International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Five-Year Results of the Preoperative Accelerated Partial Breast Irradiation (PAPBI) Trial

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Received Sep 2, 2019. Accepted for publication Dec 16, 2019.

Summary

We studied Preoperative Accelerated Partial Breast Irradiation (PAPBI) in 133 low risk patients >60 years with unifocal nonlobular adenocarcinoma with negative sentinel node in a multi center feasibility study.

Purpose: In this multicenter phase 2 feasibility study, we investigated the impact of preoperative accelerated partial breast irradiation (PAPBI) on local control, breast fibrosis, and cosmetic outcome.

Methods and Materials: Women aged >60 years with an invasive, unifocal (mammography and magnetic resonance imaging), nonlobular adenocarcinoma of the breast were treated with PAPBI. Six weeks after radiation therapy, a wide local excision was performed. Radiation therapy consisted of 10 × 4 Gy (2010-2013) or 5 × 6 Gy (after 2013) to the tumor (gross target volume) with a 25 mm margin (20 mm from gross target volume to clinical target volume, 5 mm planning target volume).

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Part of this work was presented at the ESTRO annual meeting, Milan, Italy, April 2019 (oral presentation).

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

Disclosures: none.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2019.12.037.

Acknowledgments—We would like to acknowledge the NKI-AVL Core facility Molecular Pathology & Biobanking (CFMPB) for laboratory support.

Int J Radiation Oncol Biol Phys, Vol. 106, No. 5, pp. 958–967, 2020
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2019.12.037

Before radiotherapy (10×4Gy or 5×6Gy) patient underwent SN procedure. Six weeks after RT patients were operated. PAPBI seems to be a feasible method with low acute and late toxicity and good to excellent cosmetic outcome, in several patients improving over time.

Results: One hundred thirty-three patients treated between 2010 and 2016 were analyzed with a median follow-up of 5.0 years (0.9-8.8 years). Seventy-eight (59%) patients were treated with 10 × 4 Gy in 2 weeks and 55 (41%) patients with 5 × 6 Gy in 1 week. Eighteen postoperative complications (14%) occurred in 15 patients (11%). The proportion of patients with no to mild fibrosis in the treated part of the breast at 2 years and later time points was around 90%. Cosmesis improved over time in several patients: excellent to good cosmetic score as rated by the physician was 68% at 6 months and 92% at 5 years. Seventy-seven percent (6 months) to 82% (5 years) of patients were "satisfied" or "very satisfied" with their cosmetic outcome. Three recurrences were detected in the biopsy track and 1 recurrence in the ipsilateral breast.
Conclusions: PAPBI is a feasible method with a low postoperative complication rate, limited fibrosis, and good to excellent cosmetic outcome. The local recurrence rate was 3% at 5 years; however, no local recurrences were observed since removal of the needle biopsy track.

Introduction

Accelerated partial breast irradiation (APBI) is an alternative to whole breast irradiation (WBI) after breast-conserving surgery for selected patients with low risk of local recurrence.[1,2] APBI involves irradiation of the area where the tumor was initially located with a 1- to 2-cm margin. The rationale for APBI originates from the observation that the majority of local recurrences occur in close proximity to the original tumor location. Because the target volume is smaller than with WBI, reduced toxicity is expected and a higher dose per fraction can be applied, leading to a shortened overall treatment time. Several randomized trials demonstrated equivalent local control between APBI and WBI.[3-6]

There are various methods to deliver APBI, including brachytherapy, intraoperative radiation therapy (IORT), and external beam radiation therapy (EBRT). Potential advantages of EBRT over the invasive methods (brachytherapy and IORT) are that this method is widely available, is noninvasive, provides better dose homogeneity, and is less physician dependent. An essential disadvantage of postoperative EBRT is the uncertainty in delineation, partly caused by postoperative changes in the breast. Several studies concerning EBRT reported reduced toxicity and improved cosmetic outcome after APBI in comparison with WBI.[4,6] In contrast, in the RAPID trial, toxicity was higher and cosmetic outcome worse after APBI compared with WBI.[7] Unfavorable results concerning toxicity and cosmetic outcome have been linked to large treatment volumes.[7-9]

The uncertainty in delineation can be overcome by changing from a post- to a preoperative setting. We found earlier that interobserver variability was smaller when the tumor was delineated preoperatively compared with postoperatively.[10] Thus, preoperative APBI may lead to smaller treatment volumes.[11] Considering treatment volume has been associated with adverse cosmetic outcome, this might be an important advantage of a preoperative approach. Furthermore, the part of the breast that received a high radiation dose is surgically excised, which is likely to lead to reduced fibrosis and improved cosmetic outcome. In addition, preoperative radiation therapy provides the opportunity to study radiation response.[12] A few publications reported promising results of preoperative APBI; however, they included a limited number of patients with short follow-up.[13,14]

In our preoperative accelerated partial breast irradiation (PAPBI) trial, patients were treated with preoperative APBI delivered by EBRT. In an interim analysis of 70 patients with a follow-up of 21 months, we showed limited fibrosis and good to excellent cosmetic outcome.[15] Here, we report the 5-year results of the complete prospective phase 2 trial including 133 patients, in terms of local control, fibrosis, and cosmetic outcome.

Methods and Materials

Study design and participants

The study design has been previously described in detail.[9] The PAPBI trial was conducted at the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL) in the Netherlands, Gustave Roussy in France, Karolinska Institutet in Sweden and the University Medical Centre Utrecht (UMCU) in the Netherlands. The review board of each participating center approved the study protocol, and all patients gave written informed consent. Patients were included from April 2010 to October 2016. Patients >60 years of age with a cT1-2 unifocal (based on mammogram and magnetic resonance imaging [MRI]) invasive carcinoma, pN0 (determined by a sentinel procedure before radiation therapy), and World Health Organization performance status 0 to 2 were eligible. Key exclusion criteria were extensive microcalcifications or multifocal malignant calcifications on the mammogram, ductal carcinoma in situ without invasive tumor, lobular invasive carcinoma, and systemic treatment before radiation therapy. Patients were

excluded if they had a synchronous malignant tumor in the other breast or a history of malignancy, except for T1N0 contralateral breast carcinoma treated more than 5 years before inclusion, basal cell carcinoma of the skin, and adequately treated carcinoma in situ of the cervix. In addition, the planning target volume (PTV)/ipsilateral breast volume ratio was not allowed to exceed 25%.

The workup of patients included a mammogram, an MRI, and 3 ultrasound guided pretreatment core biopsies for diagnostic and translational research purposes. MRI was performed using a 3.0-T scanner (Achieva, Philips, Best, The Netherlands) in prone position.

A marker in the tumor was placed for position verification during radiation therapy and guidance during surgery (Fig. 1). An 18F-fluorodeoxyglucose positron emission tomography scan before and after radiation therapy was optional to assess radiation therapy response (not described in this manuscript).

Treatment

For radiation therapy treatment planning, patients underwent computed tomography (CT) simulation. The gross target volume (GTV) included visible tumor on the simulation CT scan, considering information from the MRI, mammogram, and ultrasound. The clinical target volume (CTV) was defined by expanding the GTV with 20 mm and edited to the mammary gland (from 5 mm below the skin to the surface of the chest wall) and the PTV by expanding the CTV with 5 mm.

Dose distributions were planned according to the International Commission on Radiation Units and Measurement recommendations (reports 50 and 62). Several techniques were used, depending on the institute: volumetric modulated arc therapy, intensity modulated radiation therapy (IMRT), or 3-dimensional conformal radiation therapy.

Radiation therapy was initially delivered in 10 fractions of 4 Gy on 5 days per week over 2 weeks. From 2013, the radiation therapy schedule changed to 5 fractions of 6 Gy on 5 days over 1 week to reduce the overall treatment time. We considered this feasible based on results of our interim analysis, which showed an acceptable postoperative infection rate, limited fibrosis in a small volume of the breast, and good to excellent cosmetic outcome.[15] In addition, 5 fractions of 6 Gy over 10 days was well tolerated in a study by Formenti et al.[16,17]

For position verification, cone beam CT scan or electronic portal imaging was used depending on the institute. Six weeks after radiation therapy, an MRI scan (and optional positron emission tomography scan) was repeated to determine response (results not described in the present manuscript). Thereafter, a wide local excision was performed. Since 2015, the biopsy track was marked and the skin entry of the biopsy track removed during the wide local excision procedure. The reason for this adjustment was the finding of 3 ipsilateral breast tumor recurrences (IBTRs) in the biopsy tract.

Involved margins (focally or extensively) were an indication for re-excision. Patients received adjuvant systemic treatment according to institutional guidelines. All biopsies and surgical resection specimens were centrally reviewed by a dedicated breast pathologist (M.vd.V.).

Outcomes

This study was intended to study the impact of PAPBI on fibrosis, cosmetic outcome, and local control. Local recurrences should not exceed 4% at 5 years of follow-up. A secondary goal was to develop a gene expression profile for radiation therapy sensitivity (described in another manuscript).[12]

Follow-up

Toxicity was scored according to the acute and late European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group criteria[18] by a dedicated breast radiation oncologist or physician assistant. Acute skin toxicity was scored during treatment (up to 1 month after treatment). Postoperative complications were scored at the first visit after surgery (median, 15 days). Complications were categorized from grade 1 to 5 based on the invasiveness of the requirement treatment. A grade 1 complication requires no treatment, grade 2 needs pharmacologic treatment, and grade 3 requires surgical intervention. Grade 4 represents life-threatening complications, and grade 5 represents complications leading to death.

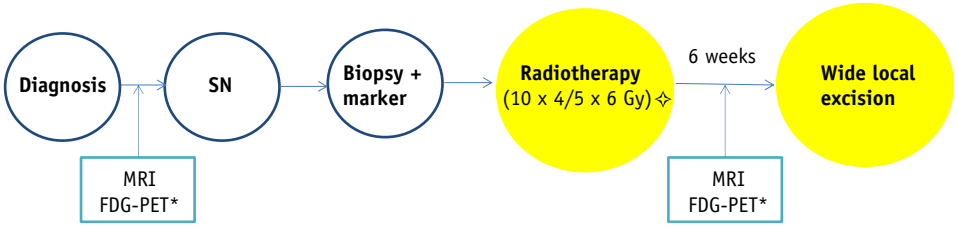

Fig. 1. Study overview: A step-by-step overview of the treatment schedule. ✧ Patients were treated with 10 × 4 Gy between 2010 to 2013 and with 5 × 6 Gy after 2013. *The fluorodeoxyglucose-positron emission tomography scan was optional. *Abbreviation:* SN = sentinel node procedure.

After treatment, toxicity was scored every 3 months in the first year, every 6 months for the first 5 years, and yearly thereafter. Induration and fibrosis were graded separately for the whole breast and the tumor bed area. Induration was used to describe edema/fibrosis up to 24 months; thereafter it was considered fibrosis.

Cosmetic outcome was scored subjectively by the treating physician and the patient and objectively before radiation therapy, 6 months after treatment, and then yearly up to 5 years. Cosmetic outcome was scored objectively using BCCT.core software.[19] Photographs for cosmetic assessment using the BCCT.core software were taken at 6 months, 1 year, 2 years, 5 years, and 7 years after treatment.

In the first year after treatment, patients underwent a mammogram and MRI; thereafter they underwent a mammogram yearly.

Patient-reported toxicity and quality of life (QoL) was assessed using the questionnaires EORTC QoL C30[20] and QLC- BR23[21] at baseline and 2 and 4 years after treatment.

Cosmesis

The physician rated the global cosmetic result by comparing the treated with breast with the contralateral breast on a 4-point categorical scale (excellent, good, fair, poor), used previously in the Young Boost trial (clinicaltrials.gov identifier NCT00212121). This was based on breast size, nipple position, shape of the areola and nipple, the appearance of the surgical scar, and the presence of telangiectasia. Dutch patients were sent a questionnaire[22] regarding their cosmetic outcome. They answered a question on the extent to which they were satisfied with the cosmetic outcome: very satisfied, satisfied, not dissatisfied, dissatisfied, or very dissatisfied. Cosmesis was scored by analyzing digital photographs in anteroposterior view using BCCT.core software, which returns an overall cosmetic outcome score (excellent, good, fair, or poor) based on the symmetry of the breasts, skin color, and scar visibility.[19] Patients who had been treated for breast cancer of the contralateral breast (n = 6) were excluded from analyses of cosmetic outcome.

Quality of life

We evaluated the following questions from the QCL-BR23 questionnaire: pain, swelling, sensitivity, and skin problems of the breast. Patients rated symptoms on a 4-point ordinal scale in which a score of 1 meant "not at all," a score of 2 "a little," a score of 3 "quite a bit," and a score of 4 "very much." Symptoms rated as "quite a bit" or higher are described in this manuscript. Additionally, all scores from the selected items are displayed in the Supplemental Table and Figures (available online at https://doi.org/10.1016/j.ijrobp.2019.12.037).

Statistical design and analyses

The sample size calculation was based on the number of patients needed to build a genetic classifier to identify responders and nonresponders to radiation therapy. Details of the sample size calculation have been described previously.[15] The inclusion of the planned 120 patients, as stated in the original protocol, was reached in 2015. An amendment that allowed enrollment of more patients, until the subsequent randomized phase 3 PAPBI-II trial was open for inclusion, was approved by the medical ethical committee.

Time intervals were calculated between the first day of radiation therapy and the date of clinical assessment during follow-up for toxicity and cosmetic outcome. For postoperative complications, time intervals were calculated between the date of surgery and the date of postoperative assessment. We performed descriptive statistical analyses of toxicity and cosmetic outcome in SPSS (IBM version 25). Explorative analyses were performed among patients with severe toxicity (moderate to severe fibrosis) and/or fair to poor cosmetic outcome to find associated risk factors (in Supplemental Table and Figures; available online at https://doi.org/10.1016/j.ijrobp.2019.12.037). We estimated local failure with cumulative incidence functions.

Results

Patient characteristics

One hundred and thirty-three patients treated between 2010 and 2016 were analyzed after a median follow-up of 5.0 years (range, 0.9-8.8 years). Seventy-eight (59%) patients were treated with 10 × 4 Gy (2010-2013) and 55 (41%) patients with 5 × 6 Gy (after 2013). Median follow-up was 5.9 years for patients treated with 10 × 4 Gy and 3.6 years for patients treated with 5 × 6 Gy. Baseline characteristics are displayed in Table 1. Median age was 68 years. The majority (65%) of patients had an ER+/PR+/HER2− invasive ductal carcinoma and low (27%) or intermediate (68%) grade.

Treatment

The median GTV was 2.00 cm^3 (range, 0.10-12.00 cm^3), the median CTV was 86.5 cc (range, 7-193 cm^3), and the mean PTV was 145.5 cm^3 (range, 64-291 cm^3). The median whole breast volume was 890 cm^3 (range, 13-2449 cm^3), resulting in a median PTV/breast ratio of 13% (range 5%-25%). All patients received the complete prescribed radiation therapy dose. In 1 patient, surgery was delayed several weeks due to comorbidity. A re-excision was performed in 8 patients (6%) (6 unifocal, 1 multifocal involved margin, and in 1 patient the wrong marker was excised), ultimately resulting in a complete resection for all patients. Breast-conserving surgery was performed in 6 patients and an ablation in 2 patients.

Acute toxicity

Acute skin toxicity (up to 1 month after radiation therapy) was scored for 115 patients: 75 (65%) patients did not have any toxicity, 39 (34%) patients grade 1, and only 1 patient grade 2. Fifty-eight percent of patients treated with 10 × 4 Gy did not have any toxicity, compared with 77% of patients treated with 5 × 6 Gy.

In total, 18 (14%) postoperative complications occurred in 15 patients. Two patients had more than 1 complication (1 with a hemorrhage and wound infection and 1 with a hemorrhage and infection of seroma). Four patients had postoperative hemorrhage, of whom 2 were treated with a reoperation, 1 with drainage, and 1 was treated conservatively. Fourteen patients had an infection (11%), of whom 11 were treated with antibiotics, 1 with drainage, and 2 with a wound toilet (1 with an abscess and 1 with an infected seroma/hematoma). Twelve patients (9%) developed long-term seroma. In 8 patients, persistent seroma was scored during the postoperative visit at a median time after surgery of 34 days. In all patients, long-term seroma was scored once and not during subsequent follow-up visits. In 4 patients (3%), seroma was scored during follow-up (median time from surgery was 55 days).

Late toxicity

In the first year of follow-up, the proportion of patients with (any grade) induration in the treated area of the breast increased from 53% at 6 months (n = 107) to 79% at 1 year (n = 119) (Fig. 2). Thereafter, this proportion gradually declined from 58% at 2 years (n = 119) to 43% after 5 years (n = 83). If breast fibrosis was present, it was mainly mild. The proportion of patients with no or mild fibrosis in the tumor area at 2 years and later time points was around 90% (Fig. 2). Fibrosis rates between the 2 treatment schedules were similar, and no differences between patients with and without fibrosis were identified (Fig. E1 and Table E1; available online at https://doi.org/10.1016/j.ijrobp.2019.12.037). Induration/fibrosis in the whole breast was scored in 21 patients (16%) and was transient in all. In 2 patients, telangiectasia was scored by the physician during assessments for cosmetic outcome. Other toxicities are displayed in Table 2.

Table 1 Clinical and pathological baseline characteristics of all patients (n = 133) and separately for patients treated with 10 × 4 Gy (n = 78) and 5 × 6 Gy (n = 55)

Characteristics	All patients (n = 133)	10 × 4 Gy (n = 78)	5 × 6 Gy (n = 55)
Age, median (range), y	68 (60-87)	67 (59-80)	69 (60-87)
Median tumor size, mm	13 (5-27)	14 (5-27)	12 (5-26)
Grade, n (%)			
1	35 (27)	24 (31)	11 (21)
2	89 (68)	50 (65)	39 (72)
3	7 (5)	3 (4)	4 (7)
Missing	2	1	1 (2)
ER+/PR+/HER2−	86 (65)	50 (65)	36 (66)
ER+PR−/HER2−	36 (27)	23 (30)	13 (24)
ER−/PR−/HER2−	8 (6)	3 (4)	5 (9)
HER2+	2 (2)	1 (1)	1 (2)
Immuno Histochemistry (IHC) missing	1	1	

Cosmetic outcome

Excellent or good cosmetic outcome as rated by the physician ranged from 68% at 6 months (n = 114) to 92% at 5 years (n = 53) (Fig. 3). Results of the 2 treatment schedules were comparable: Good to excellent cosmetic outcome was achieved in 88% at 2 years (n = 65) and 91% at 5 years (n = 42) for patients treated with 10 × 4 Gy, and 87% at 2 years (n = 39) and 100% at 5 years (n = 11) for patients treated with 5 × 6 Gy (Fig. E2; available online at https://doi.org/10.1016/j.ijrobp.2019.12.037). No differences between patients with good to excellent and fair to poor cosmetic outcome as rated by the physician at 2 years could be identified (Table E1; available online at https://doi.org/10.1016/j.ijrobp.2019.12.037).

In several patients, cosmesis improved over time. Cosmetic outcome was fair to poor in 51 patients, of whom 27 showed improvement to good to excellent cosmesis during follow-up (representative examples of improvement are displayed in Fig. 4).

Both a questionnaire (patient reported) and a physician-reported cosmetic outcome were available at the same time point for 82 patients and 321 scores in total. Physician-rated scores were in concordance with patient satisfaction. In the case of an excellent, good, fair, and poor score, 97%, 80%, 72%, and 17% of patients were very satisfied or satisfied, respectively. Overall, the majority of patients judged their cosmetic outcome as satisfactory (very satisfied or satisfied); 77% at 6 months and 82% at 5 years (Fig. 3).

Only patients for whom baseline photographs were available (n = 54) were analyzed by the BCCT.core software. Good to excellent cosmesis was scored in 92% at baseline and ranged from 78% at 6 months to 93% at 5 years (Fig. E3; available online at https://doi.org/10.1016/j.ijrobp.2019.12.037).

Loco(-regional) relapses, distant metastases, and survival

In 4 patients (3%) an invasive IBTR was detected. In 1 patient, the IBTR was detected at the skin entry of the biopsy tract after 12 months. She was treated with local

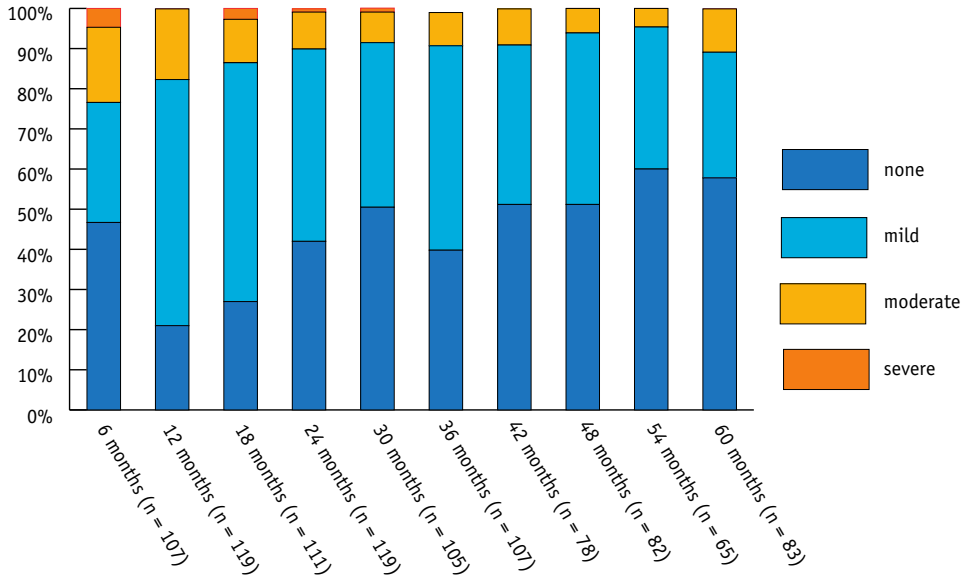

Fig. 2. Fibrosis in the tumor area: The grade of induration (<24 months) and fibrosis (>24 months) in the tumor area at different time points of all patients.

Table 2 Cumulative incidence of late side effects

Toxicities, n (%)	Total (n = 133)
Skin mamma, Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer	
Grade 0	74 (56%)
Grade 1	47 (35%)
Grade 2	10 (7%)
Grade 3	2 (2%)
Pain breast	
Grade 0	43 (32%)
Grade 1	71 (53%)
Grade 2	17 (13%)
Grade 3	2 (2%)
Pain rib	
Grade 0	99 (74%)
Grade 1	17 (13%)
Grade 2	14 (11%)
Grade 3	3 (2%)
Rib fracture	
Grade 0	131 (98%)
Grade 1	1 (1%)
Grade 2	1 (1%)
Grade 3	-
Radiation pneumonitis/pulmonary infiltrates	
Grade 0	131 (98%)
Grade 1	2 (2%)
Cough	
Grade 0	129 (97%)
Grade 1	4 (3%)
Dyspnea	
Grade 0	133 (100%)

excision and tamoxifen and developed a second IBTR after 24 months at the same location. She underwent skin-sparing mastectomy and has been free of disease since (5 years after mastectomy until last follow-up). Three other IBTRs were detected: (1) in another quadrant after 26 months, (2) in the biopsy tract after 36 months, and (3) outside the PTV area after 13 months. After revision of the pathology and imaging (ultrasonography during the biopsies, MRIs, and mammograms), 3 of 4 IBTRs were found to be tumor deposition located in the biopsy tract. Therefore, the protocol was adjusted by removing the skin at the entry of the biopsy needle track during surgery, mainly through punch biopsy of the core biopsy scar. Since the adjustment of the protocol in 2015, no invasive relapse in the breast has been detected. All 4 patients who had an IBTR had Bloom and Richardson grade 1 or 2, ER-positive invasive ductal carcinomas and have been free of disease since then.

Two other locoregional relapses were detected: 1 patient with ductal carcinoma in situ in the ipsilateral breast and in 1 patient ipsilateral nodal failure and a solitary bone metastasis were detected simultaneously. Two patients developed a contralateral breast cancer. Four patients have died of causes unrelated to breast cancer (treatment).

Patient-reported symptoms and quality of life

Mean scores of overall global health and QoL were similar at baseline, 2 years, and 4 years (Fig. E4; available online at https://doi.org/10.1016/j.ijrobp.2019.12.037). Only patients for whom QCL-BR23 questionnaires were available at all time points were analyzed (n = 54). At baseline, none of

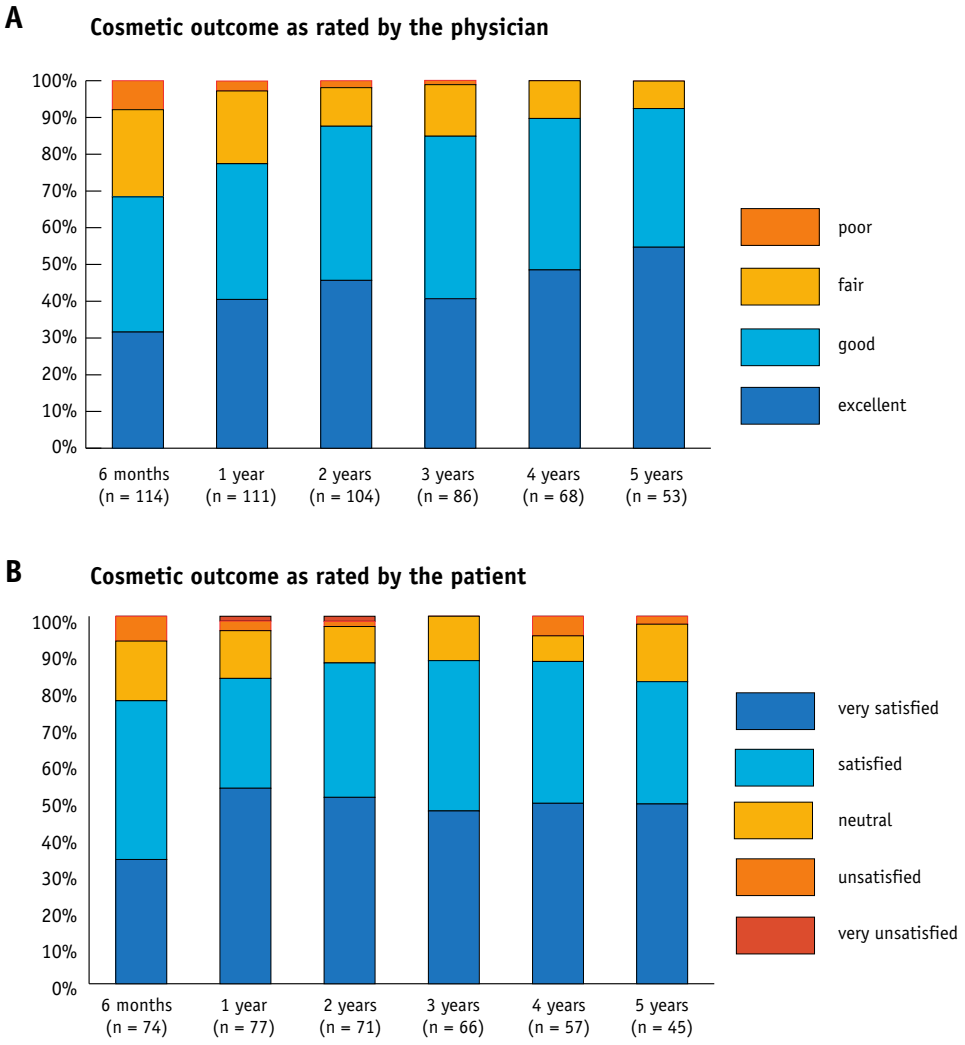

Fig. 3. Cosmetic outcome at different time points. (A) Cosmetic outcome as rated by the physician on a 4-point scale. Results of the 2 treatment schedules were comparable. (B) Cosmetic outcome as rated by the patient by questionnaires.

the patients reported symptoms rated as "quite a bit." One patient reported "quite a bit" of breast pain at 2 and 4 years. Three patients reported "quite a bit" of sensitivity at 2 years and 1 patient at 4 years. One patient reported "quite a bit" of skin problems at 2 and 4 years, 1 patient "very much" at 2 years, and none of the patients reported "quite a bit" of swelling of the breast (Fig. E5; available online at https://doi.org/10.1016/j.ijrobp.2019.12.037).

Discussion

Our PAPBI trial has shown that PAPBI is a feasible treatment with a low complication rate, limited fibrosis, and good to excellent cosmetic outcome. Approximately 90% of patients had no or only mild fibrosis in the tumor area. The cosmetic outcome as rated by the physician and patient was stable and even improved in several patients.

Good to excellent cosmetic outcome at 5 years was achieved in 92% of patients as rated by the physician with high concordance with patient scores. Conventional breast-conserving therapy with WBI results in a satisfactory cosmetic outcome in 57% to 88%, depending on the time point and in the absence of a gold standard for assessing cosmetic outcome.[23,24] Although the appearance of the breast changes negatively with longer follow-up after conventional WBI,[25-27] we observed no deterioration in cosmetic outcome over time. On the contrary, cosmetic outcome improved in over half of patients with fair to poor scores to good to excellent. It is likely that this is attributable to the diminishing of induration of the breast.

Several phase 3 trials showed less toxicity and improved cosmetic outcome in favor of APBI given by EBRT compared with WBI. The first phase 1 to 2 studies used 3-dimensional conformal radiation therapy,[8,9,17] and more recent studies used IMRT.[4,6] In the Florence trial, patients treated with APBI (30 Gy in 5 daily fractions) had significantly less grade 1 to 2 fibrosis and better cosmetic outcome than patients treated with WBI.[28] Cosmetic outcome as rated by the physician was excellent in 95% of

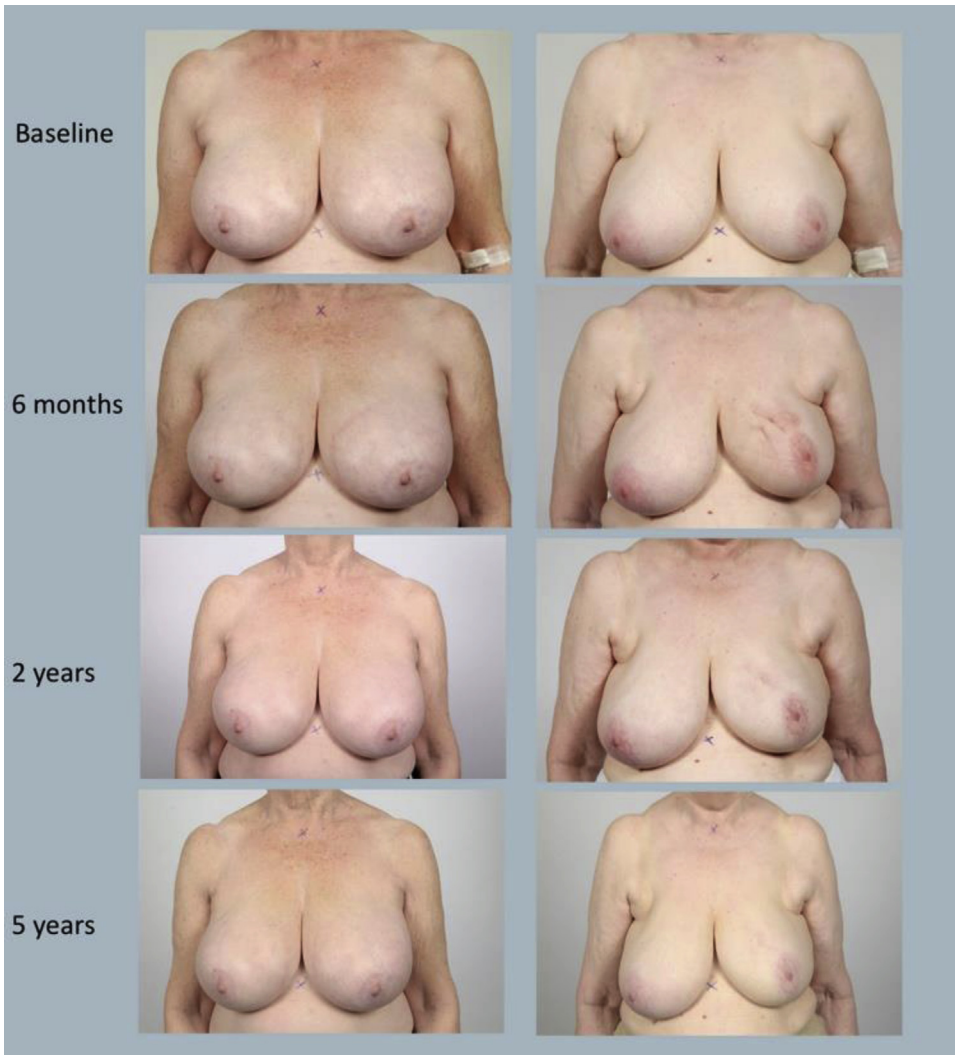

Fig. 4. Examples of cosmetic outcome. Photographs of 2 patients taken at baseline, 6 months, 2 years, and 5 years are shown. All scores were excellent for the patient on the left-hand side. Cosmesis of the patient on the right-hand side improved from poor (6 months) to fair (2 years) to good (5 years).

patients treated with APBI. In the IMPORT-LOW trial, patients treated with partial breast irradiation (PBI) reported statistically significant fewer changes in breast appearance ($P < .0001$) compared with patients treated with WBI.[6] In contrast, in the RAPID trial (n = 2128) higher adverse cosmetic outcome rates were reported in patients treated with APBI compared with WBI as scored by trained nurses (29 vs 17%; $P < .001$), patients (26 vs 18%; $P = .0022$), and physicians (35 vs 17%; $P < .001$), and cosmetic results declined over time.[7] Toxicity (any) at 3 years was significantly worse in patients treated with PBI (66%) than in patients treated with WBI (46%) ($P < .001$). Furthermore, in 2 nonrandomized trials, high rates of grade 3 soft tissue fibrosis[8] and fair to poor cosmesis (21% at 2.5 years)[9] were reported. These unfavorable results were attributed to large treatment volumes. Yet, in an exploratory analysis of the RAPID trial, the high-dose volume was not independently associated with adverse cosmetic outcome.[29] Other explanations were the twice-daily schedule resulting in incomplete repair and a higher biological dose.[30] However, the first results of the NSABP B-39 trial using the same fractionation schedule did not confirm this.[31] Hence, data concerning toxicity and cosmetic outcome after postoperative PBI are conflicting.

A Cochrane systemic review (2016) of studies concerning PBI delivered by various methods described worse cosmetic outcome and increased subcutaneous fibrosis and fat necrosis in patients treated with PBI compared with WBI with no differences in late skin toxicity.[32] However, unfavorable results of the RAPID and ELIOT trial were dominant in this meta-analysis. In the ELIOT trial, significantly more fat necrosis was noted in patients treated with IORT compared with WBI (15% vs 7%).[33] Two randomized controlled trials investigating IORT have been carried out so far.[33,34] Both trials reported less skin toxicity in patients treated with IORT compared with WBI. In a

recently published meta-analysis, PBI was associated with higher odds for toxicity (significant for fat necrosis) and 5-year local recurrence but less death without breast cancer recurrence compared with WBI. For EBRT, local control was equivalent to WBI.[35]

The excellent results in our PAPBI trial concerning cosmetic outcome and toxicity are most likely to result from our preoperative approach, as the greater part of the the high-dose radiation area of the breast is excised. Another advantage of preoperative irradiation is more accurate tumor delineation enabling smaller treatment volumes, as we have shown in a previous study.[10] Our mean PTV volume was 150.16 cm^3. Despite preoperative radiation therapy, we observed an acceptable postoperative infection rate of 11%. For comparison, in the Cambridge IMRT trial a postoperative infection rate of 19% was reported.[36] Lower infection rates of 1% to 3% have been documented during postoperative radiation therapy in other studies with conventional whole breast radiation therapy.[37,38] However, the infection rate may depend on the registration and the time of evaluation. The postoperative assessment in our trial was meticulously performed.

Some patients may have received antibiotics as a precautionary measure and not as treatment of a postoperative infection. Complications were scored 15 days (median) after surgery, which is at an earlier time point than during (postoperative) radiation therapy. In 4 patients (3%), seroma was scored once past the postoperative assessment after a median time of 55 days. This rate of long-term seroma is comparable to conventional postoperative radiation therapy with grade 1 seroma in 10% and 0% to 2% grade 2 seroma of patients after 6 months.[38]

To the best of our knowledge, this is the largest trial investigating preoperative APBI and has the longest follow-up. Only a few studies investigated preoperative APBI. Horton et al investigated single-dose radiation therapy (15, 18, or 21 Gy) in a small study with 32 patients. After a median follow-up of 23 months, no recurrences were detected, and only grade 1 to 2 toxicities and good to excellent cosmetic outcome in all patients was reported.[13] Nichols et al also reported limited toxicity and good to excellent cosmetic outcome after a median follow-up of 3.6 years in 27 patients treated with preoperative APBI (38.5 Gy in 3.85 Gy fractions delivered twice daily), followed by breast-conserving surgery after 21 days.[14] Novel trials involving preoperative APBI have been initiated.[39] Translational research associated with our PAPBI trial[40] and other trials might also provide more insight into radiation response.

In this study, IBTRs were detected in 4 patients (3%), 3 of which were located in the biopsy tract. The finding of malignant seeding along the biopsy tract was unexpected and has not been reported in other APBI studies. After adjustment of the protocol in 2015, no recurrences along the biopsy track have been detected. However, longer follow-up time is needed to assess efficacy. Long-term results concerning the efficacy of APBI originate from trials investigating brachytherapy, showing equivalent local control.[3,5] More recent trials investigated IORT and EBRT, and most trials showed equivalent local control.[4,6,41] However, adequate patient selection remains important.

A number of limitations of our study need to be acknowledged. We performed a single-arm phase 2 study, with a limited number of patients and 5 years of follow-up. For patients treated with 5 × 6 Gy median follow-up was 3.6 years. Although no differences between the treatment schedules were observed, longer follow-up is needed to draw firm conclusions. A disadvantage of our preoperative approach is an additional procedure resulting from the sentinel node procedure, which is needed for appropriate patient selection. Because studies are currently running to withdraw the sentinel node procedure in low-risk patients, this might be overcome in the future. The analysis of cosmetic outcome as scored by the BCCT.core was restricted by the limited number of available photographs. However, cosmetic outcome was assessed in several ways, and overall a sufficient number of cosmetic assessments was available to draw conclusions.

Conclusions

PAPBI is a feasible method with low acute and late toxicity and excellent cosmetic outcome. Our encouraging results have led to a randomized controlled trial, the PAPBI-II trial (started in 2017) comparing preoperative to postoperative APBI (IMRT 28.5 Gy in 5 fractions over 1 week) with cosmetic outcome as the primary outcome (NCT02913729).

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