Ann Surg Oncol (2015) 22:1140–1145
DOI 10.1245/s10434-014-4131-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

# A Comparison of Complication Rates in Early-Stage Breast Cancer Patients Treated with Brachytherapy Versus Whole-Breast Irradiation

**Nicolas Ajkay, MD[1], Abigail E. Collett, BS[1], Erica V. Bloomquist, MD[1], Edward J. Gracely, PhD[2], Thomas G. Frazier, MD[1], and Andrea V. Barrio, MD[1]**

[1]Department of Surgery, The Bryn Mawr Hospital, Bryn Mawr, PA; [2]School of Public Health, Drexel University College of Medicine & Drexel University, Philadelphia, PA

## ABSTRACT

**Background.** The adoption of breast brachytherapy into clinical practice for early-stage breast cancer has increased over the last several years. Studies evaluating complication rates following treatment with brachytherapy have shown conflicting results. We compared local toxicity in patients treated with brachytherapy with those treated with whole-breast irradiation (WBI).

**Methods.** We identified 417 early-stage breast cancer patients treated with breast-conserving surgery and radiation between 2004 and 2010, and compared 271 women treated with intracavitary brachytherapy with 146 women treated with WBI. Long-term complications were assessed using Kaplan–Meier curves with the log-rank test.

**Results.** Median follow-up was 4.6 years, and the 5-year incidence of infectious skin complications (9.7 vs. 11.0 %, $p = 0.84$), abscess (1.1 vs. 0 %, $p = 0.15$), telangiectasia (8.0 vs. 5.3 %, $p = 0.35$), and breast pain (14.2 vs. 9.4 %, $p = 0.2$) was similar between the brachytherapy and WBI cohorts. The brachytherapy cohort had a higher 5-year rate of seroma (46.5 vs. 18.5 %, $p < 0.001$), and fat necrosis (39.5 vs. 24.4 %, $p < 0.001$). Brachytherapy patients trended towards more frequent biopsies as a result of fat necrosis to rule out a recurrence (11.2 vs. 6.7 %, $p = 0.13$).

**Conclusions.** Patients treated with intracavitary brachytherapy had more local toxicity, particularly seroma and fat necrosis. Patients should be counseled on the possible increased rate of long-term complications associated with brachytherapy treatment.

Breast brachytherapy has emerged as an alternative to whole-breast irradiation (WBI) in patients with early-stage breast cancer treated with breast-conserving surgery (BCS). The rationale for brachytherapy was based on documented patterns of breast tumor recurrence demonstrating that fewer than 5 % of recurrences occur at sites remote from the lumpectomy cavity.[1] Despite a relative paucity of long-term outcomes data from randomized trials comparing brachytherapy with WBI, the adoption of brachytherapy into clinical practice has increased rapidly since 2003[2,3] for reasons which include reduced overall treatment times, decreased radiation dose to the uninvolved breast, and the assumption of 'decreased toxicity' as a result of the reduced radiation dose.[4]

However, whether treatment with brachytherapy results in decreased local toxicity compared with WBI is a question that remains largely unanswered. Data from large phase III trials will not be available for several years,[5] and recent prospective and retrospective studies have shown conflicting results. Smith et al. and Presley et al. have demonstrated increased rates of infectious and non-infectious complications in Medicare patients treated with brachytherapy,[3,6] while a review of the MammoSite Registry Trial demonstrated few toxicity events in their 1,449 cases treated with an intracavitary device.[7] Although registry and claims data provide valuable information regarding complications, information may be limited by potential underreporting of toxicities as well as variability in the quality of treatment delivery. Furthermore, lack of specific criteria to define toxicities may also limit reporting of complications.



First Received: 11 June 2014;
Published Online: 16 October 2014

A. V. Barrio, MD
e-mail: andrbarrio@aol.com

We sought to compare long-term pre-defined complication rates of intracavitary brachytherapy versus WBI in a patient cohort treated at a single institution with similar surgical techniques.

## METHODS

Following approval from our Institutional Review Board, a retrospective chart review identified 417 early-stage breast cancer patients treated with BCS and radiation at our institution between 2004 and 2010. We compared 271 women with 276 cancers treated with intracavitary brachytherapy with 146 women with 149 cancers treated with WBI. All patients underwent BCS by one of two surgeons, followed by either brachytherapy or WBI at the discretion of the treating radiation oncologist.

### *Catheter Type, Insertion Technique, and Radiation Treatment*

Of the 276 brachytherapy cases, 223 (80.8 %) were treated with MammoSite single-lumen catheters, 25 (9 %) with MammoSite multi-lumen catheters (Hologic Inc., Bedford, MA, USA), 27 (9.8 %) with Contura multi-lumen catheters (Hologic Inc.) and 1 (0.4 %) with an SAVI strut-adjusted volume implant (Cianna Medical, Aliso Viejo, CA, USA).

In patients in whom measurements were documented ($n = 218$), the median skin-to-seroma distance prior to balloon catheter placement was 12.1 mm (range 2.1–24.5 mm), with a minimum skin distance of $\geq$7 mm in 89 % ($n = 195$) of patients.

Our accelerated radiation treatment technique has been previously described in detail.[8] Each patient was seen in the Radiation Oncology Department within 24–48 h of balloon placement for computed tomography (CT)-based three-dimensional (3D) treatment planning. Patients received 34 Gy delivered 1 cm from the balloon surface, divided in two daily fractions of 3.4 Gy each, separated by 6 h and administered over 5 days.

### *Whole-Breast Irradiation Treatment*

All WBI treatments were planned with CT-based 3D conformal techniques using non-diverging tangent beams with 6 or 10 MV photons. The tumor bed was determined by surgical clips, lumpectomy scar, and tumor cavity on CT imaging plus a 1–2 cm margin. Patients were treated supine to 45–50.4 Gy for 25–28 fractions, with a boost of 10–16 Gy. For lymph node-positive patients, the supraclavicular lymph nodes received 45–50.4 Gy.

### *Outcome Measures*

Complications were predefined by the investigator prior to chart abstraction, and included infection, abscess, telangiectasia, breast pain, seroma, and fat necrosis. Patients were considered to have a non-infectious complication (breast pain, seroma, or fat necrosis) if symptoms persisted more than 6 months after the completion of radiation; in eight patients with seroma, symptoms began prior to 6 months but persisted beyond 6 months post-radiation and are therefore included in the seroma analysis. Infectious skin complications and telangiectasia could occur at any timepoint. Infection included mastitis, dermatitis, radiation recall reaction or erythema in the breast treated with antibiotics. Abscess was any infection requiring incision and drainage. Telangiectasia was recorded as vascular pigmentation over the lumpectomy scar. Breast pain was defined as physician-documented pain secondary to radiation, or severe or persistent breast pain requiring treatment such as anti-inflammatory medications, application of heat, or physical therapy. Seromas were either image-detected or physician-documented in the medical record. Seromas were considered symptomatic if they were aspirated secondary to pain or concern for infection or if a symptom referable to the seroma was documented in the chart. Fat necrosis required a clear pathologic diagnosis from fine-needle aspiration or core biopsy, a highly suggestive imaging finding (i.e., dystrophic calcifications), or high clinical suspicion documented in the medical record by the physician. The time to first complication was calculated from the time of last radiation treatment.

### *Statistical Analysis*

Characteristics of the two treatment groups were compared using unpaired $t$ tests for normally distributed data, Mann–Whitney $U$ tests when the data were non-normal but numeric, and Chi square (with the continuity correction for small expected values as needed) for nominal and dichotomous data. Kaplan–Meier curves were used to generate time-to-event curves for complication rates. Statistical significance of differences between groups was calculated using log-rank tests (for Kaplan–Meier curves). Predictions of complications by treatment type (brachytherapy vs. WBI) were assessed with Cox proportional hazards models. All analyses for complications were performed by breast (brachytherapy, $n = 276$; WBI, $n = 149$).

## RESULTS

The median follow-up for the entire group was 4.6 years (range 0.23–9.16 years), with a median follow-up of 4.8 years for the brachytherapy group and 4.1 years for the

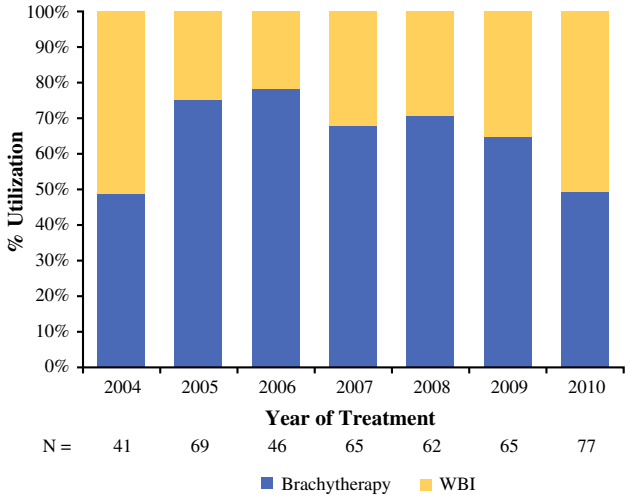


**FIG. 1** Utilization of brachytherapy and WBI by year of treatment. *WBI* whole-breast irradiation

WBI group. During the study period, brachytherapy use increased from 48.8 % in 2004 to 71 % in 2008, and subsequently declined to 49.3 % in 2010 (Fig. 1).

Table 1 shows the clinical characteristics of the 417 early-stage cancer patients by radiation therapy type. Women in the WBI group were younger (median 58 vs. 67 years, $p < 0.001$), had larger tumors (1.5 vs. 1.0 cm, $p < 0.001$), were more likely to be node positive (38.3 vs. 3.4 %, $p < 0.001$), and were more likely to receive systemic therapy (85.9 vs. 75.3 %, $p = 0.01$) compared with the brachytherapy cohort. Otherwise, the groups were similar with respect to other clinical parameters, including histology, hormone receptor status, family history, and margin status.

### *Complications*

The 5-year incidence of any complication was higher in the brachytherapy group compared with the WBI group (71.6 vs. 51.6 %, $p < 0.001$). Furthermore, patients in the brachytherapy group were more likely to have multiple (>1) complications compared with the WBI group (35.1 vs. 12.1 %, $p < 0.001$).

Table 2 shows the 5-year incidence of complication rates by treatment group. The 5-year incidence of infectious skin complications (9.7 vs. 11.0 %, $p = 0.84$), abscess (1.1 vs. 0 %, $p = 0.15$), telangiectasia (8.0 vs. 5.3 %, $p = 0.35$), and breast pain (14.2 vs. 9.4 %, $p = 0.2$) was similar between the brachytherapy and WBI groups, respectively.

Patients treated with brachytherapy had a higher 5-year rate of seroma compared with WBI patients [46.5 % vs. 18.5 %, $p < 0.001$; hazard ratio (HR) 3.30; 95 % confidence interval (CI) 2.16–5.04, $p < 0.001$] (Table 2).

**TABLE 1** Clinical characteristics of 417 patients by radiation therapy type

| Characteristic | Brachytherapy | WBI | *p* value |
|---|---|---|---|
| No. of cases | 276 | 149 | |
| Age [years; median (range)] | 67 (42–87) | 58 (32–88) | <0.001 |
| Pathologic tumor size [cm; median (range)][a] | 1.0 (0.06–5.2) | 1.5 (0.13–4.5) | <0.001 |
| Histology [*n* (%)] | | | 0.75 |
| Invasive[b] | 198 (71.7) | 115 (77.2) | |
| DCIS | 73 (26.5) | 31 (20.8) | |
| Other invasive[c] | 5 (1.8) | 3 (2) | |
| ER status [*n* (%)][d] | | | 0.46 |
| Positive | 230 (83.9) | 120 (81.1) | |
| Negative | 44 (16.1) | 28 (18.9) | |
| Family history [*n* (%)] | | | 0.42 |
| Yes | 124 (44.9) | 73 (49) | |
| No | 152 (55.1) | 76 (51) | |
| Margins [*n* (%)][e] | | | 0.375 |
| Negative/close | 245 (88.8) | 127 (85.8) | |
| Positive | 31 (11.2) | 21 (14.2) | |
| Pathologic nodal status [*n* (%)][f] | | | <0.001 |
| Negative | 198 (96.6) | 74 (61.7) | |
| Positive | 7 (3.4) | 46 (38.3) | |
| Systemic therapy [*n* (%)][g] | | | 0.01 |
| Yes | 207 (75.3) | 128 (85.9) | |
| No | 68 (24.7) | 21 (14.1) | |

*WBI* whole-breast irradiation, *ER* estrogen receptor, *DCIS* ductal carcinoma in situ

[a] Tumor size unknown in the brachytherapy ($n = 26$) and WBI ($n = 15$) groups

[b] Includes invasive ductal and lobular carcinomas

[c] Includes invasive mixed ductal and lobular ($n = 6$), metaplastic ($n = 1$), and adenoid cystic carcinomas ($n = 1$)

[d] ER status unknown in the brachytherapy ($n = 2$) and WBI ($n = 1$) groups

[e] Margin status unknown in the WBI group ($n = 1$)

[f] Nodal status calculated for patients in the brachytherapy ($n = 205$) and WBI ($n = 120$) groups with axillary surgery

[g] Systemic therapy includes chemotherapy, hormonal therapy, or both. Use of systemic therapy unknown in the brachytherapy group ($n = 1$)

Seroma formation in the brachytherapy group continued beyond 6 years, while no patients in the WBI group developed seroma after 3 years (Fig. 2). In total, 28.7 % of the 129 seromas in the brachytherapy cohort were symptomatic compared with 11.5 % (3/26) in the WBI cohort ($p = 0.07$). Of the asymptomatic seromas, 9.8 % (9/92) in the brachytherapy group underwent aspiration biopsy to rule out a recurrence compared with 4.3 % (1/23) in the WBI group ($p = 0.68$).

**TABLE 2** 5-year incidence of complication rates in the brachytherapy ($n = 276$) versus WBI ($n = 149$) cohorts

| Complication | 5-year incidence | | $p$ value[a] | Hazard ratio (95 % CI) | $p$ value[b] |
|---|---|---|---|---|---|
| | Brachytherapy [% (95 % CI)] | WBI [% (95 % CI)] | | | |
| Any | 71.6 (65.5–77.7) | 51.6 (42–61.2) | <0.001 | 1.92 (1.46–2.54) | <0.001 |
| Infection | 9.7 (6.2–13.2) | 11.0 (5.1–16.9) | 0.84 | 1.06 (0.56–2.04) | 0.84 |
| Abscess[c] | 1.1 (0–2.3) | 0 | 0.15 | – | 0.40 |
| Telangiectasia | 8.0 (4.5–11.5) | 5.3 (1.4–9.2) | 0.35 | 1.44 (0.67–3.08) | 0.35 |
| Pain | 14.2 (9.5–18.9) | 9.4 (4.1–14.7) | 0.20 | 1.52 (0.8–2.86) | 0.20 |
| Seroma | 46.5 (40.0–53.0) | 18.5 (12.0–25.0) | <0.001 | 3.30 (2.16–5.04) | <0.001 |
| Fat necrosis | 39.5 (32.6–46.4) | 24.4 (15.6–33.2) | <0.001 | 2.22 (1.46–3.38) | <0.001 |

*WBI* whole-breast irradiation, *CI* confidence interval

[a] $p$ value calculated using the log-rank test

[b] $p$ value calculated using the Cox proportional hazards model

[c] Hazard ratio not reported due to the small number of events

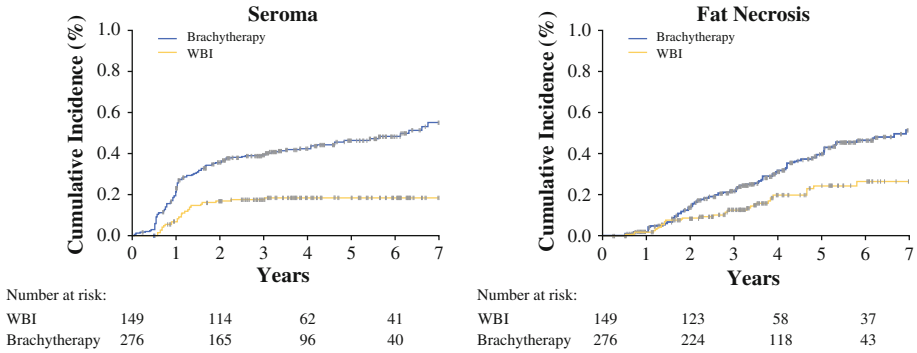


**FIG. 2** Cumulative incidence of (**a**) seroma and (**b**) fat necrosis in early-stage breast cancer patients treated with brachytherapy versus WBI. *WBI* whole-breast irradiation

The 5-year rate of fat necrosis was also higher in the brachytherapy group when compared with the WBI group (39.5 vs. 24.4 %, $p < 0.001$; HR 2.22; 95 % CI 1.46–3.38, $p < 0.001$) (Table 2), with an increasing incidence noted in both groups out to 6 years (Fig. 2). Of the 105 cases of fat necrosis in the brachytherapy group, 57 (54.3 %) were detected as a palpable mass compared with 10/29 (34.4 %) in the WBI group ($p = 0.06$). Brachytherapy patients trended towards more frequent biopsies as a result of fat necrosis to rule out a recurrence (11.2 vs. 6.7 %, $p = 0.13$).

## DISCUSSION

With the rapid adoption of breast brachytherapy reported in several recent studies,[2,3] attention has been placed on potential local toxicities associated with this accelerated treatment. Studies evaluating toxicities with brachytherapy have shown conflicting results.[3,6,7,9,10] In these studies, potential underreporting of toxicities remains a considerable limitation, which was acknowledged by Khan et al. in their 6-year toxicity analysis of the MammoSite Registry Trial.[7] In addition, in two recent large studies of Medicare beneficiaries, the 'brachytherapy' group was heterogeneous, including patients treated with either intracavitary or multi-catheter interstitial brachytherapy,[3,6] making it difficult to distinguish toxicity related to a specific brachytherapy method. Furthermore, few studies have documented a strict definition for specific toxicities, which may also limit reporting.[4] We undertook this study to compare complication rates between intracavitary brachytherapy and WBI by applying pre-defined toxicity criteria to our cohort of 417 patients.

In the current study, we noted an excess of complications associated with brachytherapy at 5 years (71.6 vs. 51.6 %, $p < 0.001$). Interestingly, infectious skin complications, telangiectasia and breast pain did not seem to account for the discrepancy in complication rate. The additional complications were largely related to a higher rate of seroma formation and fat necrosis following treatment with intracavitary brachytherapy.

Brachytherapy patients had a higher 5-year incidence of seroma compared with WBI patients (46.5 vs. 18.5 %, $p < 0.001$), with new cases continuing to develop even after 5 years. No new cases of seroma were noted after 3 years following WBI, suggesting that with continued follow-up, the difference in seroma formation between groups will likely become larger. Our findings are consistent with other studies, which have demonstrated high rates

of seroma formation ranging from 28 to 76 % following intracavitary brachytherapy, although we are the first to demonstrate ongoing seroma formation in brachytherapy patients beyond 5 years[4,7,10–12] The incidence of seroma formation following BCS and standard WBI is not well documented in the literature. However, it is noteworthy that small series by Monticciolo et al. and Woodworth et al. have shown seroma rates of 7 and 14 %, respectively, after standard therapy, which is markedly lower than the reported seroma incidence after brachytherapy.[10,13]

Few studies have further classified seromas into 'symptomatic' and 'asymptomatic' and fewer have attempted to examine their clinical significance.[7,10] Khan et al. reported that symptomatic seromas were seen in 13 % of the 1,449 cases in the MammoSite Registry trial, with 91 % requiring drainage. Similarly, 81 % of the symptomatic seromas in our study were aspirated at least once for symptom relief, and, notably, there was an excess of symptomatic seromas in the brachytherapy group (37/276; 13.4 %) compared with the WBI group (3/146; 2.0 %). Aside from the pain associated with symptomatic seromas, the repeated aspirations may be a source of psychological stress, and the impact of symptomatic seromas on quality of life post-treatment warrants further study.

Asymptomatic seromas produce no discernible symptoms in the patient, although their impact on surveillance is unclear. Monticciolo et al. reported a case of recurrence in the treatment bed obscured by overlying seroma.[10] In our study, a higher incidence of aspiration biopsies to rule out recurrence was noted among brachytherapy patients who developed an asymptomatic seroma compared with WBI patients (9.8 vs. 4.3 %, $p = 0.68$), albeit not significant in this dataset. Given the paucity of data, additional studies are needed to determine the impact of seroma formation on imaging and clinical surveillance of the lumpectomy bed.

The incidence of fat necrosis across studies is similarly quite variable, with no clear classification system to define this toxicity.[7,9] Our 5-year fat necrosis rate of 39.5 % seen in patients treated with brachytherapy is higher than that noted in other studies,[3,6,7,10] which may be related to differences in definition, follow-up time, or radiation delivery method. Fat necrosis rates in our study continued to increase over time in both groups without evidence of a plateau, demonstrating that fat necrosis is a late toxicity that requires substantial follow-up. The late onset of this toxicity is what contributes to the ambiguity regarding its diagnosis. More than half of the fat necrosis cases (54.3 %) following brachytherapy presented clinically as a palpable lump compared with 34.4 % among WBI patients ($p = 0.06$). A recent single-institution study by Rosenkranz et al. similarly noted a higher incidence of palpable masses at the lumpectomy site in patients treated with MammoSite compared with WBI (26.7 vs. 7.3 %, $p < 0.001$), which led to significantly more biopsies in the MammoSite group ($p = 0.02$).[9] The presence of a lump in the surgical bed may obscure the lumpectomy cavity, making clinical surveillance more difficult. In our study, the complex clinical examination also resulted in a non-significant increased incidence of biopsies in the brachytherapy group to rule out recurrences. Although not directly measured in our study, the need for additional biopsies, even if benign, following definitive cancer treatment has the potential to raise patient anxiety as well as cost.

The excess complication rates associated with brachytherapy treatment noted in this and other studies[3,6] remains a real concern. Smith et al. reported that for every 16 women treated with brachytherapy in their study, 1 was subjected to an 'unnecessary' postradiation complication.[3] Although the number of women receiving brachytherapy in our practice has declined since 2006, a notable 49.3 % of the radiated patients in our study received brachytherapy in 2010, representing a cohort of women that has the potential for significantly increased toxicity.

Our study has several important limitations. First, as a retrospective study, it has inherent limitations in capturing toxicity data. Although all the charts were rigorously reviewed with pre-defined toxicity criteria, there is still potential for underreporting or overreporting of complications based on physician documentation. Furthermore, the brachytherapy and WBI groups were not matched with respect to clinical characteristics. Therefore, it is possible that certain complications were secondary to inherent differences between the groups instead of the radiation treatment itself. Finally, skin-to-seroma distance was used as a surrogate for skin-to-balloon distance, the latter being the standard measurement used to report skin spacing. It is not known whether these two measurements are interchangeable, and therefore the possible discrepancy in skin spacing could potentially affect complication rates.

## CONCLUSIONS

Patients treated with intracavitary brachytherapy had a higher rate of local toxicity, particularly seroma and fat necrosis, compared with the WBI cohort. The increased rate of seroma and fat necrosis in brachytherapy patients led to more biopsies to rule out recurrence, as a result of a more complicated clinical examination. Patients should be counseled on the possible increased rate of long-term complications associated with brachytherapy treatment.

**ACKNOWLEDGMENT** This study was funded by a grant from the Sharpe-Strumia Research Foundation of The Bryn Mawr Hospital.

## REFERENCES

1. Pawlik TM, Bucholz TA, Kuerer HM. The biologic rationale for and emerging role of accelerated partial breast irradiation for breast cancer. *J Am Coll Surg*. 2004;199:479-92.

2. Czechura T, Winchester DJ, Pesce C, Huo D, Winchester DP, Yao K. Accelerated partial-breast irradiation versus whole-breast irradiation for early-stage breast cancer patients undergoing breast conservation, 2003-2010: a report from the national cancer data base. *Ann Surg Oncol*. 2013;20(10):3223-32.
3. Smith GL, Xu Y, Buchholz TA, et al. Association between treatment with brachytherapy versus whole-breast irradiation and subsequent mastectomy, complications and survival among older women with invasive breast cancer. *JAMA*. 2012;307:1827-37.
4. Chao KK, Vicini FA, Wallace M, et al. Analysis of treatment efficacy, cosmesis, and toxicity using the MammoSite breast brachytherapy catheter to deliver accelerated partial breast irradiation: the William Beaumont hospital experience. *Int J Radiat Oncol Biol Phys*. 2007:69:32-40.
5. Radiation Therapy Oncology Group. NSABP Protocol B-39/RTOG Protocol 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. Available from: www.rpc.mdanderson.org/rpc/credentialing/files/B39_Protocol1.pdf. Accessed 1 Feb 2014.
6. Presley CJ, Soulos PR, Herrin J, et al. Patterns of use and short-term complications of breast brachytherapy in the national Medicare population from 2008-2009. *J Clin Oncol*. 2012;30:4302-07.
7. Khan AJ, Arthur D, Vicini F, et al. Six-year analysis of treatment-related toxicities in patients treated with accelerated partial breast irradiation on the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial. *Ann Surg Oncol*. 2012;19:1477-1483.
8. Stull TS, Goodwin MC, Gracely EJ, Chernick MR, Carella RJ, Frazier TG, et al. A single-institution review of accelerated partial breast irradiation in patients considered "cautionary" by the American Society for Radiation Oncology. *Ann Surg Oncol.* 2012;19:553-559.
9. Rosenkranz KM, Tsui E, McCabe EB, et al. Increased rates of long-term complications after mammosite brachytherapy compared with whole breast radiation therapy. *J Am Coll Surg*. 2013;217:497-502.
10. Monticciolo DL, Biggs K, Gist AK, et al. Breast conserving therapy with accelerated partial breast versus external beam whole breast irradiation: comparison of imaging sequel and complication in a matched population. *Breast J*. 2001:17:187-190.
11. Evans SB, Kaufman SA, Price LL, Cardarelli G, Dipetrillo TA, Wazer DE. Persistent seroma after intraoperative placement of MammoSite for accelerated partial breast irradiation: incidence, pathologic anatomy, and contributing factors. *Int J Radiat Oncol Biol Phys*. 2006:65:333-339.
12. Watkins JM, Harper JL, Dragun AE, et al. Incidence and prognostic factors for seroma development after MammoSite breast brachytherapy. *Brachytherapy*. 2008:7(4):305-309.
13. Woodworth PA, McBoyle MF, Helmer SD, Beamer RL. Seroma formation after breast cancer surgery: incidence and predicting factors. *Am Surg*. 2000:66(5):444-450.