Once Daily Accelerated Partial Breast Irradiation: Preliminary Results with Helical Tomotherapy®

UGO DE PAULA[1], ROLANDO M. D'ANGELILLO[2], RAFFAELE BARBARA[1], CRISTINA CARUSO[1], SARA GOMELLINI[1], AURELIA CACCAVARI[3], LEOPOLDO COSTARELLI[4], PAOLA SCAVINA[5], MARIA MAURI[5], ELENA SANTINI[6], ADRIANA ANTONACI[7], FRANCESCO CAVALIERE[8], MASSIMO LA PINTA[8], ANDREA LORETI[9] and LUCIO FORTUNATO[8]

[1]*Department of Radiation Oncology, San Giovanni-Addolorata Hospital, Rome, Italy;*
[2]*Department of Radiation Oncology, Campus Bio-Medico University, Rome, Italy;*
[3]*Department of Medical Physics, San Giovanni-Addolorata Hospital, Rome, Italy;*
[4]*Department of Pathology, San Giovanni-Addolorata Hospital, Rome, Italy;*
[5]*Department of Medical Oncology, San Giovanni-Addolorata Hospital, Rome, Italy;*
[6]*Department of Radiology, San Giovanni-Addolorata Hospital, Rome, Italy;*
[7]*Department of Physical and Rehabilitation Medicine, San Giovanni-Addolorata Hospital, Rome, Italy;*
[8]*Breast Unit-Department of Surgery, San Giovanni-Addolorata Hospital, Rome, Italy;*
[9]*Department of Plastic Surgery, San Giovanni-Addolorata Hospital, Rome, Italy*

Abstract. *Background: Accelerated partial breast irradiation (APBI) is becoming an option for patients with low-risk breast cancer. The current practice is 38.5 Gy in 10 fractions b.i.d. over 5 days. This fractionation has a higher bioequivalent dose compared to the standard schedule. We report on preliminary results of once-daily APBI in patients treated with TomoTherapy®. Patients and Methods: Patients with unifocal-breast disease who underwent breast-conserving surgery were enrolled in the study. Treatment was administered with TomoTherapy, by contouring in accordance with the NSABP B-39/RTOG 0413 APBI protocol. Treatment schedule was 38.5 Gy in 10 once-daily fractions. EORTC Cosmetic Rating System was adopted for cosmetic outcome. Results: From 2010 to 2013, 111 patients were treated. With a median follow-up of 34 months, no ipsilateral breast recurrence was observed. Very few patients (1-4%) assessed their cosmetic outcome as fair or poor during follow-up. Conclusion: Once-daily APBI with TomoTherapy yielded good cosmetic results without compromising local control efficacy.*

Correspondence to: Ugo de Paula, MD, Department of Radiation Oncology, San Giovanni-Addolorata Hospital, via Santo Stefano Rotondo 5A 00184 Rome, Italy. Tel: +39 0677054295, Fax: +39 06770579169, e-mail: udepaula@hsangiovanni.roma.it

Key Words: Partial breast irradiation, TomoTherapy, APBI, breast cancer.

Breast-conserving therapy (BCT) represents a standard-of-care in the management of early-stage breast cancer and accelerated partial breast irradiation (APBI) is one option for post-operative treatment. APBI delivers a high dose of radiation per fraction over a shorter timeframe and may increase the proportion of women receiving BCT. Both ASTRO (2009) and ESTRO (2010) have published recommendations on appropriate patient selection criteria for treatment with APBI (1, 2).

However, the RAPID trial (3), a randomized controlled comparison of APBI *versus* whole-breast irradiation (WBI), reported less favorable 3-year cosmetic outcomes in the APBI arm, as assessed by trained nurses, physicians, and patients themselves. Bentzen and Yarnold (4), by analyzing the preliminary results of three phase II trials (5-7), have reported a quite high incidence of poor or fair outcome, and emphasized that these results could rationally call for a once-daily, rather than a twice-daily delivery.

There are several reported techniques to administer partial breast irradiation, including brachytherapy (8, 9) or external-beam irradiation (10), but there are very few reports on the use of TomoTherapy® (Accuray Incorporated, Sunnyvale, CA, USA), and when studied, data and results only reflect dosimetric comparisons (11).

We herein investigated TomoTherapy®, which had the added advantage over three Dimension Conformal Radiation Therapy (3DCRT) and Intensity Modulated Radiation Therapy (IMRT) of using image guidance for each fraction, for the purpose of improving the conformality and homogeneity of the dose to the tumor bed and reducing the

dose to normal tissues as far as possible. Based on this premise, in 2010, we established a phase II trial aiming to assess the role of once-daily accelerated partial breast irradiation (OD-APBI) in terms of cosmetic and local results.

Patients and Methods

Patient selection and eligibility. From December 2010 to April 2015, 190 patients with invasive breast cancer and at least 50 years of age were evaluated in this phase II trial but, at the time of the present study, we present results on 111 patients treated until December 2013 for whom consistent follow-up data are available.

Eligibility criteria included unifocal disease up to 3 cm in size with at least 2 mm of clear margins without extensive intraductal disease (less than 25%) or lymph or vascular invasion. Sentinel lymph node biopsy or limited axillary dissection, (I/II levels in case of positive sentinel lymph node), was required by the study protocol. Patients with one to three nodal metastases in absence of extra-capsular invasion were included. Moreover, all genetic subtypes (luminal A-like, luminal B-like, HER2-positive and triple-negative) were admitted.

Exclusion criteria included the following: extensive ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS), palpable lymphadenopathy in the axilla, Paget's disease of the nipple, extensive skin involvement from tumor, metastatic disease, significant comorbidities precluding surgical excision and/or radiation therapy, previous radiation therapy to the involved breast, history of neoplasia (excluding skin tumors totally removed by surgery). All suspicious lymph nodes, either clinical or radiological, in supraclavicular/ infraclavicular fossa or internal mammary chain have been histo/cytologically evaluated. Patients who underwent neoadjuvant chemotherapy were not included.

The study was approved by the local Ethics Committee and all patients gave their informed consent.

Radiation therapy. The patients underwent a CT scan without contrast in supine position with a customized cushion and breast board, with arms raised and head turned to the opposite side of the operated breast.

Radiopaque markers were used to mark the surgical scar and the palpable limits of the mammary tissue bilaterally. The CT scan was carried-out with a slice thickness of 2.5 cm, a distance between the slices of 2.5 cm and a matrix of 512×512; the scan extended from the scapulohumeral joint to the diaphragm. Four permanent reference marks were tattooed on the skin just before the CT scan.

The contouring of the target volume and organs at risk (OARs) was carried out using the Pinnacle Treatment Planning System in accordance with the NSABP B-39/RTOG 0413 APBI protocol. The gross target volume (GTV) was the tumor bed (TB) and its contours were drawn around the surgical clips and/or seroma. The presence of surgical clips, in a variable number from 2 to 4, was a mandatory hallmark to define the real extension of the disease, as outlined in a previous study (12), and they were positioned in about 85% of cases; in the remaining 15%, the seroma was used to identify the surgical bed. During the tumor bed contouring, surgical clips identified the GTV.

The clinical target volume (CTV) was constructed with a uniform 1.5-cm 3-D margin around the TB. The Planning Target Volume (PTV) included a uniform 1-cm 3-D margin around the CTV. A PTV_EVAL was generated by automatically withdrawing the PTV by up to 5 mm away from the skin and the lung-thoracic wall interface. Unlike in the guidelines of the NSABP B-39/RTOG 0413 ABPI protocol, the pectoral muscle was not excluded from the PTV_EVAL, which extended up to the lung-thoracic wall interface to cancel the effects of the respiratory motion.

The ipsilateral and contralateral breasts, ipsilateral and contralateral lungs, heart, and spinal cord were contoured as OARs. Moreover, for plan optimization and approval purposes, we also used the volume of the uninvolved ipsilateral breast, obtained automatically by subtracting the PTV_EVAL from the ipsilateral breast volume. NSABP B-39/RTOG 0413 APBI protocol dose constraints for normal tissues (1) were applied. In order to obtain a high conformal index (CI) regarding dose to target, in the inverse planning 100% of PTV_EVALs' volume required a dose coverage of 95% at least of prescribed dose.

All patients underwent TomoTherapy treatment with a total dose of 38.5 Gy delivered in 10 consecutive 3.85-Gy fractions. With regard to this technique and more precisely the field width (opening of the jaw size in the longitudinal direction), and pitch (ratio of the distance travelled by the couch per gantry rotation to field width), we studied two combinations: one with a field width of 2.5 cm and pitch of 0.215, and the other with a 5-cm field and a pitch of 0.172 pitch. These choices were prompted by the need to minimize "threading" of the dose distribution due to the overlapping joints of the adjacent radiation fields in helical radiotherapy. With regard to the modulation factor, the ratio of the maximum to the average intensity of the beam, was selected in order to maintain an average treatment administration time of 10 min.

Radiation treatment was to begin within three months of breast conserving surgery (BCS), but no sooner than 4 weeks after chemotherapy, if administered.

Follow-up, toxicity, and cosmesis. After RT, patients were assessed at 3, 6, and 12 months and then annually. Acute and late toxicity was graded according to Common Terminology Criteria for Adverse Events version 4.0 (13). At each visit, verbal and physical examinations were performed; bilateral mammograms were recorded annually. The patient and radiation oncologist assessed cosmesis during follow-up visits by means of the EORTC Cosmetic Rating System (14), comparing the treated breast with the untreated one and evaluating the size, shape, skin color, location, and the shape of the areola and nipple, appearance of the surgical scar, and global cosmetic score. Characteristics were graded on a 4-point scale: 0, excellent or no difference; 1, good or small difference; 2, fair or moderate difference; and 3, poor or large difference. Patients did not use a training manual and the physicians were not blinded when assessing cosmesis. All cosmetic scores were used in the current analysis.

Statistical analysis. The primary end-points of this trial were ipsilateral breast tumor recurrence (IBTR) and toxicity. Important secondary outcomes were rates of adverse cosmesis, quality of life, and compliance. Adverse cosmesis was defined as the proportion of patients with a fair or poor global cosmetic score. For an expected IBTR at 5 years of 5% (standard error of 1.6%), an established (by patients and physicians) adverse cosmesis rate (fair and poor scores) of no more than 20% of treated patients, and a power of 80%, a total of 180 patients needed to be enrolled. A preliminary analysis was conducted when at least 100 patients had reached a median follow-up of 24 months.

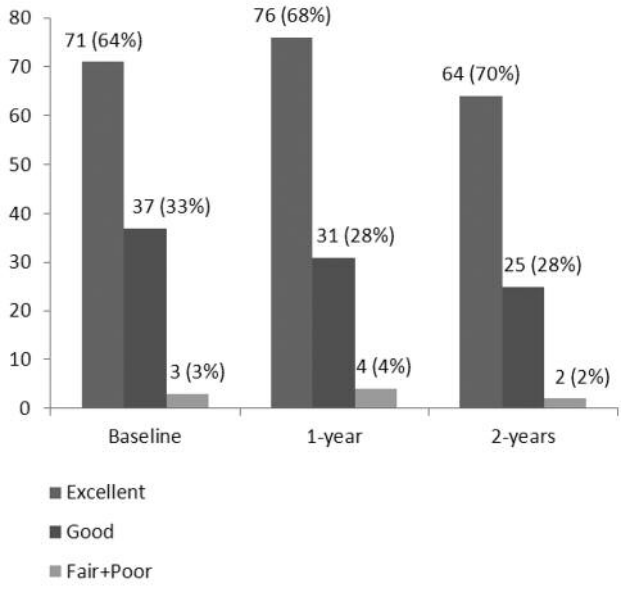

Figure 1. *Cosmetic outcome assessed by patients (111 patients evaluable at baseline and 1 year; 91 evaluable at 2 years)*

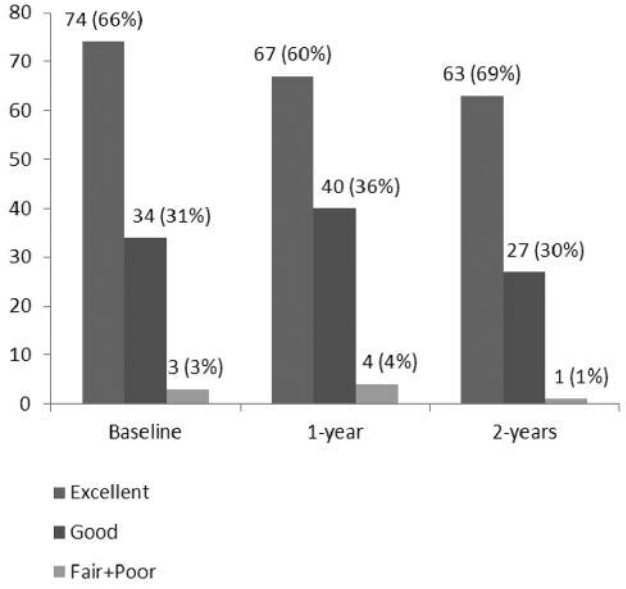

Figure 2. *Cosmetic outcome assessed by physician (111 patients evaluable at baseline and 1 year; 91 evaluable at 2 years).*

All study characteristics were determined by descriptive statistics. Time to IBTR was from the date of the end of RT to the observation of progression/recurrence in the treated breast, or to the last follow-up if no event was observed. The "time to event" curve was calculated with the Kaplan-Meier method. The proportions of patients demonstrating deterioration, no change, or improvement in cosmetic outcome from baseline were compared using a Mann-Whitney-Wilcoxon test.

Results

From December 2010 to April 2015, 190 patients were enrolled and treated in this trial of OD-PBI. In this study, we present results on 111 patients treated up to December 2013 for those, who at the time of the present study, consistent follow-up data are avaible. Their characteristics are summarized in Table I.

Median tumor diameter was 10 mm (range=3-35 mm). All except one patient received adjuvant hormone therapy, and three patients received adjuvant chemotherapy. Ductal histotype, stage I disease, and Luminal A-like disease were the most common features.

Sixty-five patients (59%) met the criteria of the suitable group according to ASTRO-2009 consensus statement (1), while 46 (41%) did not, because they lacked one (37 patients) or two (9 patients) suitable factors: age=50-59 years (30 patients), invasive lobular histology (13 patients), pN1 (eight patients), pT2 (three patients), no ER expression (one patient). Thus, 8 pN1 patients plus 1 patient with severe heart disease and T diameter of 35 mm in the left breast were classified as unsuitable according to ASTRO consensus statement. With a median follow-up of 34 months (range=15-51 months), no IBTR was reported. One patient developed a contralateral breast tumor 12 months after OD-APBI.

All patients completed the treatment without any interruption; 12 patients (11%) experienced a grade 1 or 2 (2%) acute skin toxicity. In 9 patients, a grade 1 (8%) late skin toxicity for fibrosis, according to CTCAE v 4.0, was observed. No correlation between acute and late toxicity was detected. All 111 patients completed the questionnaires at baseline and at 1 year. Ninety-one patients completed the questionnaires at 2 years, so 91 patients were evaluable for the 2-year cosmetic outcome.

The percentage of breasts with excellent/good cosmetic results at 1 and 2 years were 68% (n=76), 28% (n=31) and 70% (n=64), 28% (n=25), respectively, by patient assessments and 60% (n=67), 36% (n=40) and 69% (n=63), 30% (n=27), respectively, by physician assessments. Very few patients (1-4%) assessed their cosmetic outcome as fair or poor at any time. There seems to be no significant change in the percentage with excellent/good cosmetic outcome over time (at 1 and 2 years) in either patient and physician assessments, although additional follow-up is needed to report further, definitive results. Figures 1 and 2 show the distribution of the cosmetic outcomes (excellent, good, fair, or poor) at baseline, 1 year, and 2 years after OD-APBI assessed by the patient and physician, respectively.

Table I. *Patients' characteristics. Total number of patients included was 111.*

	N(%)
Median Age: 65 years (range=51-86 years)	
Breast	
Right	50 (45%)
Left	61 (55%)
Histology	
Ductal	92 (83%)
Lobular	13 (12%)
Others	6 (6%)
Grading	
G1	36 (32%)
G2	41 (38%)
G3	34 (30%)
T-Stage	
IA	95 (86%)
IB	11 (10%)
IIA	5 (4%)
Lymph nodes	
N0	103 (93%)
N1	8 (7%)
Adjuvant chemotherapy	
No	108 (97%)
Yes	3 (3%)
Stanford Classification	
Luminal A like	82 (74%)
Luminal B like	23 (21%)
Neu-positive	5 (4%)
Basal-like	1 (1%)
ASTRO criteria for APBI	
Suitable	65 (59%)
Cautionary	37 (33%)
Unsuitable	9 (8%)

Discussion

This study reports results on toxicity and cosmetic outcome in breast cancer patients treated with partial breast irradiation after lumpectomy. Most recent radiobiological findings in breast cancer showed that the alpha/beta ratio for breast cancer and surrounding normal tissue was not found be so different, and it is estimated in the 3-4 Gy range. This value suggests that there will be no clinical gain regarding normal-tissue sparing in giving radiotherapy in small fractions, and hypofractionation is safe and useful in the treatment of breast cancer (15). Selection of patients is a crucial point: several studies investigated which patients' features and tumor's characteristics are suitable for partial breast radiotherapy and predictive of recurrence nomograms were also formulated (16).

Even with a short follow up, our data show little incidence of acute (13%) or late toxicity (8%) and low incidence of fair/poor cosmetic outcome at any time (1-4% crude incidence).

The role of APBI, either by brachytherapy, intra-operative irradiation, or by external beam, is evolving even if toxicity and cosmetic outcome could be an issue. Previous phase II trials (5-7) have reported a fair/poor cosmesis rate of 13-21% in patients treated with APBI, and these data have been confirmed by the RAPID trial (3), in which patients were randomized between BCS to standard whole-breast irradiation (WBI) or APBI (38.5 Gy in 10 fractions twice daily) delivered by external 3D-conformal radiotherapy (3D-CRT).

In the RAPID trial, APBI patients experienced adverse cosmesis at 3 years irrespective of whether assessed by trained nurses (29% *vs.* 17%; $p<0.001$), by patients (26% *vs.* 18%; $p=0.0022$), or physicians (35% *vs.* 17%; $p<0.001$). Moreover, grade 1 and 2 toxicities were elevated among those who received APBI compared with WBI (69% *vs.* 46%; $p<0.001$).

These data were not reproduced by a recent Italian trial (17) in which APBI patients experienced a better rate of acute toxicity (19.9% *vs.* 66.5%; $p<0.0001$), late toxicity (4.5% *vs.* 11.2%; $p=0.004$), and excellent cosmetic outcome (95.1% *vs.* 89.6%; $p=0.045$).

These different data could be attributed to timing, dosimetric parameters, and technology used. Already Bentzen and Yarnold (4), through analyzing preliminary results of three phase II trials reported by Chen (5), Hepel (6), and Jagsi (7), have pointed to the role of recovery between twice-daily fractions in APBI group. In fact, using the 4.4-hours T1/2 estimate for fibrosis and $\alpha/\beta=3.4$ Gy, the ABPI schedule (38.5 Gy in 10 fractions twice daily) is estimated to be equivalent to 64.9 Gy (2 Gy/fraction). This value rises to 68 Gy if $\alpha/\beta=2.8$ Gy is applied (the value for late changes in breast appearance). On the other hand, without any time corrections, the same schedule with an $\alpha/\beta=3.4$ Gy is instead equivalent to 52 Gy (2 Gy/fraction).

Thus, adoption of once-daily treatment, as applied in this trial, should reduce adverse events such as toxicity or worse cosmetic outcome. In fact, also the Italian trial by Livi (17) applied a very high daily fraction (6 Gy) up to a total dose of 30 Gy delivered in five non-consecutive days (during 2 weeks of treatment), thus increasing the time for recovery between fractions and total treatment time.

NSABP B-39/RTOG 04-13 is an ongoing phase III trial comparing WBI to APBI delivered with 10 twice-daily 3.85-Gy fractions, adopting defined dose-volume constraints for ipsilateral breast ($V\geq50\%$ $\leq60\%$; $V100\%$ $\leq35\%$). This trial could eventually help us verify whether strict dose-volume constraints to ipsilateral breast could reduce the toxicity and cosmetic outcome.

Finally, more advanced techniques such as IMRT, VMAT, or TomoTherapy (18) could improve the ability to adhere to these dose-constraint parameters. Furthermore Tomotherapy compared to conventional 3D-CRT or IMRT reduces heart and left ventricle volumes receiving high doses in patients

with left-sided breast cancers as reported elsewhere. Both IMRT and TOMO techniques provided significant reductions in V35s compared to 3D-CRT (19).

In the meantime, we continue to enroll and follow our patients in order to confirm whether the adoption of daily fractionation, dose-volume constraints to ipsilateral breast, and TomoTherapy could ameliorate oncological and cosmetic results in breast cancer patients who have undergone conservative surgery.

References

1 Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, Julian TB, Marks LB, Todor DA, Vicini FA, Whelan TJ, White J, Wo JY and Harris JR: Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys *74*: 987-1001, 2009.

2 Polgár C, Van Limbergen E, Pötter R, Kovács G, Polo A, Lyczek J, Hildebrandt G, Niehoff P, Guinot JL, Guedea F, Johansson B, Ott OJ, Major T and Strnad V: Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group ba. Radiother Oncol *94*: 264-273, 2010.

3 Olivotto IA, Whelan TJ, Parpia S, Kim D-H, Berrang T, Truong PT, Kong I, Cochrane B, Nichol A, Roy I, Germain I, Akra M, Reed M, Fyles A, Trotter T, Perera F, Beckham W, Levine MN and Julian JA: Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol *31*: 4038-4045, 2013.

4 Bentzen SM and Yarnold JR: Reports of unexpected late side effects of accelerated partial breast irradiation--radiobiological considerations. Int J Radiat Oncol Biol Phys *77*: 969-973, 2010.

5 Chen PY, Wallace M, Mitchell C, Grills I, Kestin L, Fowler A, Martinez A and Vicini F: Four-year efficacy, cosmesis, and toxicity using three-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys *76*: 991-997, 2010.

6 Hepel JT, Tokita M, MacAusland SG, Evans SB, Hiatt JR, Price LL, DiPetrillo T and Wazer DE: Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys *75*: 1290-1296, 2009.

7 Jagsi R, Ben-David MA, Moran JM, Marsh RB, Griffith KA, Hayman JA and Pierce LJ: Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. Int J Radiat Oncol Biol Phys *76*: 71-78, 2010.

8 Polgár C, Fodor J, Major T, Németh G, Lövey K, Orosz Z, Sulyok Z, Takácsi-Nagy Z and Kásler M: Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma – 5-year results of a randomized trial. Int J Radiat Oncol Biol Phys *69*: 694-702, 2007.

9 Vicini F, Beitsch P, Quiet C, Gittleman M, Zannis V, Fine R, Whitworth P, Kuerer H, Haffty B, Keisch M and Lyden M: Five-year analysis of treatment efficacy and cosmesis by the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial in patients treated with accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys *79*: 808-817, 2011.

10 Chafe S, Moughan J, McCormick B, Wong J, Pass H, Rabinovitch R, Arthur DW, Petersen I, White J and Vicini FA: Late toxicity and patient self-assessment of breast appearance/satisfaction on RTOG 0319: a phase 2 trial of 3-dimensional conformal radiation therapy-accelerated partial breast irradiation following lumpectomy for stages I and II breast cancer. Int J Radiat Oncol Biol Phys *86*: 854-859, 2013.

11 Qiu J-J, Chang Z, Horton JK, Wu Q-RJ, Yoo S and Yin F-F: Dosimetric comparison of 3D conformal, IMRT, and V-MAT techniques for accelerated partial-breast irradiation (APBI). Med Dosim *39*: 152-158, 2014.

12 Lewis L, Cox J, Morgia M, Atyeo J and Lamoury G: A clip-based protocol for breast boost radiotherapy provides clear target visualisation and demonstrates significant volume reduction over time. J Med Radiat Sci *62*: 177-183, 2015.

13 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Natl Cancer Inst, 2010.

14 Aaronson NK, Bartelink H, van Dongen JA and van Dam FS: Evaluation of breast conserving therapy: clinical, methodological and psychosocial perspectives. Eur J Surg Oncol *14*: 133-140, 1988.

15 Wenz F, Sedlmayer F, Herskind C, Welzel G, Sperk E, Neumaier C, Gauter-Fleckenstein B, Vaidya JS and Sütterlin M: Accelerated Partial Breast Irradiation in Clinical Practice. Breast Care (Basel) *10*: 247-252, 2015.

16 Wobb JL, Chen PY, Shah C, Moran MS, Shaitelman SF, Vicini FA, Mbah AK, Lyden M and Beitsch P: Nomogram for predicting the risk of locoregional recurrence in patients treated with accelerated partial-breast irradiation. Int J Radiat Oncol Biol Phys *91*: 312-318, 2015.

17 Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, Paiar F, Scotti V, De Luca Cardillo C, Bastiani P, Orzalesi L, Casella D, Sanchez L, Nori J, Fambrini M and Bianchi S: Accelerated partial breast irradiation using intensity-modulated radiotherapy *versus* whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer *51*: 451-463, 2015.

18 Njeh CF, Saunders MW and Langton CM: Accelerated partial breast irradiation using external beam conformal radiation therapy: a review. Crit Rev Oncol Hematol *81*: 1-20, 2012.

19 Coon AB, Dickler A, Kirk MC, Liao Y, Shah AP, Strauss JB, Chen S, Turian J and Griem KL: Tomotherapy and multifield intensity-modulated radiotherapy planning reduce cardiac doses in left-sided breast cancer patients with unfavorable cardiac anatomy. Int J Radiat Oncol Biol Phys *78*: 104-110, 2010.

Received February 26, 2016
Revised April 18, 2016
Accepted April 25, 2016