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Accelerated partial breast irradiation

Clinical implementation of combined modulated electron and photon beams with conventional MLC for accelerated partial breast irradiation

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ABSTRACT

Purpose: To report the clinical implementation of a novel external beam radiotherapy technique for accelerated partial breast irradiation treatments based on combined electron and photon modulated beams radiotherapy (MERT+IMRT) with conventional MLC.

Materials and methods: A group of patients was selected to test the viability of the technique. The prescribed dose was 38.5 Gy, following a hypofractionated schema, and the structures were defined following the NSABP-B39/RTOG-0413 protocol. The plans were calculated with an in-house Monte Carlo based planning system to consider explicitly the particle interactions with the MLC. An ad-hoc breast phantom was designed for a specific QA protocol. A reduced SSD was used for electron beams. Toxicity and cosmetic effects were assessed at every follow-up visit.

Results: All the plans achieved the dosimetric objectives and fulfilled the specific quality assurance protocol. Treatment delivery did not entail additional drawbacks for the clinical routine. Moderate or severe grade of toxicity was not reported, and the cosmetic results were comparable to those obtained with other APBI techniques.

Conclusions: Results showed that MERT+IMRT with the MLC is a feasible and secure technique, and easy to be extended to other centers with the implementation of the adequate software for planning.

In the light of low recurrence rates and in particular, the low focal local relapse rate, the concept of accelerated partial-breast irradiation (APBI) has gained widespread interest, and is being currently applied using various methods. The TARGIT-A trial [1] showed the advantages of using intraoperative radiotherapy after a five-year follow-up of the first one thousand patients treated with APBI. The findings from GEC-ESTRO randomized I trial [2], which used sole interstitial multicatheter brachytherapy, provided further support to the implementation of partial breast irradiation. In spite of some controversy regarding the more adequate breast treatment [3], it is clear that APBI has taken place within the set of possible treatments.

In contrast to brachytherapy and intraoperative techniques, external beam radiotherapy (EBRT) is less invasive and, in particular, EBRT has the advantage of having software that allows a highly accurate dose calculation and an efficient planning process. Different techniques, e.g. three-dimensional conformal RT [4], tomotherapy [5], proton beam therapy [6,7], and intensity-modulated RT (IMRT) [8] are being applied by different centers as international reference. This wide range of possibilities seems to go against multicenter study on APBI-EBRT application. For all these techniques, PTV coverage is achieved with a similar high success. However, some differences can be observed in doses to the ipsilateral lung, heart and contralateral breast. Also, some adverse cosmetic effects that are observed with these techniques may be attributed to the high dose received in a large portion of the non-target breast tissue volume (NTBTV) [9].

Breathing motion and treatment set-up variations are the main problems concerning EBRT. The latter can be managed by implementing image guided radiation therapy. However, the inherent respiratory motion uncertainty remains a problem, despite the commercially available cutting-edge hardware and software developed for photons EBRT. This uncertainty translates into higher integral dose to uninvolved normal breast tissue. Therefore, conventional EBRT based only on photon beams could not compete versus the other techniques.

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In order to reduce the uncertainty inherent to respiratory motion and, at the same time to take advantage of the most recent technological innovations in EBRT, several groups have suggested the use of modulated electron beams for the treatment of breast cancer. Modulated electron beam radiotherapy (MERT) has been extensively evaluated [10–15], showing a higher organs-at-risk (OARs) dose sparing by means of different approaches. In the case of partial breast (PB), the variable depth presented by the tumor bed in the breast suggests and, for some cases, demands to add the use of photon beams in combination with electron beams for deeper targets [10,16]. The best scenario would be, being able to use the same software for the planning of combined electron-photon beams radiotherapy, and even more convenient, to use the same modulation device for the combined electron-photon beams treatment delivery [16].

Nevertheless, the inclusion of electron beams could imply dose calculation inaccuracies when using the pencil beam algorithm implemented in the commercial treatment planning systems (TPS) for the electron component, especially in dose to heart and lung [13]. Monte Carlo (MC) method can accurately calculate dose distributions including calculations in heterogeneous tissues, and also can take into account electron interactions with the photon multileaf collimator (xMLC), which cannot be correctly handled by conventional dose calculation algorithms [17].

To address these challenges and to find a technique accessible to as many centers as possible for a potential multicenter study on APBI-EBRT, we developed an accurate enough solution by means of Monte Carlo method, and using the xMLC, already installed in most of the LINAC heads, as beam modifier to carry out the combined electron-photon beams modulation. At the first stage, a set of cases were planned using MERT+IMRT, and considering the same xMLC as collimation device [16]. This work showed that the MERT+IMRT plans were comparable or even better than those planned with conventional IMRT, and proved the possibility of planning APBI treatments by using MERT+IMRT without any additional equipment or specific device. Those plans were calculated using CARMEN, a full Monte Carlo treatment planning system developed by our group [18].

At the second stage, we tested the clinical application of our approach by including the minimum number of patients necessary to evaluate the safety of the technique, determine a safe dose damage range, and observe the acute effects, and cosmetic results. This work reports the clinical implementation of this technique and also includes a quality assurance protocol specifically developed for the delivery of such APBI treatments.

Material and methods

Clinical considerations

As a previous step toward a clinical trial, the main objective of this study was to determine the feasibility of implementing MERT +IMRT by means of the xMLC for APBI into the clinic. We started this study in January 2012 at Virgen Macarena Hospital in Seville based on seven women with histologically confirmed invasive cancer confined to the breast. All patients were informed about the study, and they signed the consent form prior to enrollment.

Patient eligibility

Eligible patients met the low-risk criteria, a group for whom APBI outside the context of a clinical trial is an acceptable treatment option, including patients that were 50 years of age or older, with unicentric, unifocal, pT1–2 ($\leq$30 mm) pN0, non-lobular invasive breast cancer without the presence of an extensive intraductal component (EIC) and lympho-vascular invasion (LVI), and with negative surgical margins of at least 2 mm [19]. Re-excision of the surgical margin was permitted. The boundaries of the lumpectomy cavity (superior, inferior, medial, and lateral surgical resection margins) were marked with surgical clips during surgery. Estrogen and progesterone receptors analysis was performed to all the primary tumors, and HER2 receptor status was determined by immunohistochemistry and/or fluorescence in situ hybridization. Hormonal therapy in the indicated patients was administrated concurrently or after the completion of APBI. Candidates for adjuvant chemotherapy were not included in this study.

Treatment planning and delivery

A computed tomography (CT) scan was performed in supine position for each patient. Besides patient eligibility criteria, the cases were also chosen according to the target volume size and its position within the breast aiming to sample a representative collection of different anatomical scenarios. The structures of interest were defined following the NSABP-B39/RTOG-0413 protocol [20] which included lumpectomy cavity, CTV, PTV and PTV_EVAL, as well as clinically relevant normal structures. In this study we used the PTV_EVAL structure for plan evaluation. According to the protocol, PTV_EVAL has to be defined by uniformly expanding the excision cavity volume by 25 mm excluding the first 5 mm of tissue under the skin surface and the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included). An additional structure of 5 mm thick skin was also contoured over the ipsilateral breast region.

The more demanding limits of the protocol were considered by imposing a prescribed dose (Dp) of 38.5 Gy in ten fractions and limiting the dose to normal tissues as follows: (1) <60% and <35% of the ipsilateral uninvolved normal breast should receive $\geq$50% Dp and 100% Dp, respectively; (2) any point in the contralateral breast to <3% of Dp; (3) <15% of the ipsilateral and of the contralateral lung volumes to <30% and <5% Dp, respectively; and (4) <40% and <5% of the heart volume to $\leq$5% Dp for left-sided and for right-sided lesions, respectively. A 5% tolerance in these limits was acceptable according to the protocol.

A reduced SSD ranging from 60 to 70 cm was used for electron beams, in order to minimize electron scattering in air (Fig. 1). The treatment plans calculated by means CARMEN system consisted of one or two frontal modulated electron beams, plus one or two tangential modulated photon beams of 6MV for targets deeper than the therapeutic range of the clinically available electron beams (6, 9, 12, 15 and 18 MeV) [16]. An alternative IMRT plan was simultaneously calculated using the commercial TPS PINNACLE v8.0 m (Philips). Dose volume histograms (DVH) from the two plans were compared in order to apply MERT+IMRT only when the DVH improved the one of the conventional IMRT plan (planned with PINNACLE). For all the evaluated cases, this comparison was always favorable to MERT+IMRT planned with CARMEN system.

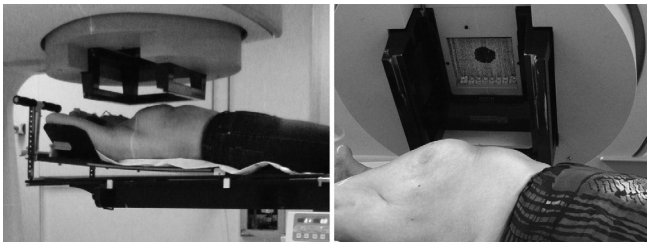

Fig. 1. The use of a reduced SSD (60–70 cm) required a couch position closer to the linac head than usual. The xMLC of the Siemens Primus linac was used for delivering combined MERT+IMRT treatments.

The treatments were initiated on average 90 days after the lumpectomy. The prescribed dose of 38.5 Gy was delivered in 10 fractions over 5 consecutive days, with a twice-a-day hypofractionated schema, separated by a minimum interval of 6 h. The set-up was verified using portal images taken before the first, fifth and ninth fractions. Also, as an additional control, a tattoo contouring the projection corresponding to the first electron segment of the planned sequence was marked over the breast skin to visually confirm that the isocenter shift from photon to electron modes was done correctly. Due to the reduced SSD, potential LINAC collisions for the electron beams delivery were considered by including in the patients CT images a virtual plane at the position corresponding to the bottom of the LINAC head. The leaves movement of the xMLC during the electron beam irradiation was possible thanks to specific implementations done by Siemens technical staff. This allowed the automatic delivery of the sequence of electron segments similarly to the photon beams delivery.

Quality assurance protocol

The clinical application of this technique required a specific pretreatment experimental verification. An ad-hoc breast phantom with semi-spherical geometry was designed for the experimental verification (Fig. 2). The phantom, called NAOMI, consists of 5 mm-thick high-impact polystyrene slabs which can be placed one on top of each other [21]. Breasts with different sizes, including chest-wall, can be emulated. NAOMI allows placing different types of ionization chambers and radiochromic films at different depths inside the phantom. In addition, a quality assurance (QA) protocol was created. We aimed to compare the absolute and relative dose distributions estimated by CARMEN TPS with the dose measured using ionization chambers and films placed at different depths of interest inside NAOMI. For relative dosimetry we applied a multi-plane verification by placing Gafchromic EBT3 film. After the irradiations, we did a standard gamma analysis based on the distance-to-agreement (3 mm)/dose-difference (3%) criteria and a 95% passing rate. Calibration curves for optical density to dose conversion were done for each batch of film. This calibration was performed for a dose ranging from 0 to 500 cGy including more than 12 points as proposed by Bouchard et al. [22]. A multichannel method [23] was used for the conversion of the film pixel value into dose, and also corrections for the non-uniformity lateral dose dependence response of the scanner were applied to the three channels.

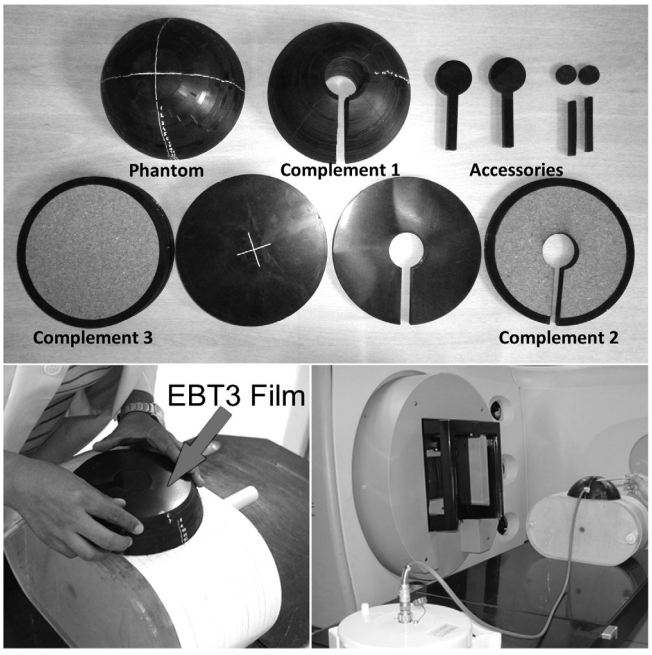

Fig. 2. Components of NAOMI phantom, including accessories for holding different ionization chambers, and slices with cork to emulate lung density.

Initially, absolute dose was measured at a representative point with a plane-parallel Roos chamber PTW 34001 for electron beams and ion chamber Wellhoffer CC04 for photon beams. A 3% of deviation in absolute dose was considered acceptable for each type of beam. A PTW 0.125 cm^3 Semiflex 31010 showed similar feasibilities for both, electron and photon beams. Therefore, for practical reasons, this same ion chamber was used for the last cases.

Follow-up and cosmetic evaluation

Patients were evaluated by the radiation oncologist after each treatment session. Follow-up visits were scheduled one month post-treatment, every three months for the first year, and every six months for the second year. The patients consented to have a photograph taken to document skin toxicity at the first and last day of treatment, and at the follow-up visits.

Toxicity was assessed using the Common Toxicity Criteria Adverse Events (CTCAE v3.0). Presence of hypoplasia, fibrosis, induration, telangiectasia, hyperpigmentation, breast pain, wet desquamation, edema and erythema were graded according to these criteria. Cosmetic effects were evaluated according to the appearance of the surgical scar and the skin, the size and shape of the treated breast and the presence of telangiectasia or fibrosis. It was graded using the four-point Harris scale (1 = excellent, 2 = good, 3 = fair, 4 = poor) [24].

Results and discussion

Planning parameters are listed in Table 1. As it can be seen, the different relative location of tumor bed and the breast size drove to a varied set of these parameters. Patients were, in general, treated with a combination of one frontal modulated electron beam and two tangential modulated photon beams of 6 MV. Planning for patient number 4 required two electron beams with different incidence-angles, instead of one, in order to avoid high dose to the nipple, and planning for patient number 2 required a single photon beam due to the morphology of the target. The deeper the tumor bed, the higher the electron energy required. The contribution of electrons was always minor than those provided by photon beams. Nevertheless, electron beam showed being essential to obtain the desired dose distributions and also to reduce the breathing motion uncertainty.

PTV_EVAL coverage was, in general, similar to the achieved by conventional IMRT, although the latter presented slightly higher target homogeneity in the solution provided by means of Pinnacle. However, dose to OARs was significant lower for MERT+IMRT plans, which supported the decision of taking the proposed plans as the best treatment choice. All cases fulfilled the dose limits established by the NSABP protocol for the considered normal tissues. DVHs of all patients in Fig. 3 show an adequate coverage of target volumes and dose homogeneity of MERT+IMRT plans. The prescribed dose (38.5 Gy) covered 90% of the clinical target volume for all patients, and the maximum dose did not exceed 120% Dp. Regarding avoidance structures, DVHs showed, on average, that the V30 of ipsilateral lung was 3.6% (0.3–12%), and the V5 of contralateral lung was 0.2% (0–1.2%). The V5 of heart was 8.6% (1.9–12.4%) in the left-sided RT group (3 patients), and 2.9% (0.9–5%) in the right-sided RT group (4 patients). The V50 and the V100 of ipsilateral breast were 38.2% (28.5–47.5%) and 6.9% (5.9–8.9%),

Table 1
Tumor bed locations and irradiation parameters of MERT+IMRT treatment plans calculated with CARMEN system for all the cases.

Patient	Location	Max/Average depth (cm)	Gantry angle (e−/ph)	Beam energies (e−/ph)	Segments (e-/ph)	Monitor units (e-/ph)
1	R, JUQ	5.7/3.7	357°/70°, 245°	15 MeV/6 MV	6/13	63/492
2	R, UIQ	5.4/3.5	330°/46°	15 MeV/6 MV	3/4	112/184
3	L, LIQ	4.6/3.2	40°/130°, 310°	12 MeV/6 MV	1/7	26/450
4	L, SUB	3.9/2.8	25°, 40°/139°, 317°	9 MeV/6 MV	2/3	59/461
5	L, UOQ	4.7/3.2	40°/137°, 314°	12 MeV/6 MV	1/7	58/367
6	R, JLQ	6.4/3.6	325°/45°, 220°	12, 15 MeV/6 MV	3/7	68/454
7	L, LOQ	7.1/4.1	45°/140°, 315°	12, 15 MeV/6 MV	2/7	85/375

Abbreviations: e−, electrons; ph, photons; L, left breast; R, right breast; UOQ, upper outer quadrant; UIQ, upper inner quadrant; LOQ, lower outer quadrant; LIQ, lower inner quadrant, JUQ, junction of the upper quadrants; JLQ, junction of the lower quadrants; SUB, sub-areolar area.

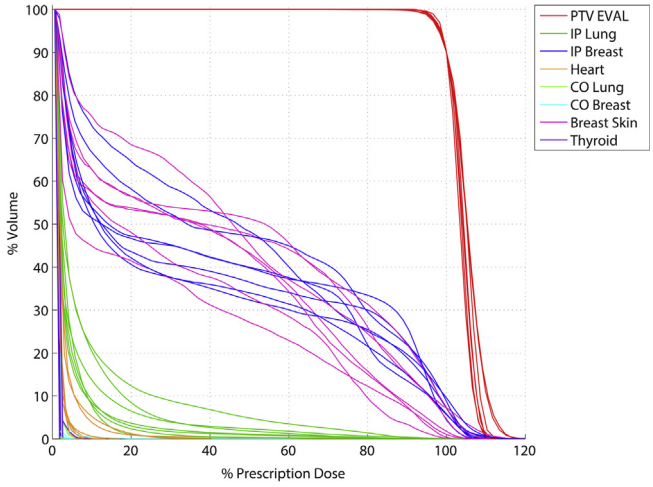

Fig. 3. Dose-volume histogram (DVH) from all patients MERT+IMRT treatment plans (planned with CARMEN system). Abbreviations: IP, ipsilateral; CO, contralateral.

respectively. The V3 of contralateral breast was 0.5% (0–1.2%). The V10, the V50 and the V90 of the breast skin were 59.8% (43.1–74.8%), 41.8% (28.5–51.3%) and 11.6% (4.6–22.3%), respectively.

All the treatment plans passed the acceptance criteria of the quality assurance protocol described above, both the absolute dosimetry and the relative dose distribution, under the specific pre-treatment verification based on NAOMI phantom. The reduced SSD did not generate any additional inconvenience for the patients neither for the positioning process, nor for the slightly larger treatment time due to the unavoidable isocenter transition (two different SSDs). In any case, the total treatment time was not superior to the typical static IMRT treatment time.

The median patient age was 70 years (59–79 years). Of the seven patients, five (71%) were pathologically diagnosed with invasive ductal carcinomas, one (14%) with invasive mucinous carcinoma, and one (14%) with colloid carcinoma. All patients had pathologic T1 stage tumors and six (86%) had histologic grade I tumors. Only one of the seven patients had intraductal component ≥25%. All patients had a negative pathologic margin; the median pathologic margin was 9 mm (5–20). The general characteristics related to the patients and the corresponding tumors are summarized in Table 2. All patients were hormone receptor-positive and received hormone therapy: 3 received tamoxifen and 4 received letrozole. None of the patients received adjuvant chemotherapy. The median follow-up time was 51 months (46–58 months). None of the seven patients had ipsilateral breast recurrence or regional or distant metastasis, and all were alive at the last follow-up.

Severe toxicity was not reported. Maximum observed toxicity for erythema-hyperpigmentation was grade 1, as well as for breast pain or fibrosis. In most patients, the erythema-hyperpigmentation disappeared after the first month post-treatment. Three of the patients developed fibrosis grade 1, detected after 6 months post-treatment. All the patients suffered mild breast pain at some point. However, they did not require analgesia and only anti-

Table 2
Dosimetric values of MERT+IMRT treatment plans and conventional IMRT plans calculated for all the cases.

	APBI1		APBI2		APBI3		APBI4		APBI5		APBI6		APBI7		
	MERT +IMRT	CONV IMRT	MERT +IMRT	CONV IMRT	MERT +IMRT	CONV IMRT	MERT +IMRT	CONV IMRT	MERT +IMRT	CONV IMRT	MERT +IMRT	CONV IMRT	MERT +IMRT	CONV IMRT	Protocol limits
PTV_EVAL															
D_{90}	100.0%	100.0%	100.0%	100.0%	99.8%	99.7%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	100.0%	≥90%
D_{max}	108.1%	107.3%	110.6%	111.3%	110.0%	107.0%	114.1%	110.0%	110.0%	110.3%	114.1%	111.5%	108.3%	109.6%	<120%
Ipsilateral breast															
V_{50}	33.8%	47.9%	28.5%	55.2%	39.8%	51.0%	36.5%	53.4%	47.0%	47.9%	34.0%	50.3%	47.5%	57.7%	< 60%
V_{100}	7.3%	21.0%	6.0%	28.2%	6.1%	30.2%	7.8%	29.7%	5.9%	31.7%	6.1%	38.4%	8.9%	39.1%	< 35%
Contralateral breast															
V_3	0.3%	1.7%	1.2%	5.9%	1.0%	0.0%	0.3%	1.5%	0.0%	0.0%	0.4%	0.3%	0.0%	0.0%	0%
Ipsilateral lung															
V_{30}	0.3%	0.0%	12.0%	15.4%	2.2%	1.8%	1.7%	3.2%	4.0%	0.3%	1.0%	1.6%	4.1%	1.1%	< 15%
Contralateral lung															
V_5	0.0%	0.0%	1.2%	11.1%	0.0%	2.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	< 15%
Heart															
V_5	2.6%(R)	1.5% (R)	5.0%(R)	0.5% (R)	12.4% (L)	39.2% (L)	1.9%(L)	37.3% (L)	3.2%(L)	11.0% (L)	0.9%(R)	4.1% (R)	11.6% (L)	27.3% (L)	< 5% (R) <40%(L)
Breast skin															
V_{10}	57.4%	54.7%	43.1%	44.7%	60.4%	52.0%	57.6%	51.9%	62.5%	47.2%	62.9%	57.5%	74.8%	60.8%	
V_{50}	43.2%	39.8%	28.5%	30.7%	37.0%	32.2%	47.6%	37.5%	42.2%	32.4%	51.3%	43.1%	42.8%	43.5%	
V_{90}	8.2%	8.0%	8.6%	7.4%	4.6%	6.0%	15.2%	9.2%	6.1%	8.9%	22.3%	14.2%	15.9%	11.5%	

Abbreviations: R, right sided lesion; L, left sided lesion.

Table 3
Treatment-related toxicities ($N = 7$).

Toxicity	Incidence, % of patients													
	At RT end		At 1 month		At 6 months		At 1 year		At 2 years		At 3 years		At 4 years	
	G0	G1	G0	G1	G0	G1	G0	G1	G0	G1	G0	G1	G0	G1
Breast pain	0 (0)	7 (100)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)
Breast edema	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)
Erythema/Hyperpigmentation	0 (0)	7 (100)	0 (0)	7 (100)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)
Wet desquamation	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)
Induration	7 (100)	0 (0)	7 (100)	0 (0)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)	4 (57)	3 (43)

Abbreviations: RT, radiation therapy; G, grade; G0, no toxicity; G1, mild; G2, moderate; G3, severe.

inflammatory drugs were sporadically prescribed. After six months post-treatment only three patients had breast pain at some point. None of the cases showed edema or scaling skin. No pulmonary or cardiac toxicity, or rib fractures were observed. Physician-assessed breast toxicities are shown in Table 3.

Using the Harris scale cosmetic outcome, the radiation oncologist graded four as excellent, two as good and one as poor. On the other hand, four of the patients graded the results as good, two as fair, and one as poor. It should be taken into account that Harris scale applies a subjective assessment, and surgery effects were evaluated together with those produced by the radiotherapy treatment. In this sense, no cosmetic scores differences were appreciated before and after the treatment.

Conclusions

MERT+IMRT technique using the xMLC to treat breast cancer with APBI was successfully applied, thanks to a software solution without any additional equipment or specific device. The plans calculated by CARMEN system achieved the dosimetric objectives recommended by the NSABP-B39/RTOG-0413 protocol in a similar way to the conventional IMRT plans for the targets, but with a better sparing for the OARs.

The quality assurance protocol, specifically developed for this new technique, was fulfilled for all the planned cases. The treatments delivery did not mean any inconvenience for the patients neither extra work for the clinical staff, and the spent times for positioning and irradiation were similar to the typical IMRT treatment.

During the follow-up period, moderate or severe grade of toxicity was not reported in any of the cases. The cosmetic results were comparable to those reported with other APBI techniques.

These results showed the feasibility of the MERT+IMRT technique as EBRT approach able for a widespread clinical application. The xMLC already installed in many LINACS would allow for extending this technique to many institutions, just by means of the implementation of the adequate software as the developed here for CARMEN system. Commercial treatment planning systems could be carried out this task.

Once it has been proved the viability and the safety of this technique in our center, a future clinical trial will be started to evaluate cosmetic outcomes, late complications and disease control.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.06.011.

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