Radiotherapy and Oncology 114 (2015) 322–327

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

PAPBI trial

First results of the preoperative accelerated partial breast irradiation (PAPBI) trial ☆

Femke van der Leij [a,1], Sophie C.J. Bosma [a,1], Marc J. van de Vijver [b], Jelle Wesseling [a], Sandra Vreeswijk [a], Sofia Rivera [c], Celine Bourgier [c], Jean-Rémi Garbay [c], Theodoros Foukakis [d], Tobias Lekberg [d], Desiree H.J.G.D. van den Bongard [e], Corine van Vliet-Vroegindeweij [a], Harry Bartelink [a], Emiel J. Rutgers [a], Paula H.M. Elkhuizen [a,*]

[a] Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam; [b] Academical Medical Center, Amsterdam, The Netherlands; [c] Institut Gustav e-Roussy, Villejuif, France; [d] Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [e] University Medical Center, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 17 October 2014
Received in revised form 26 January 2015
Accepted 3 February 2015
Available online 17 February 2015

Keywords:
Breast cancer
Partial breast irradiation
Preoperative

ABSTRACT

Background and purpose: The aim of this study is to assess the toxicity and cosmetic outcome of preoperative accelerated partial breast irradiation (PAPBI) for breast cancer patients with low risk on local recurrence.

Material and methods: Women aged ⩾60 years with an invasive, unifocal ⩽3 cm on MRI, (non-lobular) adenocarcinoma of the breast and a negative sentinel node received PAPBI (40 Gray in 10 fractions over 2 weeks). Six weeks after radiotherapy a wide local excision was performed.

Results: 70 patients with a median follow-up of 23 months (3–44 months) were evaluated. The overall postoperative infection rate was 11%. At 1, 2 and 3 years of follow-up respectively 89%, 98% and 100% of patients had no or mild induration-fibrosis. Fibrosis was only found in a small volume of the breast. The global cosmetic outcome was good to excellent in 77% at 6 months to 100% at 3 years. Two patients developed a local recurrence.

Conclusion: Our first results show limited fibrosis in a small volume and good to excellent cosmetic outcome. In selected patients, preoperative radiotherapy appears to be a good option for breast conserving therapy.

After breast-conserving therapy (BCT) for the treatment of invasive breast cancer most ipsilateral local recurrences occur at or close to the original tumor site [1,2]. Therefore, accelerated partial breast irradiation (APBI) has been studied as an alternative to whole breast irradiation (WBI) for patients with low-risk for local recurrence [3,4]. With APBI radiotherapy (RT) is only targeted to the surgical cavity and a limited area of surrounding tissue instead of the whole breast. Also, a higher dose to a smaller volume can be delivered in a shorter period of time.

Several methods of APBI have been developed: the frequently used invasive techniques including intraoperative radiotherapy (IORT), interstitial or intracavitary brachytherapy and the non-invasive three-dimensional conformal external-beam radiation (3D-CRT). The invasive methods normally treat smaller volumes of normal tissue compared with 3D-CRT APBI, but a disadvantage of IORT is that pathology information at time of the irradiation is absent, including information about tumor free margins. Since the tumor is often not centrally located in the surgical resection specimen, this may lead to under- or overtreatment of the target area [5,6]. Advantages of postoperative 3D-CRT APBI are the availability of pathology information at the time of treatment, optimization of the radiotherapy plan and more dose homogeneity, which can lead to less radiotherapy side effects including fibrosis. Furthermore, it is widely available, less physician-dependent, non-invasive and accessible to large groups of patients.

Several studies on postoperative 3D-CRT APBI showed variable results concerning toxicity and cosmetic outcome [7–11]. The

☆ Part of this trial is presented previously at the San Antonio Breast Cancer Symposium, San Antonio, USA, December 2013 and at the 9th European Breast Cancer Conference, Glasgow, Scotland, March 2014.

* Corresponding author at: Department of Radiotherapy, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail address: p.elkhuizen@nki.nl (P.H.M. Elkhuizen).

[1] Contributed equally.

http://dx.doi.org/10.1016/j.radonc.2015.02.002
0167-8140/

unfavourable results are associated with large treatment volumes. Large inter-observer variability in defining the tumor bed for postoperative irradiation has been shown in many studies, resulting in larger irradiated volumes [12–14].

In a previous study we showed less inter-observer variation in tumor delineation preoperatively compared to postoperatively [15]. When RT is given preoperatively more accurate tumor delineation can be performed. After RT surgery is performed, thereby removing the area of the breast that received the highest RT dose. As a result, limited fibrosis and a good cosmetic result are expected.

In the multi-center phase II preoperative accelerated partial breast irradiation (PAPBI) trial (registered with ClinicalTrials.gov, Number NCT01024582) low risk patients of 60 years and older are irradiated preoperatively instead of postoperatively with external beam APBI. In total 120 patients will be included in the trial. In this paper we present the results of the interim-analysis of the first 70 patients. This interim-analysis was carried out in order to allow continuation of this trial, taking into account treatment complications, local control and cosmetic outcome. The main objective is to investigate the impact on local control, cosmesis and breast fibrosis of a short fractionated schedule given preoperatively.

Patients and methods

The PAPBI trial started in April 2010 at the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL) in the Netherlands. Other institutes joined the trial later: Institut Gustave Roussy (IGR) in France, Karolinska Institutet in Sweden and University Medical Centre Utrecht (UMCU) in The Netherlands.

Patients

Patients were eligible for the PAPBI trial if they met the following criteria: age $\geqslant$60 years; cT1–2 (tumor size $\leqslant$3 cm) on magnetic resonance imaging (MRI); histologically proven adenocarcinoma; unifocal lesion on mammogram and MRI; pN0 (determined by a sentinel node procedure before start of RT); ECOG performance scale $\leqslant$2. Patients were excluded in case of extensive microcalcifications on mammogram; ductal carcinoma in situ of the breast, without invasive tumor; lobular invasive breast cancer; treatment prior to radiotherapy; a planning target volume (PTV)/ipsilateral breast ratio >25%. Also, patients with a previous history of malignancy or synchronous malignant tumor in the other breast were excluded with the exception of pT1N0 contralateral breast carcinoma more than 5 years previously, basal cell carcinoma of the skin and adequately treated carcinoma in situ of the cervix. Written informed consent was obtained prior to start of the treatment protocol. The institutional review boards of the participating centers approved the study protocol.

Treatment and trial procedures

Prior to RT, tumor biopsies were taken for histopathological evaluation by a breast pathologist. At the time of the biopsies a marker was placed in the tumor, which was used for daily setup verification as well as guidance for the surgeon during the operation. RT consisted of 10 fractions of 4 Gray over 2 weeks. The gross target volume (GTV) was defined as the visible tumor on the planning computed tomography (CT) scan using additional information from MRI, mammogram and ultrasound. The clinical target volume (CTV) was constructed by extending the GTV with 2 cm. The PTV was constructed by extending the CTV with 0.5 cm. Dose distributions were planned according to the International Commission on Radiation Units and Measurements recommendations. Position verification was performed by cone-beam CT-scan or Electronic Portal Imaging according to the institutes' protocol. Conformal 3D CRT, Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) were used as RT techniques, depending on the institute. Six weeks after the last day of RT, a wide local excision was performed. In case of positive resection margins a re-excision was performed. Adjuvant systemic treatment was applied according to local guidelines in the participating institutes (based on tumor size on MRI and histological grading of the tumor on biopsies). To evaluate response to RT, MRI was performed prior to the start and six weeks after completion. A 18F-fluorodeoxyglucose positron emission tomography (PET)-scan was optional and was performed at the same time as MRI.

Outcomes

The primary endpoints were local recurrence, breast fibrosis and cosmetic outcome. Local recurrences should not exceed 4% at 5 years of follow-up.

An additional goal was to develop a classifier that predicts radiosensitivity. For this translational research gene expression profiling of the tumor will be correlated to response of the tumor as measured by pathologic response, MRI and PET-scan 6 weeks after irradiation.

Statistical design

The calculation of the number of patients to be included for the full phase II trial was based on the amount needed to develop a gene expression signature for radiosensitivity. It was estimated that 60 patients were needed in the training set. The classifier was considered to be clinically useful if the positive predictive value was >90% and the negative predictive value was >50%. Based on the assumption that the proportion of responders and non-responders would be close to 50% the number of patients needed in the validation set was 50. In total 120 patients will be included in the trial.

Follow up

During RT acute skin toxicity (up to 1 month after treatment) was scored by the attending radiation oncologist or trained physician assistant according to the EORTC/RTOG acute radiation morbidity scoring scale. After RT, patients underwent clinical evaluation every 3 months in the first year. Thereafter, follow-up visits were conducted every 6 months and annually after 5 years. Patients underwent a screening mammography annually and in the first year of follow-up with an additional MRI. Postoperative complications were scored for all patients.

At each visit clinical induration was scored separately for the tumor bed area and the whole breast. Induration was used as a surrogate of the effect after radiotherapy and surgery (edema and fibrosis) [16,17]. After 24 months induration was considered to be fibrosis. Also breast pain, rib pain and the presence of rib fracture(s) were evaluated according to the EORTC/RTOG/late radiation morbidity scoring.

Cosmesis was evaluated by the physician before start of RT, 6 months after completion of treatment and thereafter every year. The treated breast was compared to the contralateral breast for visible sequelae, telangiectasia and global cosmetic result scored as (0) excellent, (1) good, (2) fair, (3) poor or (4) not evaluable. Dutch patients received a questionnaire concerning cosmetic outcome yearly. Digital photos of both breasts were taken before the start of RT, 6 months after completion of treatment and thereafter every year. The photos will be used in the future for objective assessment of cosmetic outcome by the BCCT.core project software program.

Statistical analysis

Time intervals were calculated using the first day of RT as treatment day 1. Descriptive analyses were used to show the proportion of patients with grade 0, grade 1, ⩾grade 2 events at each follow-up visit.

Patients who underwent a mastectomy due to a local recurrence or incomplete resection were excluded from the cosmetic analysis after the mastectomy.

Results

Patient characteristics

A total of 70 patients, treated between April 2010 and December 2013, were evaluated from all participating centers; NKI-AVL ($n = 47$), IGR ($n = 14$), Karolinska ($n = 6$) and UMCU ($n = 3$). The median follow-up was 23 months (range 3–44). The mean tumor size was 1.5 cm (0.4–3.2). All patients were node negative, determined by a sentinel node procedure before RT. At histological examination of the pre-treatment biopsy, ninety-four per cent of the tumors were classified as invasive ductal carcinoma (IDC), and the majority as histological grade 1–2 (96%), which was estrogen receptor (ER)/progesterone receptor (PR) positive and HER2 negative (Table 1).

Treatment

The mean GTV was 2.7 cc (SD 2.0, range 0.1–12.0), the mean CTV was 87 cc (SD 32, range 7–193) and the mean PTV was 121 cc (SD 42, range 13–263). The mean whole breast volume was 1028 cc (SD 474, range 107–2265) resulting in a PTV/ipsilateral breast ratio of 13.3% (SD 4.9, range 5–24). None of the 70 patients interrupted or stopped the treatment. 69 Patients underwent a wide local excision with negative resection margins. One patient had a focally positive resection margin. A subsequent mastectomy followed because a poor cosmetic result was expected with a re-excision. 46/70 patients (66%) received adjuvant hormonal treatment and 4/70 patients (6%) adjuvant chemotherapy.

Treatment-related toxicities and complications

Acute skin toxicity was scored for all 70 patients; 39 patients (56%) had no acute toxicity, 30 patients had grade 1 (43%) and one patient (1%) grade 2 acute skin toxicity. Postoperative complications were noted in 11 of the 70 patients (16%); two patients had direct post-operative bleeding requiring re-surgery performed on the same day, one patient developed a hematoma two months after surgery and needed re-surgery, eight patients developed a postoperative wound infection, one of whom needed re-surgery for a wound abscess and in one patient a small fistula was formed which closed within ten months after treatment with antibiotics. The other six patients were successfully treated with oral antibiotics. No other wound healing problems were observed. Seven patients (10%) developed persistent seroma (see Fig. 1).

Table 1
Patient characteristics.

Variables	Number ($n = 70$)
Median age (years)	67.3 (60–80)
Median tumor size (cm)	1.3 (0.4–3.2)
Histological grade biopsy	
1	22 (32%)
2	44 (64%)
3	3 (4%)
Not gradable	1
Estrogen receptor	
Positive	67 (96%)
Negative	3 (4%)
Progesterone receptor	
Positive	53 (76%)
Negative	17 (24%)
HER2 neu-status	
Positive	2 (3%)
Negative	68 (97%)

Induration-fibrosis

In four patients transient edema in the whole breast was observed, in all other patients the breast tissue outside the irradiated tumor area showed no side effects. In the first year an increase of induration was seen at the tumor area: from 52% (31/60 patients) to 69% (41/59 patients) to 80% (40/50 patients) after 3, 6 and 9 months respectively. Over time the proportion of patients with (any grade of) induration-fibrosis declined as well as the grade (Fig. 2 and Supplemental Table 1). At 12 months induration was scored for 57 patients; 11 (19%) had none, 40 (70%) mild and six (11%) moderate induration. At 24 months 19 of 41 patients (46%) had mild fibrosis and one (2%) patient moderate fibrosis. At 30 months the majority of patients (15/23 patients) had no fibrosis (65%). After 36 months fibrosis was scored for only 11 patients, all had none-mild fibrosis. The area of fibrosis was limited to a clinically estimated volume of 1–2 cm.

Other toxicity

During total follow-up, 27 of 70 patients (39%) reported grade 1 breast pain (transient in 21, persistent in six patients) and seven

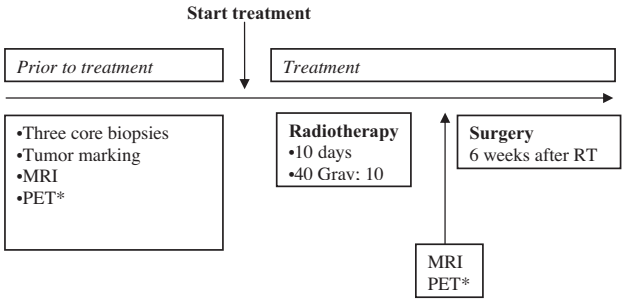

Fig. 1. Outline of investigations before and during therapy. * = optional.

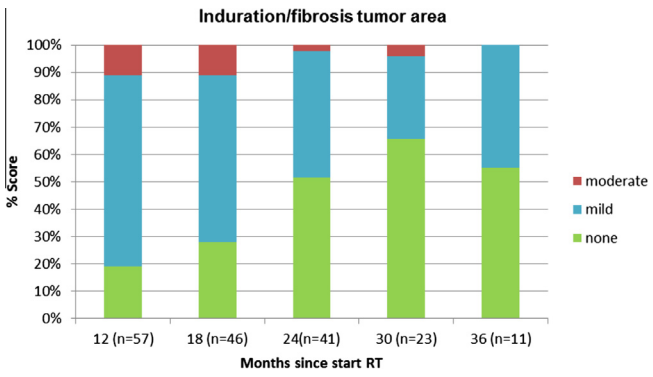

Fig. 2. The grade of induration/fibrosis at different time-points.

patients (10%) grade 2 breast pain. In one patient the breast pain diminished from grade 2 to grade 1 and in five patients the pain was transient (grade 0). One patient reported grade 3 breast pain, which had diminished to grade 2 at last follow-up date. 11 patients (16%) reported rib pain, of whom nine scored grade 1 (six transient) and two patients grade 2 (persistent). No rib fractures were observed.

Cosmetic results

Cosmesis, as scored by the physician, improved over time (Fig. 3 and Supplemental Table 2). After 0.5 years global cosmetic outcome was scored for 66 patients; 51 (77%) had a good to excellent, 13 (20%) a fair and two (3%) a poor cosmetic result. After 1 ($n = 56$), 2 ($n = 41$) and 3 years ($n = 13$) the proportion of patients with a good to excellent cosmetic outcome was 89%, 88% and 100% respectively. The cosmetic assessment by the Dutch patients ($n = 50$) was also evaluated (Fig. 4 and Supplemental Table 3). The majority of patients was satisfied to very satisfied with the cosmetic result; 81%, 86%, 80% and 79% after respectively 0.5, 1, 2 and 3 years. Examples of cosmetic outcome are shown in Fig. 5.

Treatment efficacy

In two patients an ipsilateral tumor recurrence (IBTR) was diagnosed. In both cases the primary tumor was grade 1, ER/PR positive, HER2 negative; in one patient the IBTR was diagnosed at the skin entry of the biopsy tract after 12 months, outside the radiation field; one patient was diagnosed with an IBTR in another quadrant of the breast after 26 months. For both patients, the IBTR was outside the radiation field and loss of heterozygosity-analysis showed true recurrences. No distant failure has occurred. One patient died due to pneumonia, not related to the breast cancer or PAPBI treatment.

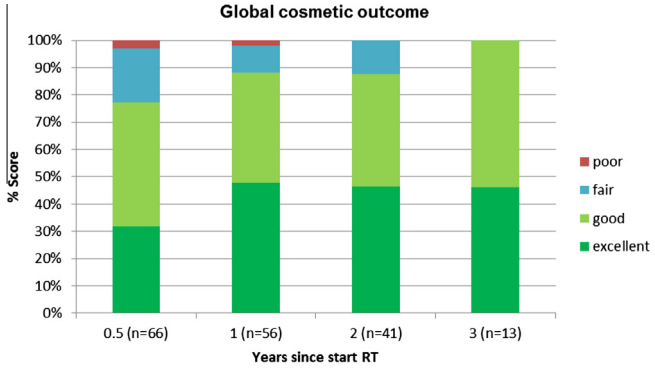

Fig. 3. Physician's cosmetic assessment over time.

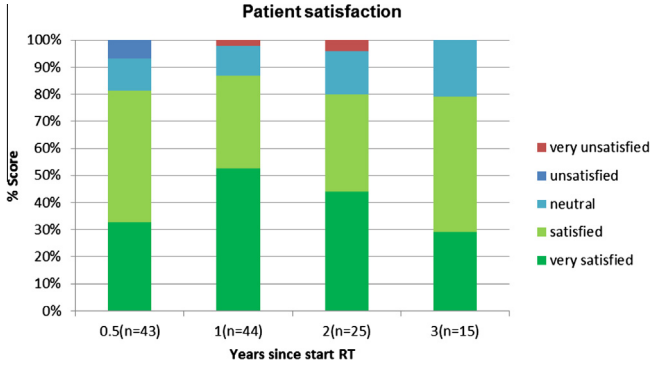

Fig. 4. Patient's questionnaire on cosmetic outcome.

Discussion

This is, to the best of our knowledge, the first study of preoperative as opposed to postoperative APBI in low risk breast cancer patients. Seventy patients treated with preoperative APBI show low complication rates, limited fibrosis in a small volume and good to excellent cosmetic results with an acceptable local recurrence rate.

Despite preoperative irradiation, our postoperative complication rate compares favourably to conventional radiotherapy with modern techniques. In the Cambridge IMRT Trial, 648 patients were treated with BCT of which 19.7% had a postoperative infection and 7.9% postoperative hematoma [18], although lower infection rates have been reported in brachytherapy trials. We observed an overall postoperative infection rate of 11% and a 5.7% postoperative hematoma rate.

The majority of the patients in the PAPBI trial had no or only mild fibrosis. During the trial it was noted that the volume of fibrosis was very small, beyond expectation. The volume was clinically estimated 1–2 cm in most patients, generally at the boundaries of the previously irradiated area, suggesting a leftover of the irradiated volume. After conventional BCT with WBI, fibrosis rates are higher; in the EORTC 22881-10882 boost–no boost trial the 10 year rate of moderate or severe fibrosis increased from 13% to 28% with a boost [19]. These rates are similar to the study of Hepel et al., which showed moderate to severe fibrosis in 25% of the patients after a median follow-up time of 15 months in a study of 64 patients [10]. The presence of fibrosis was the strongest correlate of a fair/poor cosmetic outcome. The results concerning toxicity of other external beam APBI studies are varied. Several studies show limited toxicity, comparable with our results [7–9,20,21]. In the multicenter study of Berrang et al. with a median follow-up of 3 years, grade 2 fibrosis was the most prominent late effect and was observed in 7 of 87 patients (8%) [7].

The global cosmetic outcome, scored by the physician, was good to excellent in 77% at 0.5 years and 100% at 3 years in our patients. Cosmesis did not deteriorate since treatment with a tendency to improvement over time, in contrast to other external beam APBI trials where cosmetic outcome gets worse with longer follow up [11,16]. Results concerning cosmetic outcome in other trials, concerning postoperative RT, range from good to excellent cosmetic outcome in 97% of the patients [22] to 21% unacceptable cosmesis at a median follow up of 2.5 years [11]. Most published results involve single-center studies with small numbers of patients and short follow up. Larger trials include the RAPID trial, which showed significantly more poor cosmetic results at 3 years in the 3D-CRT APBI group compared to WBI (29% versus 16.5%) [16]. The volume of breast that receives 95% of the prescribed dose was restricted to <35% in that trial. It was speculated that this volume may have been too large in some patients. Hepel et al. and Jagsi et al. have also linked their poor cosmetic results to the large volumes of breast tissue receiving relatively high irradiation doses [10,11]. In the trial of Hepel et al. a mean PTV/ whole breast volume of 18% in patients with excellent/good cosmesis and 24% in patients with fair/poor cosmesis was seen.

It is expected that preoperative external beam APBI results in smaller treatment volumes compared to postoperative APBI because of more accurate target definition. The mean PTV/breast ratio in the PAPBI study was 13%. Compared to the study of Hepel et al. the mean tumor size in the PAPBI was larger (1.5 cm in the PAPBI versus 0.9 cm in the study of Hepel et al.). Although similar

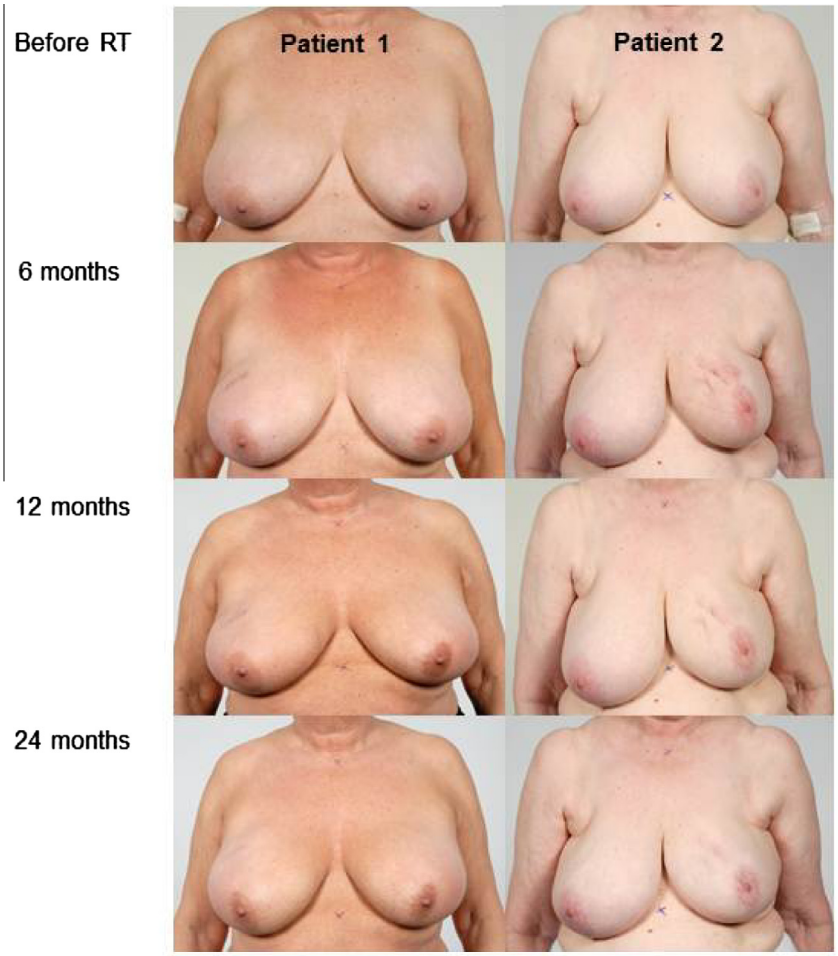

Fig. 5. Examples of improvement over time of cosmetic outcome in 2 patients (photographs of baseline and 6, 12 and 24 months since the start of RT).

CTV and PTV margins were used, we found significantly smaller PTV volumes in our preoperatively treated patients (mean PTV 122 cc versus 296 cc in the Hepel et al. series). This was also seen in a study of Palta et al. [23]. A virtual plan for preoperative single fraction external beam APBI resulted in a substantial reduction in ipsilateral breast tissue dose compared with postoperative APBI. Also Nichols et al. showed that preoperative APBI could decrease the planning target volume and the dose to normal tissues compared to postoperative APBI in a cohort of 40 patients [24]. Our good cosmetic results are likely to be explained by the small irradiated volume (mean PTV 122 cc) and the surgical removal of the breast tissue that received the highest radiation dose, with very limited fibrosis as a result.

Comparison between studies can be difficult because varying toxicity and cosmetic result scoring systems and dose and fractionation regimens are used. For instance, we applied an RT scheme of 10 times 4 Gray once a day while other external beam APBI trials used schedules with RT twice a day. Furthermore, dosimetric constraints differ between studies. For most patients in the PAPBI trial IMRT is used, while in other APBI trials most patients were treated with conformal 3D-CRT.

The treatment efficacy results of postoperative external beam APBI phase I and II studies are limited and overall show low local recurrence rates after limited follow up time [7–11]. Most long-term data concerning APBI originate from trials using brachytherapy. In the study of Polgar et al. equal local control for multicatheter brachytherapy or electron beam irradiation after 10.2 years was observed [25,26]. Other trials that randomised between external beam RT and IORT showed higher IBTR rates in the IORT group [27,28]. In our PAPBI trial, two patients had an IBTR. Longer follow-up is needed to conclude more about breast relapse rates in our and other external beam APBI studies. Therefore, adequate patient selection remains important [3,4].

Limitations of the current study are the non-randomized set-up and the relatively small sample size. As a consequence of the low number of patients and incomplete follow-up the progress of cosmesis and fibrosis must be carefully interpreted. A clinical disadvantage of preoperative compared to postoperative APBI, is that a sentinel procedure has to be obtained before RT, requiring an additional surgical procedure.

The first results of this preoperative APBI trial show low complication rates, limited induration-fibrosis in a small volume and good to excellent cosmetic results. Preoperative APBI is a feasible and widely available technique with promising results for low risk breast cancer patients.

Funding

This study was financially supported by the Dutch Cancer Society-KWF Grant NKI 2009-4389 and by the Cancer Society in Stockholm.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgment

We thank Erik van Werkhoven for collecting and providing data.

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.2015.02.002.

References

[1] Elkhuizen PH, van de Vijver MJ, Hermans J, Zonderland HM, van de Velde CJ, Leer JW. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys 1998;40:859–67.
[2] Sanders ME, Scroggins T, Ampil FL, Li BD. Accelerated partial breast irradiation in early-stage breast cancer. J Clin Oncol 2007;25:996–1002.
[3] Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, 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.
[4] Polgar C, Van Limbergen E, Potter R, Kovacs G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol 2010;94:264–73.
[5] Stroom J, Schlief A, Alderliesten T, Peterse H, Bartelink H, Gilhuijs K. Using histopathology breast cancer data to reduce clinical target volume margins at radiotherapy. Int J Radiat Oncol Biol Phys 2009;74:898–905.
[6] Bartelink H, Bourgier C, Elkhuizen P. Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic? Radiother Oncol 2012;104:139–42.
[7] Berrang TS, Olivotto I, Kim DH, Nichol A, Cho BC, Mohamed IG, et al. Three-year outcomes of a Canadian multicenter study of accelerated partial breast irradiation using conformal radiation therapy. Int J Radiat Oncol Biol Phys 2011;81:1220–7.
[8] Chen PY, Wallace M, Mitchell C, Grills I, Kestin L, Fowler A, et al. 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 2010;76:991–7.
[9] Lei RY, Leonard CE, Howell KT, Henkenberns PL, Johnson TK, Hobart TL, et al. Four-year clinical update from a prospective trial of accelerated partial breast intensity-modulated radiotherapy (APBIMRT). Breast Cancer Res Treat 2013;140:119–33.
[10] Hepel JT, Tokita M, MacAusland SG, Evans SB, Hiatt JR, Price LL, et al. Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 2009;75:1290–6.
[11] Jagsi R, Haffty BG. External-beam accelerated partial-breast irradiation: exploring the limits of tolerability. J Clin Oncol 2013;31:4029–31.
[12] van Mourik AM, Elkhuizen PH, Minkema D, Duppen JC, van Vliet-Vroegindeweij C. Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. Radiother Oncol 2010;94:286–91.
[13] Petersen RP, Truong PT, Kader HA, Berthelet E, Lee JC, Hilts ML, et al. Target volume delineation for partial breast radiotherapy planning: clinical characteristics associated with low interobserver concordance. Int J Radiat Oncol Biol Phys 2007;69:41–8.
[14] Landis DM, Luo W, Song J, Bellon JR, Punglia RS, Wong JS, et al. Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. Int J Radiat Oncol Biol Phys 2007;67:1299–308.
[15] van der Leij F, Elkhuizen PH, Janssen TM, Poortmans P, van der Sangen M, Scholten AN, et al. Target volume delineation in external beam partial breast irradiation: less inter-observer variation with preoperative-compared to postoperative delineation. Radiother Oncol 2014;110:467–70.
[16] Olivotto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, et al. 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 2013;31:4038–45.
[17] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086–94.
[18] Mukesh MB, Barnett G, Cumming J, Wilkinson JS, Moody AM, Wilson C, et al. Association of breast tumour bed seroma with post-operative complications and late normal tissue toxicity: results from the Cambridge Breast IMRT trial. Eur J Surg Oncol 2012;38:918–24.
[19] Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 2007;25:3259–65.
[20] Formenti SC, Hsu H, Fenton-Kerimian M, Roses D, Guth A, Jozsef G, et al. Prone accelerated partial breast irradiation after breast-conserving surgery: five-year results of 100 patients. Int J Radiat Oncol Biol Phys 2012;84:606–11.
[21] Rodriguez N, Sanz X, Dengra J, Foro P, Membrive I, Reig A, 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;87:1051–7.
[22] Taghian AG. Interim results of a phase I/II Trial of 3-D conformal external beam accelerated partial breast irradiation in patients with early breast cancer. Int J Radiat Oncol Biol Phys 2008;72.
[23] Palta M, Yoo S, Adamson JD, Prosnitz LR, Horton JK. Preoperative single fraction partial breast radiotherapy for early-stage breast cancer. Int J Radiat Oncol Biol Phys 2012;82:37–42.
[24] Nichols EM, Dhople AA, Mohiuddin MM, Flannery TW, Yu CX, Regine WF. Comparative analysis of the post-lumpectomy target volume versus the use of pre-lumpectomy tumor volume for early-stage breast cancer: implications for the future. Int J Radiat Oncol Biol Phys 2010;77:197–202.
[25] Polgar C, Fodor J, Major T, Nemeth G, Lovey K, Orosz Z, et al. 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 2007;69:694–702.
[26] Polgar C, Fodor J, Major T, Sulyok Z, Kasler M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol 2013;108:197–202.
[27] Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14:1269–77.
[28] Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014;383:603–13.