not expanded into the lungs. The volume of the PTV_EVAL was recorded in the assessment sheet. The air and seroma that were contiguous with the cavity were contoured as a single region of interest and the volume was recorded. The volume of the air and seroma was divided by the PTV_EVAL volume to determine non-conformance. If the non-conformance was within 5%, the planning continued. All contours were limited in the superior-inferior direction by the extent of the PTV_OPT in order to better standardize the contours.

Treatment planning

All patient plans were optimized with the IPSA optimization algorithm [10]. A class solution was loaded as a starting point and then iteratively adjusted until our clinical goals were achieved. Table 1 lists our clinical goals for dose volume coverage for the PTV_EVAL as well as the OARs. These goals were derived from the NSABP B-39 RTOG 0419 protocol [11], previously published planning recommendations for the SAVI™ device [12] and our clinical experience. The goals for the PTV_EVAL_1.5 and PTV_EVAL_1.25 plans were derived as a compromise between the NSABP B-39 RTOG 0419 protocol, published planning recommendations for the SAVI™ device [12] and dose volume side effect response data of Wazer *et al.* [13-15].

At least two plans were generated for each patient. All clinical plans had a 1.0 cm PTV_EVAL (PTV_EVAL) expansion. Subsequent to the clinical plan, a 1.5 cm PTV_EVAL expansion was generated. This 1.5 cm PTV_EVAL (PTV_EVAL_1.5) expansion was created in similar fashion as the 1.0 cm PTV_EVAL; the cavity was expanded 1.5 cm isotropically and limited by the ribs, pectoralis major muscle and 2 mm in from the skin surface, while subtracting out the cavity. The PTV_EVAL_1.5 plans were optimized subject to the treatment planning goals in Table 1. All PTV_EVAL_1.5 plans not meeting the goals in Table 1 were re-planned with a 1.25 cm PTV_EVAL expansion (PTV_EVAL_1.25). The PTV_EVAL_1.25 plans were optimized subject to identical treatment planning goals as the PTV_EVAL_1.5 plans.

Data analysis

For each treatment plan, the percentage of volume of PTV_EVAL, PTV_EVAL_1.25 and PTV_EVAL_1.5 receiving 306, 323, and 340 cGy, denoted by V90, V95, and V100, respectively, was extracted from each DVH. These values correspond to 90%, 95%, and 100% of the prescription dose. The volume of PTV_EVAL, PTV_EVAL_1.25 and PTV_EVAL_1.5 (cc) that received 150% and 200% of the prescription dose was then recorded. This was repeated for the OARs, except the % volumes extracted were 0.1 cc of the volume receiving the highest dose. The above data was collected also for the PTV_EVAL after optimizing the PTV_EVAL_1.5 to achieve V90 of 90% of the PTV_EVAL_1.5 volume. This was performed to assure that the original PTV_EVAL coverage and OAR maximum doses were still acceptable. Comparisons between OAR maximum doses (0.1 cc) (1.0 cm PTV_EVAL OARs vs. either 1.25 or 1.5 cm PTV_EVAL OARs) were performed with a nonparametric Wilcoxon rank test. Differences were considered significant if the calculated p-value was less than or equal to 0.05. Matlab version 7.4 (the MathWorks, Inc., Natick, MA) was used to perform all statistical calculations. Non-conformance for the PTV_EVAL was extracted from each of the clinical plans and reported.

Table 1. Planning guidelines that were used to generate the treatment plans

Treatment Planning Goals	Acceptable Dose Constraints
V95 ≥ 95% for PTV_EVAL	V90 ≥ 90% for PTV_EVAL
V90 ≥ 90% for PTV_EVAL_1.5	V90 ≥ 90% for PTV_EVAL_1.5
V150 ≤ 50 cc for PTV_EVAL	V150 ≤ 50 cc for PTV_EVAL
V150 ≤ 52.5 cc for PTV_EVAL_1.5[2]	V150 ≤ 52.5 cc for PTV_EVAL_1.5[2]
V200 ≤ 20 cc for PTV_EVAL	V200 ≤ 20 cc for PTV_EVAL
V200 ≤ 21 cc for PTV_EVAL_1.5[2]	V200 ≤ 21 cc for PTV_EVAL_1.5[2]
Max dose[1] ≤ 100% of Rx dose for skin and rib	Max dose[1] ≤ 125% of Rx dose for skin and rib

[1]Maximum dose was defined as the 0.1 cc of OAR receiving the highest dose. [2]Based on a compromise between NSABP B-39/ RTOG 0413, manufacturer recommendations [12], and dose response data of Wazer [13-15]

Results

Table 2 displays the demographics of the 30 clinical plans. Coverage of 90% of the prescription dose of the PTV_EVAL in all cases exceeded 97% of the volume. Coverage of 95% of the prescription dose of the PTV_EVAL in all cases exceeded 94.7% of the volume. Median V150 and V200 volumes were 31.0 cc and 14.2 cc, respectively. The median maximum skin dose was 105.7% of the prescription dose. The median maximum rib dose was 97.4% of the prescrip-

Table 2. Demographics of the clinical plans. Values in the cells represent the median over the patient population. Values in the parenthesis indicate the number of patient cases for each applicator size

Device	Cavity (cc)	PTV_EVAL (cc)	V90%	V95%	V150% (cc)	V200% (cc)	Skin % (0.1 cc)	Rib % (0.1 cc)
6-1 (4)	15.7	54.4	97.4	94.7	25.9	12.7	103.7	82.2
8-1 (15)	33.1	70.5	98.7	96.7	31.0	14.2	105.7	97.4
10-1 (11)	51.3	102.2	98.5	95.8	43.0	18.2	100.6	92.7

Table 3. Demographics of the 1.5 cm PTV_EVAL plans that met V150% and V200% criteria of 52.5 cc and 21 cc, respectively (criteria based on a compromise between NSABP B-39/RTOG 0413, manufacturer recommendations [12] and dose response data of Wazer [13-15]). Values in the cells represent the median over the patient population. Values in parenthesis indicate the number of plans meeting the criteria

Device	PTV_EVAL_1.5 (cc)	V90%	V95%	V150% (cc)	V200% (cc)	Skin % (0.1 cc)	Rib % (0.1 cc)
6-1 (0)	–	–	–	–	–	–	–
8-1 (6)	112.2	90.4	86.1	35.8	18.5	114.2	106.4
10-1 (3)	162.2	90.2	85.8	44.0	20.2	110.2	117.6

Table 4. Patient case demographics of the 1.25 cm PTV_EVAL plans. Values in the cells represent the median over the patient population. Values in parenthesis indicate the number of plans meeting the V150% and V200% criteria of 52.5 cc and 21 cc, respectively (criteria based on a compromise between NSABP B-39/RTOG 0413, manufacturer recommendations [12] and dose response data of Wazer [13-15])

Device	PTV_EVAL_1.5 (cc)	V90%	V95%	V150% (cc)	V200% (cc)	Skin % (0.1 cc)	Rib % (0.1 cc)
6-1 (4)	70.4	95.2	92.1	35.3	19.5	105.8	96.5
8-1 (9)	95.4	94.0	90.5	39.8	18.8	109.2	102.5
10-1 (8)	135.7	93.4	87.4	48.7	19.9	98.1	84.9

tion dose. The median non-conformance over all 30 patient plans was 0.7%, whereas it was 0.85%, 0.75%, and 0.3% for the 6-1, 8-1, and 10-1 device groups, respectively. The distance from the SAVI™device to skin and ribs ranged from 1.0 mm to 33.5 mm over the patient cohort. Table 3 displays the demographics of the PTV_EVAL_1.5 plans that met the criteria in Table 1. Nine cases (30% of the total number of cases) met the criteria established in Table 1. Zero of four 6-1 (0%), six of fifteen 8-1 (40%), and three of eleven 10-1 (27%) cases were expanded to a 1.5 cm PTV_EVAL successfully. Coverage of 90% of the prescription dose of the PTV_EVAL_1.5 in all cases exceeded 90.2% of the volume. Coverage of 95% of the prescription dose of the PTV_EVAL_1.5 in all cases exceeded 85.8% of the volume. The median volume of the PTV_EVAL increased by 41.7 cc (37%) and 60 cc (59%), for the 8-1 and 10-1 applicators, respectively. Median V150 and V200 volumes were 39.2 cc and 19.3 cc, respectively. The median maximum skin dose was 114.2% of the prescription dose. The 1.5 cm PTV_EVAL maximum skin doses did not differ statistically from the 1.0 cm PTV_EVAL maximum skin doses ($p \leq 0.36$). The median maximum rib dose was 117.6% of the prescription dose. The 1.5 cm PTV_EVAL maximum rib doses did not differ statistically from the 1.0 cm PTV_EVAL maximum rib doses ($p \geq 0.11$). Coverage of the PTV_EVAL volume increased post optimization of the PTV_EVAL_1.5; as the median coverage of 90%, 95% and 100% of the prescription dose of the PTV_EVAL was 99.9%, 98.9%, and 96.7% of the volume, respectively. The V150 and V200 median volumes for the PTV_EVAL post PTV_EVAL_1.5 optimization were 34.4 cc and 19.3 cc, respectively.

Table 4 displays the demographics of the PTV_EVAL_ _1.25 plans that met the criteria in Table 1. This group was composed of the remainder of the cases (21) from the PTV_EVAL_1.5 group that did not meet the criteria established in Table 1. All 21 cases met the criteria showed in Table 1. Coverage of 90% of the prescription dose of the PTV_EVAL_1.25 in all cases exceeded 93.7% of the volume. Coverage of 95% of the prescription dose of the PTV_ _EVAL_1.25 in all cases exceeded 87.4% of the volume. Median volume of the PTV_EVAL increased by 16 cc (29%), 24.9 cc (35%), and 33.5 cc (33%), for the 6-1, 8-1, and 10-1 applicators, respectively. Median V150 and V200 volumes were 41.2 cc and 19.3 cc, respectively. The median maximum skin dose was 109.2% of the prescription dose. The 1.25 cm PTV_EVAL maximum skin doses did differ statistically from the 1.0 cm PTV_EVAL maximum skin doses ($p \geq 0.02$). However, the median maximum skin dose for the 1.25 cm PTV_EVAL actually decreased for the 10-1 subgroup of patients. The median maximum rib dose was 102.5% of the prescription dose. The 1.25 cm PTV_EVAL maximum rib doses did not differ statistically from the 1.0 cm PTV_EVAL maximum rib doses ($p \geq 0.76$).

Discussion

The question as to whether it is dosimetrically possible to treat to a 1.25 cm or 1.5 cm expansion of the cavity with a commercial single-entry multi-catheter APBI brachytherapy device was examined. All patients in this study could have been treated with a 1.25 cm expansion of their cavity. 30% of this patient cohort could have been treated with a 1.5 cm expansion of the cavity. OARs did not experience a statistically significant increase in median dose except for the 1.25 cm PTV_EVAL skin maximum dose. This difference could be due to the small sample size. However, the 1.25 cm PTV_EVAL median maximum skin dose was still within the NSABP B-39/ RTOG 0413 guidelines for acceptable skin doses of 145% of prescribed dose to the skin surface. In addition, the median maximum skin dose was below the 125% of prescribed dose to the skin surface recommended by other single-entry hybrid breast brachytherapy devices.

Several patient groups may benefit from an increased PTV_EVAL volume. Holland *et al.* [16] found noninvasive carcinoma within 2 cm or greater from the primary tumor

in 75% of 282 of invasive carcinomas with tumor size ≤ 5 cm and 37% of 130 tumors 2 cm or less. So, treating beyond the typical 1.0 cm PTV_EVAL expansion may benefit currently accepted patients. The longest efficacy data with APBI is in patients treated with multi-catheter interstitial brachytherapy. The targeted breast tissue was 1-2 cm beyond the lumpectomy bed in the patients treated at William Beaumont Hospital [17]. In the RTOG 95-17 phase II trial of brachytherapy alone after lumpectomy, the treatment target was defined as a 2 cm margin peripheral to the surgical cavity and 1 cm anteriorly and posteriorly [18]. Ohtake *et al.* [4] found intraductal extension for the age group of 40-49 yr old to have a maximum extent of 14.3 mm. Thus, it may be possible to treat a younger cohort of patients by expanding the cavity to a 1.25-1.5 cm PTV_EVAL. Patients that are not able to tolerate an interstitial breast brachytherapy implant or centers not equipped to handle such a procedure, may also benefit from treating to a 1.25-1.5 cm PTV_EVAL with the SAVI™device.

The limitations of this study are the sample size of thirty patients and the fact that this study only examined theoretical dosimetric aspects of treating beyond a 1.0 cm expansion of cavities. Larger sample sizes could predict with greater accuracy the unintended consequences of treating to a larger volume PTV_EVAL. We hypothesize that the consequences could be an increased risk of fat necrosis, skin reactions (e.g. telangiectasia) and rib fracture. The highest skin dose in the PTV_EVAL_1.25 and PTV_EVAL_1.5 groups that passed V150 and V200 criteria was 134% of the prescription dose. This value is less than the accepted highest dose recommended by NSABP B-39/RTOG 0413 of 145% of the prescription dose. Turesson *et al.* [19] noted that telangiectasia risk increases with escalating dose above 40 Gy. However, based on current analysis and available data [13-15,20,21], the risk of these reactions is no different than treating with a 1.0 cm PTV_EVAL.

Conclusions

It is dosimetrically possible to treat to beyond the currently advised 1.0 cm PTV_EVAL. Most patients should be able to be treated with a 1.25 cm PTV_EVAL and a select group with a 1.5 cm PTV_EVAL. Applicator size appears to determine the ability to expand to 1.5 cm PTV_EVAL as smaller devices (6-1) were not as propitious in this regard. Further studies may identify additional patient groups that would benefit from this approach. However, the clinical benefit, risks and toxicity can only be determined within the confines of an investigational review board clinical protocol.

References

1. Dragun AE, Harper JL, Taylor CE et al. Patient satisfaction and quality of life after MammoSite breast brachytherapy. *Am J Surg* 2008; 196: 545-548.
2. Yashar CM, Blair S, Wallace A et al. Initial clinical experience with the Strut-Adjusted Volume Implant brachytherapy applicator for accelerated partial breast irradiation. *Brachytherapy* 2009; 8: 367-372.
3. Imamura H, Haga S, Shimizu T et al. Relationship between the morphological and biological characteristics of intraductal components accompanying invasive ductal breast carcinoma and patient age. *Breast Cancer Res Treat* 2000; 62: 177-184.
4. Ohtake T, Abe R, Kimijima I, et al. Intraductal extension of primary invasive breast carcinoma treated by breast-conservative surgery. Computer graphic three-dimensional reconstruction of the mammary duct-lobular systems. *Cancer* 1995; 76: 32-45.
5. The American Society of Breast Surgeons Consensus Statement for Accelerated Partial Breast Irradiation. 10/7/2008; http://www.breastsurgeons.org/statements/PDF_Statements/-APBI_statement revised_100708.pdf. Accessed 2/5/ 2010.
6. Arthur DW, Vicini FA, Kuske RR et al. Accelerated partial breast irradiation: an updated report from the American Brachytherapy Society. *Brachytherapy* 2002; 1: 184-190.
7. Vicini FA, Kestin LL, Goldstein NS. Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: a pathologic analysis. *Int J Radiat Oncol Biol Phys* 2004; 60: 722-730.
8. Edmundson GK, Vicini FA, Chen PY et al. Dosimetric characteristics of the MammoSite RTS, a new breast brachytherapy applicator. *Int J Radiat Oncol Biol Phys* 2002; 52: 1132-1139.
9. Nuutinen J, Lahtinen T, Turunen M et al. A dielectric method for measuring early and late reactions in irradiated human skin. *Radiother Oncol* 1998; 47: 249-254.
10. Lessard E, Pouliot J. Inverse planning anatomy-based dose optimization for HDR-brachytherapy of the prostate using fast simulated annealing algorithm and dedicated objective function. *Med Phys* 2001; 28: 773-779.
11. NSABP Protocol B-39/RTOG Protcol 0413: A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer. 11/2/2009; www.rtog.org/members/protocols/0413/0413.pdf. Accessed 2/5/2010.
12. Scanderbeg DJ, Yashar C, Rice R et al. Clinical implementation of a new HDR brachytherapy device for partial breast irradiation. *Radiother Oncol* 2009; 90: 36-42.
13. Wazer DE, Berle L, Graham R et al. Preliminary results of a phase I/II study of HDR brachytherapy alone for T1/T2 breast cancer. *Int J Radiat Oncol Biol Phys* 2002; 53: 889-897.
14. Wazer DE, Kaufman S, Cuttino L et al. Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2006; 64: 489-495.
15. Wazer DE, Lowther D, Boyle T et al. Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2001; 50: 107-111.
16. Holland R, Veling SH, Mravunac M et al. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985; 56: 979-990.
17. Benitez PR, Chen PY, Vicini FA et al. Partial breast irradiation in breast conserving therapy by way of intersitial brachytherapy. *Am J Surg* 2004; 188: 355-364.
18. Arthur DW, Winter K, Kuske RR et al. A Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: tumor control and survival outcomes of RTOG 95-17. *Int J Radiat Oncol Biol Phys* 2008; 72: 467-473.
19. Turesson I, Thames HD. Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation, and telangiectasia after 3 and 5 year's follow-up. *Radiother Oncol* 1989; 15: 169-188.
20. Brashears JH, Dragun AE, Jenrette JM. Late chest wall toxicity after MammoSite breast brachytherapy. *Brachytherapy* 2009; 8: 19-25.
21. Vicini FA, Beitsch PD, Quiet CA et al. First analysis of patient demographics, technical reproducibility, cosmesis, and early toxicity: results of the American Society of Breast Surgeons MammoSite breast brachytherapy trial. *Cancer* 2005; 104: 1138-1148.