International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Long-Term Outcomes of Once-Daily Accelerated Partial-Breast Irradiation With Tomotherapy: Results of a Phase 2 Trial

Ugo de Paula, MD,[*] Rolando Maria D'Angelillo, MD,[†] Angela Damiana Andrulli, MD,[*] Giuseppina Apicella, MD,[*] Cristina Caruso, MD,[*] Christian Ghini, MD,[*] Sara Gomellini, MD,[*] Elisabetta Ponti, MD,[*] Marco Pompei, MSc,[*] Aurelia Caccavari, MP,[‡] Alessandra Petrocchi, MP,[‡] Leopoldo Costarelli, MD,[§] Marco Giordano, MD,[§] Massimo La Pinta, MD,[‖] Emanuele Zarba Meli, MD,[‖] Maria Mauri, MD,[¶] Mauro Minelli, MD,[¶] Rosalinda Rossi, MD,[¶] Paola Scavina, MD,[¶] Laura Broglia, MD,[#] Tatiana Ponzani, MD,[#] Andrea Loreti, MD,[**] and Lucio Fortunato, MD[‖]

Radioterapia Oncologica, Ospedale San Giovanni Addolorata, Rome, Italy; [†]Radioterapia, Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma Tor Vergata, Rome, Italy; [‡]Fisica Sanitaria Ospedale San Giovanni Addolorata, Rome, Italy; [§]Anatomia Patologica Ospedale San Giovanni Addolorata, Rome, Italy; [‖]Chirurgia Senologica Ospedale San Giovanni Addolorata, Rome, Italy; [¶]Oncologia Medica, Ospedale San Giovanni Addolorata, Rome, Italy; [#]Diagnostica per Immagini, Ospedale San Giovanni Addolorata, Rome, Italy; **Chirurgia Plastica e Ricostruttiva, Ospedale San Giovanni Addolorata, Rome, Italy

Received Aug 17, 2020. Accepted for publication Oct 7, 2020.

Purpose: We report long-term outcomes of phase 2 trial on patients with invasive breast cancer treated with accelerated partial-breast irradiation (APBI) using tomotherapy after breast conservative surgery.

Methods and Materials: From December 2010 to December 2018, we treated 338 women with APBI-tomotherapy: 38.5 Gy in 10 once-daily fractions. Patients selected were age ≥50 years old, with ≤3 cm in size unifocal tumor and at least 2 mm of clear margins. Disease outcomes were analyzed by clinicopathologic characteristics, molecular phenotypes, and American Society for Radiation Oncology (ASTRO) 2017 updated consensus groupings.

Results: The median age was 65 years (range, 50-86). The invasive ductal (87.5%) and the luminal A-like molecular phenotype (70%) were the most common tumors. Overall 242 patients (71.6%) were considered "suitable" for enrollment in APBI according to the eligibility criteria of the ASTRO-2017 consensus statement. With a median follow-up of 76 months (range, 17-113), 2 patients (0.6%) had an invasive ipsilateral breast tumor recurrence (IBTR), and 2 patients (0.6%) had an axillary ipsilateral failure. The rate of local control in terms of free of IBTR was 99.4% and locoregional control (no recurrence in ipsilateral breast as well as in regional nodes) was 98.8%. Progression-free survival was 98.4% and 92% at 5 and 10 years,

Corresponding author: Ugo de Paula, MD; E-mail: udepaula@hsangiovanni.roma.it

Disclosures: The authors have nothing to disclose.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Int J Radiation Oncol Biol Phys, Vol. 109, No. 3, pp. 678–687, 2021

https://doi.org/10.1016/j.ijrobp.2020.10.009

respectively. Acute and late skin toxicity, graded according to the Common Terminology Criteria for Adverse Events, were 7.7% (G1) and 0.6% (G2) and 4.4% (G1) and 1.1% (G2), respectively. There were no grade 3/4 toxicities, however. Very few patients (2%) or physicians (2%) assessed cosmetic outcome as fair or poor at the 2-year follow-up.

Conclusions: This phase 2 trial on APBI-tomotherapy shows excellent long-term results. Once-daily fractionation schedule was well tolerated with a low rate of adverse events and worse cosmetic outcome. In this series, even among those deemed cautionary or unsuitable for APBI by ASTRO criteria, we demonstrated a low rate of IBTR.

Introduction

Breast-conserving therapy and accelerated partial-breast irradiation (APBI) has been widely diffused in the clinical practice since 2009, after American Society for Radiation Oncology (ASTRO) consensus statement[1] and GEC-ESTRO recommendations,[2] as a standard of care in the management of early breast cancer.

In APBI, the tumor bed rather than the whole breast may be targeted with a larger fraction delivered more rapidly over 1 to 2 weeks.[3] In recent years, several APBI trials were begun with different techniques to demonstrate the non-inferiority compared with the standard of care of the conventionally fractionated regimen.[4-9] The first reported techniques to administer partial-breast irradiation included only brachytherapy (intracavitary or interstitial).[10-12] Subsequent 3-dimensional (3D) and intensity modulated radiation therapy (IMRT) planning techniques have allowed adoption of external beam APBI technologies. Two randomized trials (Rapid[13] and NSABP B-39/RTOG 0413[14]) were recently published reporting outcomes in more than 6000 women followed up for 8 to 10 years. These 2 trials, however, had broad eligibility criteria, leading to a large, heterogeneous pool of patients and sufficient power to detect treatment equivalence. They were not designed to determine equivalence in patient subgroups or outcomes from different APBI techniques. At the same time there are very few studies on the use of TomoTherapy (Accuray Incorporated, Sunnyvale, CA) for APBI, and their data and results only reflect dosimetric comparisons.[15]

In 2010, we designed a phase 2 trial of APBI with tomotherapy to test patient outcome. The purpose was improving the conformality and homogeneity of the dose to the tumor bed and reducing the dose to normal tissues as much as possible. We investigated the advantage of tomotherapy using IMRT and image guided radiation therapy.

Methods and Materials

Patient selection and eligibility

From December 2010 to December 2018, 338 eligible patients after breast-conserving surgery (BCS) were treated at Radiation Oncology Department of San Giovanni - Addolorata Hospital, Rome, Italy. Key inclusion criteria were 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 axillary dissection with surgical clips (2-4) to define the tumor bed were required by the study protocol. Patients with a positive sentinel lymph node biopsy for macrometastases were required to undergo a level I/II axillary node dissection. Patients otherwise selected for omission of lymphadenectomy in this setting were excluded, according to the results of the ACOSOG Z11 trial.[16] Patients with 1 to 3 nodal metastases in absence of extracapsular invasion were included. According to Stanford classification, all genetic subtypes (luminal A-like, luminal B-like, HER2-enriched, and triple negative) were admitted. Exclusion criteria included lobular carcinoma in situ, pure or extensive ($\geq$25%) ductal carcinoma in situ, Paget's disease of the nipple, extensive skin involvement from tumor, palpable lymphadenopathy in the axilla, previous radiation therapy to the involved breast, significant comorbidities precluding surgical excision and/or radiation therapy, metastatic disease, and history of neoplastic disease (excluding skin tumors totally removed by surgery). All suspicious clinical or radiologic lymph nodes in supraclavicular or infraclavicular fossa or internal mammary chain were histologically or cytologically evaluated with fine needle aspiration or a microbiopsy. Patients who underwent neoadjuvant chemotherapy were not included. The main clinical-pathologic and/or treatment-related factors considered as prognostic were the following: T-stage, N-stage, histology, grade, adjuvant medical treatment, molecular phenotype, and update ASTRO suitability group.[17] Ethics approval was obtained by the local institutional review board (#9902/2011), and all patients gave their written informed consent.

Radiation treatment

The target volume and organs at risk, including constraints for contralateral breast and lungs, heart, and spinal cord, were contoured using the Pinnacle Treatment Planning System in accordance with the NSABP B-39/RTOG 0413 APBI protocol. The clinical target volume was constructed with a uniform 1.5 cm 3D margin around the tumor bed. The planning target volume (PTV) included an isotropic

margin of 1 cm around the clinical target volume. Surgical clips were a mandatory hallmark to define the tumor bed, as outlined in a previous study.[18] The gross target volume was the tumor bed, and its contours were drawn around the surgical clips and seroma. A planning target volume evaluation (PTV_EVAL) was generated by automatically withdrawing the PTV by up to 5 mm away from the skin and the lung−thoracic wall interface (Fig. 1). The maximum dose of uninvolved ipsilateral breast was limited to <50% of the prescription dose. The contralateral breast received ≤3% of the prescribed dose to any point. Less than 15% of the ipsilateral lung received ≤30% of the prescribed dose, and ≤15% of contralateral lung received ≤5% of the prescribed dose. Less than 40% of the heart in left-breast APBI received ≤5% of the prescribed dose. In right-breast APBI, <5% of the heart received ≤5% of prescribed dose (Table 1). All patients underwent tomotherapy treatment with a total dose of 38.5 Gy delivered in 10 consecutive 3.85-Gy daily fractions, 5 days per week. The ratio of the maximum to the average intensity of the beam was selected to maintain an average treatment administration time of 10 minutes and reduce the risk of patient movement. Radiation treatment began at least 4 weeks after adjuvant chemotherapy, if administered, and within 3 months of BCS.

Study design and outcomes

The primary endpoints were local control and acute and late toxicity. The trial was designed as a prospective observational study, assuming an ipsilateral breast tumor recurrence of 5% at 5 years with a standard error of 1.6% and a reduction in acute and late toxicity of 20%. With a power of 80%, a minimum of 180 patients had to be enrolled, and assuming a 10% patient loss during follow-up, the final target sample size was defined as 198 patients. During the study, the early results of increased toxicity in the RAPID trial (adverse cosmetic results for APBI 29% vs 17% for whole-breast radiation therapy) suggested that we increase the sample size to assess any negative effect of APBI on late toxicity and cosmetic outcome. The sample of 198 patients was deemed essential to evaluate cosmetic

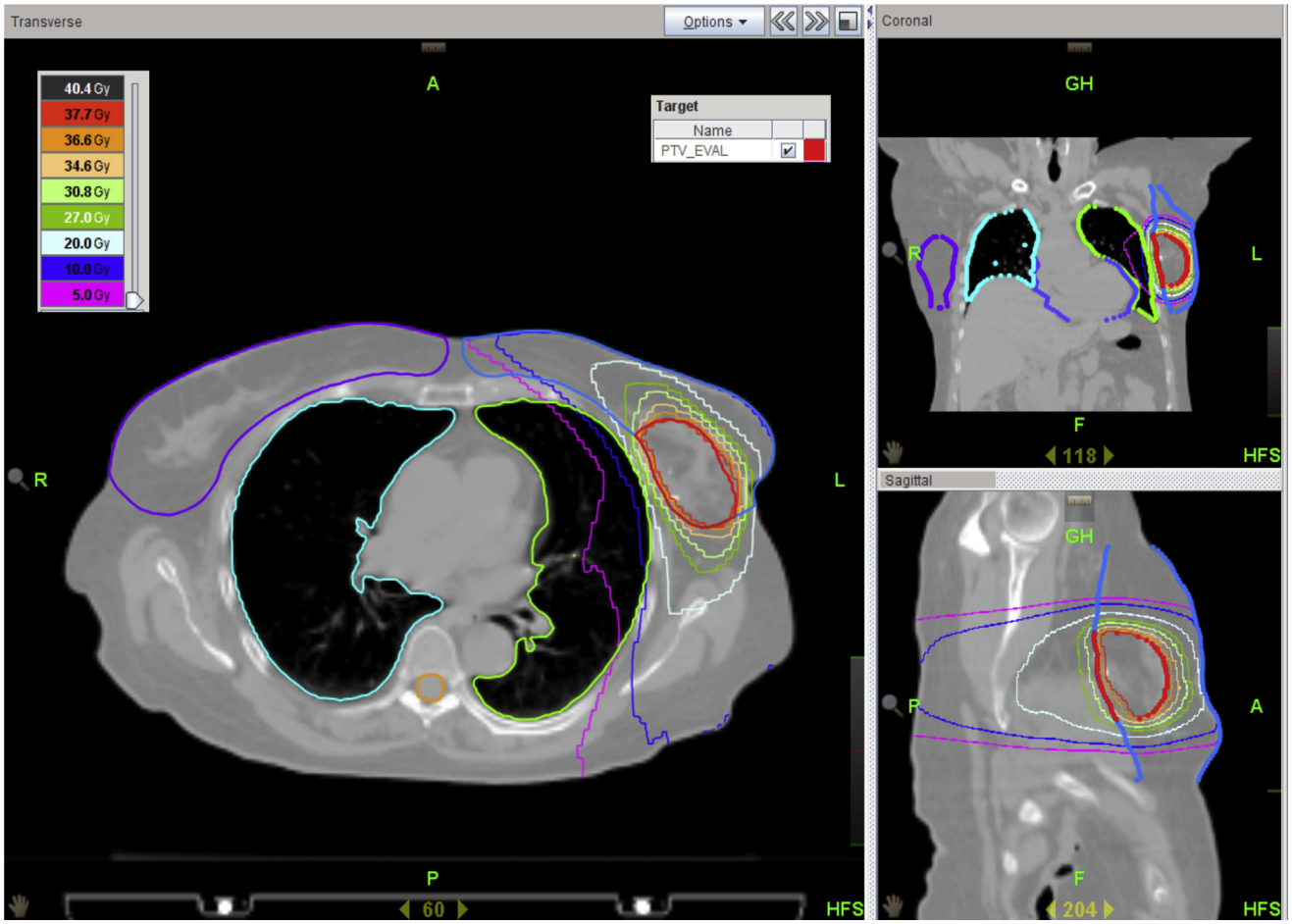


Fig. 1. Contouring and dose distribution of tomotherapy plan. The gross target volume was the tumor bed, and its contours were drawn around the surgical clips. The PTV included an isotropic margin of 1 cm around the CTV. PTV_EVAL was generated by automatically withdrawing the PTV by up to 5 mm away from the skin and the lung−thoracic wall interface. *Abbreviation:* PTV_EVAL = planning target volume evaluation.

Table 1 Quality assurance and dose constraints

Volumes	Reference dose
PTV_Evaluation	• 90% of the prescribed dose should cover ≥90% of the PTV_EVAL. • Dmax should not be >120% of the prescribed dose.
Ipsilateral uninvolved breast	• <60% of the whole breast reference volume should receive ≤50% of the prescribed dose. • <35% of the whole breast reference volume should receive the prescribed dose.
Contralateral breast	At each point, Dmax should be ≤3% of the prescribed dose.
Ipsilateral lung	<15% of lung volume should receive ≤30% of the prescribed dose.
Contralateral lung	<15% of lung volume should receive ≤5% of the prescribed dose.
Heart (for right APBI)	<5% of the heart should receive ≤5% of the prescribed dose.
Heart (for left APBI)	The volume of the heart receiving ≤5 % of the prescribed dose should be ≤ 40%
Spinal cord and thyroid	Report maximum and average dose

Abbreviations: APBI = accelerated partial-breast irradiation; PTV_EVAL = planning target volume evaluation.

results. Therefore, to reach the necessary number of patients who completed cosmetic outcome up to 2 years after treatment, 338 patients were enrolled.

Local control was defined in terms of freedom of ipsilateral breast tumor recurrence (IBTR) as histologic evidence of invasive or in situ disease in the irradiated breast. Elsewhere recurrence outside the ipsilateral, irradiated breast, like nodal regional failure or contralateral breast tumor, were considered separately. Secondary endpoints were progression-free survival (PFS) and cosmetic outcome. PFS was defined as no recurrence in breast (ipsilateral and contra-lateral) in addition to nodes or distant site. Multivariate analysis aimed to examine the single prognostic significance of various clinicopathologic features such as T-stage, N-stage, histology and grade, adjuvant medical treatment, molecular phenotype, and ASTRO-2017 suitability group. Some of these clinicopathologic factors, such as the lobular histology and non-luminal receptor status, are considered as "cautionary" by the ASTRO 2017 Consensus Statement, therefore having an unfavorable prognostic meaning. Other clinicopathologic factors, such as lymph nodal involvement, are recognized as "unsuitable" for APBI. We sought to determine whether patients who were classified as "cautionary" or "unsuitable" exhibited adverse outcomes in comparison to their "suitable" counterparts.

Follow-up, toxicity, and cosmesis

After APBI, patients were assessed at 3, 6, and 12 months and then annually. Verbal and physical examinations were performed at each visit; annual ultrasound and bilateral mammograms were recorded. Acute and late toxicity was scored according to Common Terminology Criteria for Adverse Events version 4.0.[19] The first assessment for acute toxicity was performed during the first visit within 1 month after radiation therapy. The patient and radiation oncologist followed the EORTC Cosmetic Rating[20] during follow-up visits to assess cosmesis, comparing the treated breast with the untreated one. They evaluated the skin color, size, location, and the shape of the breast, areola, and nipple; evaluated the appearance of the surgical scar; and determined a global cosmetic score. Patients provided a self-assessment of cosmetic outcome using a questionnaire similar to the physician. 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.

Statistical analysis

Statistical analysis was performed using Statistical Program or Social Sciences software for Windows (SPSS Inc, version 20). Demographic and clinical features were compared across "cautionary" and "suitable" groups. Clinical outcomes studied included IBTR, regional node recurrence, PFS, and overall survival (OS). Time-to-event curve was calculated by Kaplan−Meier method. All the time-to-event data were calculated from the date of surgery. The difference between 2 sample means of continuous variables were analyzed using the Student unpaired t test. Tumor and treatment characteristics across the subgroups were compared using the Pearson χ^2 test or Fisher's exact test when sample sizes were small. P value <.05 was considered statistically significant for all tests. Analysis was performed to estimate the risks of IBTR and PFS, using clinical pathologic variables described earlier.

Results

Patient characteristics

Table 2 shows a summary of characteristics of patients enrolled in the trial. The median age was 65 years (range,

50-86), and 271 women (80%) were postmenopausal. The mean tumor size was 12.5 mm (range, 3-30). The invasive ductal (87.5%) and the luminal A-like molecular phenotype (70%) were the most common type. The histologic Scarff-Bloom-Richardson modified grade[21] was 1 (low) in 91 (27%), 2 (intermediate) in 133 (39%), and 3 (high) in 114 (34%). Thirty-four patients (11%) had metastases in 1 to 3 axillary lymph node(s). Thirty-two patients (10%) received adjuvant chemotherapy, typically driven by molecular phenotype (triple negative or HER2-enriched) or elevated Oncotype DX score. Overall, 242 patients (71.6%) were considered "suitable" for enrollment in APBI according to the eligibility criteria of the ASTRO Consensus Statement of 2017. Sixty patients (17.8%) were considered "cautionary" because they had 1 or more risk factors, and 36 (10.6%) were "unsuitable." Among the 60 "cautionary" patients, 42 had a lobular histology, 13 had a nonluminal molecular phenotype (ER−), and 5 had a T2 tumor <3 cm but >2.1 cm. Among 36 patients considered "unsuitable," 34 had a pathologic lymph node state (N+). Of these, 23 patients (67%) underwent axillary dissection after sentinel lymph node positivity, resulting positive for a number of lymph nodes equal to or not greater than 3. Eleven patients had only micrometastasis (<2 mm) after sentinel node biopsy (stage ≤pN1a), 15 patients had 1 lymph node involved, 7 patients had 2 metastatic lymph nodes, and 1 patient had 3 lymph nodes with metastases.

Table 2 Patient characteristics, N = 338

Age, median y (range)	65 (50-86)	n (%)
pT stage	pT1a	29 (8%)
	pT1b	121 (36%)
	pT1c	157 (46%)
	pT2 (≤3 cm ∅)	31 (10%)
Histology	Invasive ductal (NST)	296 (87.5%)
	Invasive lobular	42 (12.5%)
Grade	1 (low)	91 (27%)
	2 (intermediate)	133 (39%)
	3 (high)	114 (34%)
Axillary status	pN0	304 (89%)
	pN1a	34 (11%)
Molecular phenotype	LLA	238 (70%)
	LLB	74 (22%)
	TN	13 (4%)
	HER2 +	13(4%)
Adjuvant chemotherapy	No	306 (90%)
	Yes	32 (10%)
APBI suitability group (ASTRO 2017)	Suitable	242 (71.6%)
	Cautionary	60 (17.8%)
	Unsuitable	36 (10.6%)

Abbreviations: APBI = accelerated partial-breast irradiation; ASTRO = American Society for Radiation Oncology; HER2+ = HER2 enriched; LLA = luminal-like A; LLB = luminal-like B; NST = no special type; TN = triple negative.

Recurrence and survival

With a median follow-up of 76 months (range, 17-113), 2 of 338 patients (0.6%) had an invasive IBTR and 2 patients (0.6%) had an axillary ipsilateral failure. We obtained a rate of local control in terms of free of IBTR of 99.4% and locoregional control (no recurrence in ipsilateral breast as well as in regional nodes) of 98.8% (Table 3; Fig. 2). The 2 IBTRs occurred at 8 and 15 months from BCS. Both the patients underwent salvage mastectomy and are alive without evidence of disease after 13 and 22 months. One patient with isolated nodal axillary recurrence after 44 months from BCS for a ductal carcinoma stage pT1cpN0(s)/G3 had axillary surgery followed by radiation to lymph node areas. The other patient with regional nodes recurrence had a HER2-enriched tumor, and she had a rapid metastatic disease and died after 42 months. Three patients (2 with invasive lobular histology) developed contralateral cancer 26, 39, and 80 months after the end of APBI. Progression-free survival was 98.4% and 92.0% at 5 and 10 years. Five-year and 10-year PFS were 97.8% and 97.8% in the suitable group and 91.9% and 78.8% in the cautionary group, and no event was registered among the unsuitable patients ($P = .03$ for suitable vs cautionary).

There were no cases of IBTR among the N+, "cautionary," or "unsuitable" ASTRO 2017 group. In the axillary failure rate, we observed a statistically significant difference between patients with luminal and nonluminal molecular phenotype (luminal: 0.3% vs nonluminal: 7.7%; $P = .041$).

Out of 338 patients, 8 deaths were recorded: 2 deaths were due to breast cancer, and 6 deaths were due to others causes. Five and 10-year OS was 96.8% and 95.5%, respectively. Two patients died of pancreatic cancer, 3 patients (2 treated on the left breast) of cardiac disease, and 1 patient for non-Hodgkin lymphoma 25 months after the APBI. The 3 patients who died of cardiological disease had no preexisting cardiovascular risk factors, and their deaths

Table 3 Outcomes and survival

Median follow-up: 76 months (range, 17-113)	No. pts	Characteristics
IBTR	2	Both IBTR outside irradiation fields
Axillary failure	2	1 pt with concomitant distant metastases
Contralateral breast cancer	3	2 pts with lobular histology
Cause-specific death	2	1 pt HER2 enriched 1 pt triple negative
Cancer-nonspecific death	6	3 pts: heart disease (2 left breast cancer) 2 pts: pancreatic cancer 1 pt: non-Hodgkin lymphoma

Abbreviation: IBTR = ipsilateral breast tumor recurrence.

were independent of the irradiation. The average dose to the heart was 0.34 Gy (range, 0.24-0.43 Gy).

In the 2 patient deaths for the progressive breast cancer, one (triple negative) developed distant metastases (lung, liver, and bone metastases) without regional nodal recurrence after 26 months and died after 31 months, and the other (HER2-enriched) had distant metastases associated with axillary failure after 30 months and died after 34 months.

No other prognostic factor considered "cautionary" or "unsuitable" from ASTRO criteria, including lobular histology and lymph node involvement, significantly affected OS and CSS in respect to their "suitable" counterparts.

Analysis of breast failure

Figure 3 shows the clinical details of the 2 patients who had local recurrence at 8 (patient #1) and 15 (patient #2) months after BCS and 6 and 13 months from APBI, respectively. Both had a primary tumor with a ductal histology located in the left breast but in different quadrants with respect to the site where tumor recurrence subsequently developed. In both cases, the distance between the primary tumor and the recurrence site is significant. The isodose distribution of the initial APBI treatment showed a very low dose in the IBTR area (<3 Gy). The stage of the primary tumor was, respectively, pT1b (7 mm) pN0 R0 luminal A and pT1c (16 mm) pN0 R0 luminal B. Regarding IBTR, in both cases it was always a ductal carcinoma. One patient had the same molecular phenotype as the primary tumor (luminal A-like); in the other one, the recurrence had a completely different receptor state (triple negative). Only 1 patient among those with nonluminal phenotype showed, after 30 months, a recurrence to the regional axillary lymph nodes (axillary failure). The patient had a tumor with ductal histology, TNM stage pT1c, N0 with a HER2 overexpression, and had undergone adjuvant chemotherapy. This case of axillary failure was in a patient with progressive disease and was part of a systemic disease of cancer (pulmonary and hepatic metastases). The other patient who died of distant disease had a tumor with a triple-negative receptor state (ER−/PR−, HER2−).

Toxicity and cosmesis

Twenty-seven patients (7.7%) showed acute skin toxicity of grade G1, and 3 patients (0.6%) of grade G2. There was no acute toxicity of type G3 and G4. Thirteen (4.4%) patients had late G1 skin toxicity (hyperchromia and atrophy), 3 (1.1%) late G1 subcutaneous toxicity (fibrosis), and 3 (1.1%) late skin toxicity G2 (telangiectasias). We have not observed any cases of late toxicity such as pneumonitis or rib fractures. No correlation was found between acute and late toxicity.

Questionnaires on cosmetics were completed by physicians and patients in 233 women at baseline, 12 months, and 24 months. Figure 4 shows the physicians' and patients' cosmetic assessments at baseline and after radiation therapy. The percentage of breasts with excellent or good cosmetic results assessed by patients was 78% and 18% at 1 year and 82% and 16% at 2 years; when assessed by physicians, the results were 89% and 10% at 1 year and 84% and 14% at 2 years. Very few patients (1%-4%) judged their cosmetic outcome as fair or poor at any time. We did not see any significant difference between the results of the cosmetic tests obtained by the patients and physicians evaluations ($P > .5$).

Discussion

The results of this single-institution phase 2 trial confirm that APBI is as an effective option after BCS for early-stage invasive breast carcinoma with an extremely low recurrence rate and that the once-daily schedule is effective and is associated with a very low incidence of acute and late toxicities. We report IBTR and regional nodal failure rates at 5 and 9 years of 0.6% and 0.6%, respectively. These are

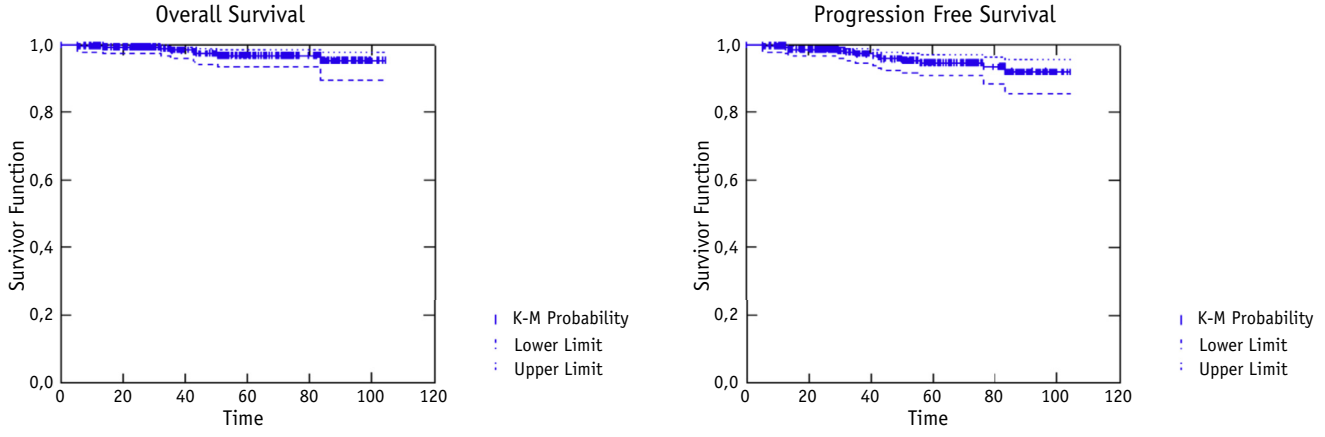
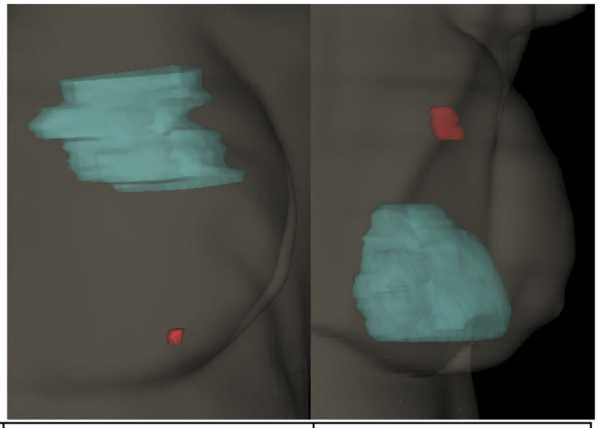


Fig. 2. Kaplan−Meier estimated for overall survival (96.8% and 95.5% at 5 and 10 years, respectively) and progression-free survival (98.4% and 92.0% at 5 and 10 years, respectively).



	Patient 1		Patient 2	
Astro APBI Category	Suitable		Suitable	
	Primary tumor	**IBTR**	**Primary tumor**	**IBTR**
Tumor size (cm)	0.7	0.3	1.6	1.1
Site	Left UOQ	Left LOQ	Left LOQ	Left UOQ
TNM stage	pT1b,No R0	pT1a, R0	pT1c,No R0	pT1c, R0
Stanford's state	LLA	LLA	LLB	TN
LVI	No	No	No	No
Adjuvant CHT	No	No	No	Ycs
Hormonotherapy	Yes	Yes	Yes	No

Fig. 3. Clinical details of 2 patients who developed IBTR. Upper panels show the site of primary tumor with PTV-APBI (turquoise) and ipsilateral recurrence (red). Characteristics of 2 patients are listed for primary tumor and IBTR. *Abbreviations:* APBI = accelerated partial-breast irradiation; IBTR = ipsilateral breast tumor recurrence; LOQ = lower outer quadrant; LVI = lymphovascular invasion; LLA = luminal-like A; LLB = luminal-like B; PTV = planning target volume; TN = triple negative; UOQ = upper outer quadrant.

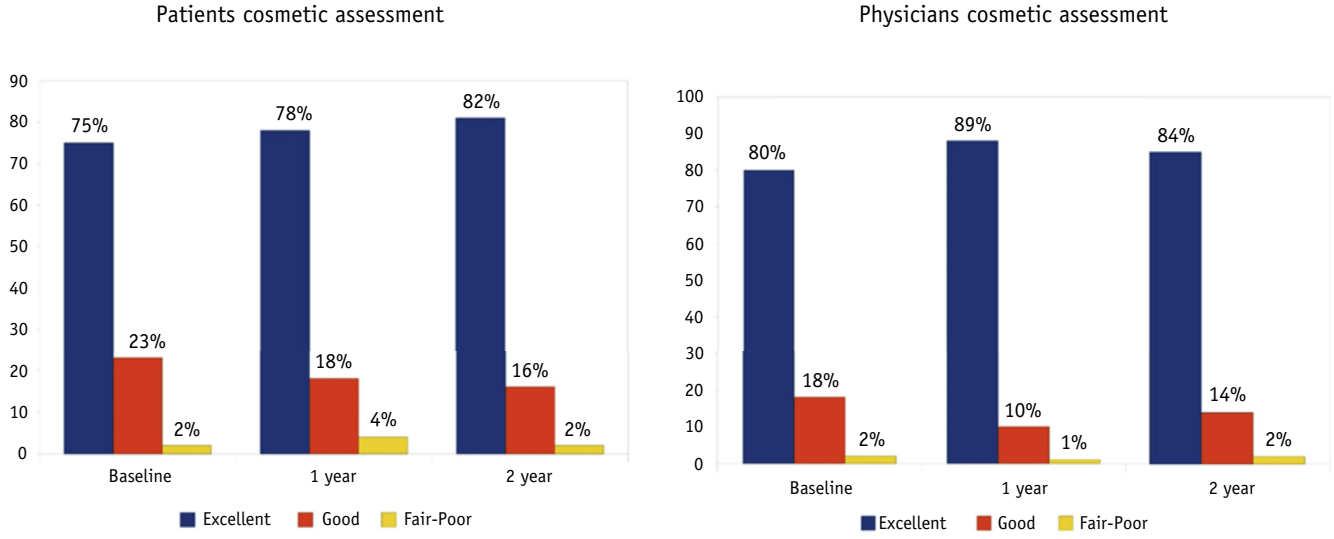


Fig. 4. Patients' and physicians' cosmetic assessment at baseline and after radiation therapy. Very few patients or physicians assessed cosmetic outcome as fair or poor at 2-year follow-up. No significant difference between the results of the cosmetic tests obtained by the patients' and physicians' evaluations ($P > .5$).

similar or lower than several once-daily APBI series with 5-year outcomes.[22-25] Shaiky et al.,[26] with a median follow-up of 49 months, obtained IBTR of 1.9% and 1.0% of axillary failure. Goyal et al.,[27] although only on 45 patients treated with once-daily APBI with 3D conformal radiation therapy technique, observed an IBTR of 0% at 3 years. Their 3-year OS and PFS were 100%. In both cases of our IBTR, the distance between the primary tumor and the recurrence site was significantly beyond the irradiated area. What's more, one of our relapses presented a different molecular phenotype than those shown by the primary tumor, making us think more of a second, different tumor rather than "true recurrence" (Fig. 3).

Randomized trials RAPID and NSABP B-39/RTOG 0413 reporting long-term outcomes in patients receiving 38.5 Gy APBI in 10 twice-daily fractions over 5 to 8 days. After a median follow-up of 8.6 years, the cumulative incidence of IBTR reported in the RAPID trial is 3.0% and 2.8% in APBI and in whole-breast groups, respectively (hazard ratio [HR] 1.27; 90% CI 0.84-1.91). This result reaches the assigned conditions of the trial for one-sided non-inferiority of the primary endpoint. In the NSABP B-39/RTOG 0413 trial, the 10-year cumulative incidence of IBTR is 4.6% and 3.9% in APBI/PBI and in whole-breast groups, respectively (HR 1.22; 90% CI, 0.94-1.58). This result does not satisfy the assigned conditions of the trial for 2-sided equivalence, defined as maximum 50% increase in relative risk. In any case, our incidence rate of IBRT was also lower than these twice-daily APBI landmark trials. RAPID also described unfavorable cosmesis with APBI (32% vs 16%), and NSABP B-39/RTOG 0413 showed a slight increase in grade 3 toxicity (9.6% vs 7.1%). Both trials conclude that moderate late toxicity as well as adverse cosmesis could probably be related to the twice-daily treatment and suggest other approaches, like once-daily APBI. The first results regarding this evidence were obtained from an Italian trial[6] that applied a very high daily fraction (6 Gy) up to a total dose of 30 Gy delivered in 5 nonconsecutive days (during 10 days of treatment), thus increasing the time for recovery between fractions and total treatment time. The authors observed better results in terms of acute and late toxicity in favor of the once-daily APBI schedule: grade $\geq$2 acute toxicity in 2.0% and 37.7% of patients treated with APBI and whole-breast irradiation, respectively; no late grade $\geq$2 toxicity in APBI arm compared with 2.7% of whole-breast irradiation arm.[28]

Finally, the IMPORT LOW trial[29] describes results comparing standard whole-breast radiation therapy with one arm receiving a reduced dose and another reduced volume. In the latter arm, with a median follow-up of 72 months, IBTR was 0.5% at 5 years, while 7% of breast shrinkage at 5 years was recorded. In particular, with a similar median follow-up (72 months in IMPORT LOW and 76 months for present study), a similar IBTR rate was recorded among IMPORT LOW (0.5%) and the present study (0.6%). Table 4 shows results of the present study and 4 randomized trials.

In our phase 2 trial, we prescribed a total dose of 38.5 (3.85 once daily in 10 fractions). The selection of this schedule was based on excellent preliminary tolerability and efficacy data coming from other institutions,[30,31] and patient preference for the convenience of once-daily fractionation compared with twice-daily.[32]

The increase of late normal tissue toxicity with external beam APBI using a twice-daily regimen was predicted about 10 years ago by Yarnold et al,[33] who suggested that 38.5 Gy in 10 twice-daily fractions was equivalent to a theoretical dose of 62 Gy administered in daily fractions of 2 Gy. However, without any time corrections, once-daily treatment with $\alpha/\beta = 3.4$ Gy is equivalent to 52 Gy (2 Gy/fraction). In the same year, the University of Michigan reported unacceptable cosmesis in their cohort of 34 patients treated with 3.85 Gy twice daily fractions to 38.5 Gy with IMRT.[34] Upon development of unacceptable cosmesis in 7 patients, the study was aborted. The authors hypothesized that the poor cosmetic outcome was due to larger volumes receiving 20%, 50%, 80%, and 100% of the prescription dose despite meeting criteria for the NSABP-B39 protocol. Compared with our results, in the women treated with twice-daily fractionation, both acute and late toxicity (grade $\geq$2) occurred more frequently, at 28% and 32% in the RAPID (acute and late respectively) and 44% in the NSABP B-39/RTOG 0413 (as highest Common Terminology Criteria for Adverse Events toxicity grade). Also for cosmetic outcomes at 1 and 2 years with once-daily fractionation, we observed an excellent cosmesis rate of 78% and 82%, respectively, by patient assessment and 89% and 84% by physician assessment—higher than the 71% reported in RAPID and 64% reported in Radiation Therapy Oncology groups.

To our knowledge, our study is the first testing Helicoidal TomoTherapy HI-ART in APBI enrolling select women with early-stage breast cancer after BCS. Our trial includes a large number of patients with a long-term follow-up. Thanks to the use of image guided radiation therapy techniques for each single dose fractionation, tomotherapy offers both the great advantage of improving the dose conformation and homogeneity of the tumor bed, also thanks to the surgical clips positioned in agreement with the surgeon, and reducing as much as possible the distribution of the same to the surrounding normal tissues (organs at risk). With a median follow-up of 76 months, our data show a low incidence not only of acute G1 (7.7%) and G2 (0.6%) toxicity but also of late G1 (4.4%) and G2 (1.1%) toxicity. Cosmetic assessments by patients and physicians after breast conservation surgery and APBI with tomotherapy were excellent, with outcome fair or poor in only 2% of cases at 2 years.

Overall, 17.8% of patients were "cautionary" and 10.6% were "unsuitable." Like other studies,[30,35] we observed that these cohorts did not have a statistical difference in IBTR or PFS in comparison to their "suitable" counterparts. The only predictive factor for progression at the lymph node level (axillary failure) was found to be the nonluminal

Table 4 APBI clinical trials

Trial	Median follow-up, y	IBTR	RT dose, Gy	OTT, d	Toxicity/cosmesis
RAPID[14]	8.6	3% at 8 y	38.5 (3.85 bid)	5-8	Grade ≥2 late toxicity: 32%
NSABP B-39/ RTOG 0413[13]	10.2	4.6% at 10 y	38.5 (3.85 bid)	8	grade 3 toxicity: 9.6%
IMPORT LOW[29]	6	0.5% at 5 y	40 (2.67 daily)	19	7% breast shrinkage at 5 y
Florence[28]	10.7	3.7% at 10 y	30 (6 eod)	10	Grade ≥2 acute: 2% Grade ≥2 late: 0% Good/excellent cosmesis score: 90%
Present study	6.3	0.6% at 5yrs	38.5 (3.85 daily)	12-14	Grade: 2 acute: 0.6% Grade: 2 late: 1.1% Good/excellent cosmesis score: 98%

Abbreviations: bid = twice-daily; eod = every other day; IBTR = ipsilateral breast tumor recurrence (refers to patients treated with partial-breast irradiation only); OTT = overall treatment time; RT = radiation therapy.

molecular phenotype (luminal like: 0.3% vs nonluminal like: 7.7%; $P = .041$). Differences in outcomes between different patients seem more determined by their molecular assessment than the "classical" clinicopathologic prognostic factors.[36,37] Some authors have reported that patients with HER2 overexpression are at high risk for locoregional recurrence, and the negativity of estrogen receptor expressions is a major factor for IBTR or axillary failure.[38,39]

Our experience highlights that the strict selection of patients for local control and the uniformity of technique as well as once-daily fractionation schedule are essential issues for APBI.

Conclusions

Our large institutional experience in this phase 2 trial shows that in a selected group of patients, a locoregional failure rate as low as 1% at 7 years can be obtained and highlights the advantages of multimodal and multidisciplinary treatment in the management of patients with early breast cancer. In the cohort of patients with ASTRO "cautionary" or "unsuitable," criteria, locoregional control was not worse than those in the "suitable" category. A once-daily fractionation schedule was well tolerated and reduced adverse events such as toxicity or worse cosmetic outcome. Helical tomotherapy represents a suitable platform for APBI, offering improvements to existing techniques. It could be a good option in selected women with early breast cancer after BCS. Other prospective, multicentric trials are needed to confirm these findings and endorse more liberal criteria for APBI.

References

1. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009;74:987-1001.
2. GEC-ESTRO Recommendations: Patient selection for accelerated partial breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology breast cancer working group based on clinical evidence (2009). *Radiat Oncol* 2010;94:264-273.
3. Hickey BE, Lehman M, Francis DP. See AM. Partial breast irradiation for early breast cancer. *Cochrane Database Syst Rev* 2014;18: CD007077.
4. Strnad V, Ott OJ, Hildebrandt G, et al. Five-years results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: A randomised, phase 3, non-inferiority trial. *Lancet* 2016;387:229-238.
5. Polgár C, Fodor J, Major T, Sulyok Z, Kásler M. Breast conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197-202.
6. Livi L, Meattini I, Marrazzo L, et al. 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* 2015;51:451-463.
7. Rodríguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2013;87:1051-1057.
8. Vicini F, Cecchini R, White J, et al. Abstract GS4-04: Primary results of NSABP B-39/RTOG 0413 (NRG Oncology): 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. *Cancer Res* 2019;79:GS4-04-GS04-04.
9. Whelan T, Julian J, Levine M, et al. Abstract GS4-03: RAPID: A randomized trial of accelerated partial breast irradiation using 3-dimensional conformal radiotherapy (3D-CRT). *Cancer Res* 2019; 79:GS4-03-GS04-03.
10. Njeh CF, Saunders MW, Langton CM. Accelerated partial breast irradiation (APBI): A review of available techniques. *Radiat Oncol* 2010;5:90.
11. Ott OJ, Strnad V, Hildebrandt G, et al. GEC-ESTRO multicenter phase 3-trial: Accelerated partial breast irradiation with interstitial multicatheter brachytherapy versus external beam whole breast irradiation: Early toxicity and patient compliance. *Radiother Oncol* 2016;120:119-123.
12. Polgar C, Major T, Mangel L, et al. 48 Sole HDR-brachytherapy after breast conserving surgery: 4-year results of a pilot study and initial findings of a randomized phase III trial. *Radiother Oncol* 2000;55:31.
13. Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-

negative breast cancer (RAPID): A randomised controlled trial. *Lancet* 2019;394:2165-2172.
14. Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet* 2019;394:2155-2164.
15. Qiu J-J, Chang Z, Horton JK, Wu Q-RJ, Yoo S, Yin F-F. Dosimetric comparison of 3D conformal, IMRT, and V-MAT techniques for accelerated partial-breast irradiation (APBI). *Med Dosim* 2014;39:152-158.
16. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA* 2017;318:918-926.
17. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO Evidence Based Consensus Statement. *Pract Radiat Oncol* 2017;7:73-79.
18. De Paula U, D'Angelillo MR, Barbara R, et al. Once daily APBI: preliminary results with helical tomotheapy. *Anticancer Res* 2016;36:3035-3040.
19. *Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0*. Elk Grove Village, IL: National Cancer Institute; 2010.
20. Aaronson NK, Bartelink H, van Dongen JA, van Dam FS. Evaluation of breast conserving therapy: Clinical, methodological and psychosocial perspectives. *Eur J Surg Oncol* 1988;14:133-140.
21. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. *Histopathology* 1991;19:403-410.
22. Formenti SC, Hsu H, Fenton-Kerimian M, et al. Prone accelerated partial breast irradiation after breast-conserving surgery: Five-year results of 100 patients. *Int J Radiat Oncol Biol Phys* 2012;84:606-611.
23. Mózsa E, Mészáros N, Major T, et al. Accelerated partial breast irradiation with external beam three-dimensional conformal radiotherapy. Five-year results of a prospective phase II clinical study. *Strahlenther Onkol* 2014;190:444-450.
24. Horst KC, Fasola C, Ikeda D, et al. Five-year results of a prospective clinical trial investigating accelerated partial breast irradiation using 3D conformal radiotherapy after lumpectomy for early stage breast cancer. *Breast* 2016;28:178-183.
25. Liss AL, Ben-David MA, Jagsi R, et al. Decline of cosmetic outcomes following accelerated partial breast irradiation using intensity modulated radiation therapy: Results of a single-institution prospective clinical trial. *Int J Radiat Oncol Biol Phys* 2014;89:96-102.
26. Shaikh AY, La Combe MA, Du H, Raghavan VT, et al. Accelerated partial breast irradiation using once-daily fractionation: analysis of 312 cases with four years median follow-up. *Radiat Oncol* 2012;6:7-17.
27. Goyal S1, Daroui P, Khan AJ, Kearney T, et al. Three-year outcomes of a once daily fractionation scheme for accelerated partial breast irradiation (APBI) using 3-D conformal radiotherapy (3D-CRT). *Cancer Med* 2013;2(6):964-971.
28. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence Trial. *J Clin Oncol* 2020;JCO2000650.
29. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017;390:1048-1060.
30. Fitzgerald K, Flynn J, Zhigang Z, Cost Z. Patterns of recurrence among higher-risk patients receiving daily external beam accelerated partial-breast irradiation to 40 Gy in 10 fractions. *Adv Radiat Oncol* 2019;5:27-33.
31. Trovo M, Roncadin M, Polesel J, et al. Toxicity and cosmesis following partial breast irradiation consisting of 40 Gy in 10 daily fractions. *Breast* 2013;22:744-747.
32. Hoopes DJ, Kaziska D, Chapin P, et al. Patient preferences and physician practice patterns regarding breast radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82:674-681.
33. Yarnold J, Bentzen SM, Coles C, Haviland J. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. *Int J Radiat Oncol Biol Phys* 2011;79:1-9.
34. Jagsi R, Ben-David MA, Moran JM, et al. Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. *Int J Radiat Oncol Biol Phys* 2010;76:71-78.
35. Kennedy WR, Roach CM, Thomas MA, et al. Long-term outcomes with 3-dimensional conformal external beam accelerated partial breast irradiation. *Pract Radiat Oncol* 2020;10:128-135.
36. Wo JY, Taghian AG, Nguyen PL, et al. The association between biological subtype and isolate regional nodal failure after breast-conserving therapy. *Int J Radiat Oncol Biol Phys* 2010;77:188-196.
37. Buonomo OC, Caredda E, Portarena I, et al. New insights into the metastatic behavior after breast cancer surgery, according to well-established clinicopathological variables and molecular subtypes. *PLoS One* 2017;12:e0184680.
38. Kwan W, Al-Tourah AJ, Speers C, et al. Does HER2 status influence locoregional failure rates in breast cancer patients treated with mastectomy for pT1-2pN0 disease? *Ann Oncol* 2010;21:988-993.
39. Shah C, Wilkinson JB, Lyden M, Beitsch P, Vicini FA. Predictors of local recurrence following accelerated partial breast irradiation: A pooled analysis. *Int J Radiat Oncol Biol Phys* 2012;82:e825-e830.