5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial

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Summary

Background In a phase 3, randomised, non-inferiority trial, accelerated partial breast irradiation (APBI) for patients with stage 0, I, and IIA breast cancer who underwent breast-conserving treatment was compared with whole-breast irradiation. Here, we present 5-year follow-up results.

Methods We did a phase 3, randomised, non-inferiority trial at 16 hospitals and medical centres in seven European countries. 1184 patients with low-risk invasive and ductal carcinoma in situ treated with breast-conserving surgery were centrally randomised to either whole-breast irradiation or APBI using multicatheter brachytherapy. The primary endpoint was local recurrence. Analysis was done according to treatment received. This trial is registered with ClinicalTrials.gov, number NCT00402519.

Findings Between April 20, 2004, and July 30, 2009, 551 patients had whole-breast irradiation with tumour-bed boost and 633 patients received APBI using interstitial multicatheter brachytherapy. At 5-year follow-up, nine patients treated with APBI and five patients receiving whole-breast irradiation had a local recurrence; the cumulative incidence of local recurrence was 1·44% (95% CI 0·51–2·38) with APBI and 0·92% (0·12–1·73) with whole-breast irradiation (difference 0·52%, 95% CI −0·72 to 1·75; p=0·42). No grade 4 late side-effects were reported. The 5-year risk of grade 2–3 late side-effects to the skin was 3·2% with APBI versus 5·7% with whole-breast irradiation (p=0·08), and 5-year risk of grade 2–3 subcutaneous tissue late side-effects was 7·6% versus 6·3% (p=0·53). The risk of severe (grade 3) fibrosis at 5 years was 0·2% with whole-breast irradiation and 0% with APBI (p=0·46).

Interpretation The difference between treatments was below the relevance margin of 3 percentage points. Therefore, adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery in patients with early breast cancer is not inferior to adjuvant whole-breast irradiation with respect to 5-year local control, disease-free survival, and overall survival.

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Introduction

Breast cancer is the most common cancer diagnosed in women in Europe. Previous uncertainties about the role of adjuvant radiation therapy after breast-conserving surgery have been clarified after publication of randomised trials showing the benefits of radiation therapy added to breast-conserving surgery, and adjuvant radiation therapy became widely accepted as standard for the treatment of early-stage breast cancer over the past three decades.[1] The standard technique of radiation therapy after breast-conserving surgery is to treat the entire breast up to a total dose of 40–50 Gy, with or without a tumour-bed boost.[2] Despite the evident equivalence of breast-conserving therapy with adjuvant whole-breast irradiation compared with mastectomy alone, up to 50% of patients in the USA who are clinically qualified for breast conservation still undergo mastectomy with the goal to omit radiation therapy.[3] One of the most important reasons for underuse of breast-conserving treatment is the length of adjuvant radiation therapy.

Accelerated partial breast irradiation (APBI) is an attractive treatment strategy, not only to shorten the course of radiation therapy from 3–7 weeks to 2–5 days but also to very effectively reduce radiation exposure to the breasts, the skin, the lungs, and, in particular, the heart.[4] Over the past 15 years, different modalities of APBI have been introduced into clinical practice.[5–11] Several phase 2 trials[9] and one small single-institution

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For the **protocol** see http://www.apbi.uni-erlangen.de/outline/EUROPEAN_BRACHYTHERAPY_PHASE_III_Trial_final_Edition_2004.pdf

Research in context

Systematic review

We searched PubMed and MEDLINE for any prospective studies published in English, and ClinicalTrials.gov for studies ongoing or completed, in which accelerated partial breast irradiation (APBI) alone was investigated as an adjuvant treatment modality after breast-conserving surgery. Our search terms were: "early breast cancer", "radiation therapy", "partial breast irradiation", "accelerated partial breast irradiation", "APBI", "brachytherapy", "multicatheter brachytherapy", "balloon brachytherapy", "intraoperative irradiation", "IORT", and "adjuvant therapy". We identified only a few phase 2 trials with mature results, mostly showing low recurrence after breast-conserving treatment and APBI, which were comparable with adjuvant whole-breast irradiation. However, questions remained, particularly with respect to patients' selection and whether equivalence of recurrence can also be observed in the era of modern adjuvant systemic therapies and modern surgical techniques. Additional uncertainty originated with respect to the technique of APBI; alongside the proven approach of multicatheter brachytherapy, different techniques were tested, including single-balloon brachytherapy, intraoperative irradiation with a linear accelerator, and a 50 kV x-ray device and external beam radiation therapy. Hence, we initiated a randomised trial to investigate the value of multicatheter brachytherapy for APBI as sole adjuvant radiation therapy for selected patients with early invasive and in-situ breast cancer. Our aim was to prove non-inferiority compared with conventional whole-breast irradiation with respect to local recurrence, disease-free survival, and overall survival.

Added value of this study

Our long-term follow-up outcomes show that APBI using multicatheter brachytherapy yields equivalent local control, disease-free survival, and overall survival after breast-conserving treatment compared with conventional whole-breast irradiation. In view of the exceptionally low overall recurrence in our trial (about 1% at 5 years), we believe that our selection criteria are adequate. The equivalence of local recurrence was evident in all age groups, in all histological subgroups, and was independent of the type of systemic therapy. However, the very low number of events limited the statistical power of subgroup analyses, which will be done with longer follow-up. Obviously, the selected technique of APBI (multicatheter brachytherapy) is a technique with high versatility, flexibility, reproducibility, and quality standards. Our findings contrast with disappointing and controversial results reported in recent phase 3 trials with other APBI techniques (eg, intraoperative and external beam radiation therapy).

Implication of all the available evidence

Our trial is the first phase 3 study proving non-inferiority of APBI compared with whole-breast irradiation for selected patients with early-stage breast cancer. Based on our results, APBI using multicatheter brachytherapy can be regarded as a valid alternative treatment option after breast-conserving surgery and can be offered for all low-risk breast cancer patients in clinical routine.

phase 3 trial,[5] in which multicatheter interstitial brachytherapy was used for delivery of APBI, have shown promising long-term local control and cosmetic outcomes, comparable with the results of whole-breast irradiation series. Results of other clinical trials using alternative APBI techniques have been inconclusive or negative.[7,9–12]

To our knowledge, our prospective, randomised, phase 3 trial is the first to compare the efficacy of conventional whole-breast irradiation plus tumour-bed boost with APBI using exclusively multicatheter interstitial brachytherapy. The analysis presented here reports 5-year local control and survival outcomes. We assessed whether APBI using multicatheter brachytherapy yields is non-inferior to whole-breast irradiation with respect to local control in patients with low-risk invasive carcinoma and low-risk ductal carcinoma in situ (DCIS) of the female breast after breast-conserving treatment, and whether this non-inferiority translates into disease-free survival and overall survival. Basic findings on treatment-related late side-effects are also reported. However, a detailed analysis on patients' adherence, early and late side-effects, quality of life, and cosmetic results will be reported elsewhere.

Methods

Study design

We analysed long-term results from the Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO) multicentre, phase 3, randomised controlled trial. The trial was undertaken at 16 hospitals and medical centres in Austria, Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland. Ethics committees of the participating institutes approved the protocol, which is available online.

Patients

Patients were considered eligible for the trial if they were aged 40 years or older, had pTis or pT1–2a (lesions of ≤3 cm diameter), pN0/pNmi, and M0 breast cancer (stage 0, I, and IIA), had undergone local excision of the breast tumour with microscopically clear resection margins of at least 2 mm in any direction (in cases of invasive lobular carcinoma or DCIS, at least 5 mm), and had no lymph or blood-vessel invasion (L0, V0). Resection margins were assessed for the presence of invasive carcinoma and for DCIS. Among DCIS lesions, only those classified as low or intermediate risk

(Van Nuys prognostic index <8)—ie, lesions with a low risk of recurrence[13]—were eligible for the study. For patients with invasive carcinoma, either an axillary dissection with minimum of six nodes in the specimen or a negative sentinel node was required; in case of pure DCIS, axillary staging—ie, sentinel lymph node biopsy—was optional. The time interval between breast-conserving surgery and radiation therapy was set at less than 12 weeks. For patients who received adjuvant chemotherapy, radiation therapy was allowed to start later, but within 4 weeks after the end of adjuvant chemotherapy. Patients were excluded if they were younger than 40 years, had multiple tumour foci or an extensive intraductal component, had Paget's disease or pathological skin involvement, had synchronous or previous breast cancer, had a history of other malignant disease, or were pregnant or lactating.

We included all eligible patients in our analyses. We obtained written informed consent according to Good Clinical Practice guidelines and local and national rules of participating institutes.

Randomisation and masking

Patients were randomised centrally at the Department of Medical Informatics, Biometry and Epidemiology, University Erlangen-Nuremberg, Germany, via an online interface. The randomisation was stratified by study centre, menopausal status, and tumour type (eg, invasive carcinoma *vs* DCIS), with a block size of ten, according to an automated dynamic algorithm. Patients were allocated in a 1:1 ratio to receive either whole-breast irradiation with a tumour-bed boost or APBI using multicatheter brachytherapy targeted to the original tumour bed. Neither patients nor investigators were masked to treatment allocation.

Procedures

All patients had to undergo surgical excision of the primary tumour, with a clear resection margin of at least 2 mm (with lobular or DCIS histology, at least 5 mm); in case of invasive disease, surgical axillary staging was also done (eg, sentinel lymph node biopsy or axillary dissection). Patients with risk factors for systemic disease received adjuvant systemic treatment according to local treatment protocols; in general, hormone receptor-negative and premenopausal patients received chemotherapy, and hormone receptor-positive patients received hormone therapy.

For patients allocated irradiation of the whole breast, two tangential opposing megavoltage (4–10 MV) photon beams were typically used. A total dose of 50·0–50·4 Gy was delivered to a reference point during a 5-week period, with daily fractions of 1·8–2·0 Gy in 25–28 fractions (appendix p 5), in agreement with International Commission of Radiation Units and Measurements (ICRU) report 50. The tumour-bed boost dose was 10 Gy in five fractions, delivered with electrons. The electron boost dose was prescribed to the point of maximal dose (D_{max}) on the beam axis, assuring that the 85% isodose line enclosed the tumour bed. Adequate field size, localisation, and electron energy was defined with fluoroscopic treatment simulator or CT scans. No dose reductions were allowed.

For patients allocated APBI, the clinical target volume consisted of the tumour bed with an adequate safety margin in all directions. The size of the safety margin (calculated as the sum of the width of the clear pathological surgical margin plus the radiation safety margin) had to be at least 20 mm, and this margin was defined individually for every patient. Preimplant CT (for planning of implant geometry) and post-implant CT (for treatment planning and documentation of multicatheter brachytherapy) were mandatory. Dose prescription and calculation was strictly in agreement with the ICRU 58 report. Geometric optimisation for volume implants was provided to keep the dose non-uniformity ratio (V100/V150) below 0·35. Dose-volume histogram analyses were also used to confirm that 100% of the prescribed dose covered at least 90% of the target volume (coverage index ≥0·9). The maximum skin dose was restricted to less than 70% of the prescribed dose. APBI was delivered with high-dose-rate (HDR) or pulsed-dose-rate (PDR) multicatheter brachytherapy. A total dose of 32·0 Gy in eight fractions (8×4·0 Gy) or 30·3 Gy in seven fractions (7×4·3 Gy), with fractionation twice a day, was used for HDR brachytherapy. A total dose of 50 Gy with pulses of 0·60–0·80 Gy/h (one pulse per h, 24 h/day) was given by PDR brachytherapy (appendix p 5).

Patients were followed up every 3 months for 2 years after radiation therapy, every 6 months for the next 3 years, and annually thereafter. Clinical examination included documentation of late side-effects with Common Terminology Criteria for Adverse Events and with the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema.[14] Follow-up mammography was scheduled at 6, 12, 18, and 24 months after radiation therapy and annually thereafter. Before starting radiation therapy and during follow-up, patients were asked to fill in a quality-of-life questionnaire (EORTC QLQ-C30) including the breast cancer module QLQ-BR23.[15]

Outcomes

The primary endpoint was ipsilateral local recurrence (tumour recurrence in the treated breast). We calculated the time to event with respect to local control from the date of breast-conserving surgery to the date of first local recurrence or to the day of last visit for patients alive and free of recurrence (censored cases). Secondary objectives were incidence and severity of acute and late side-effects, cosmesis, cumulative incidence of regional recurrence and distant metastasis, survival time (overall survival,

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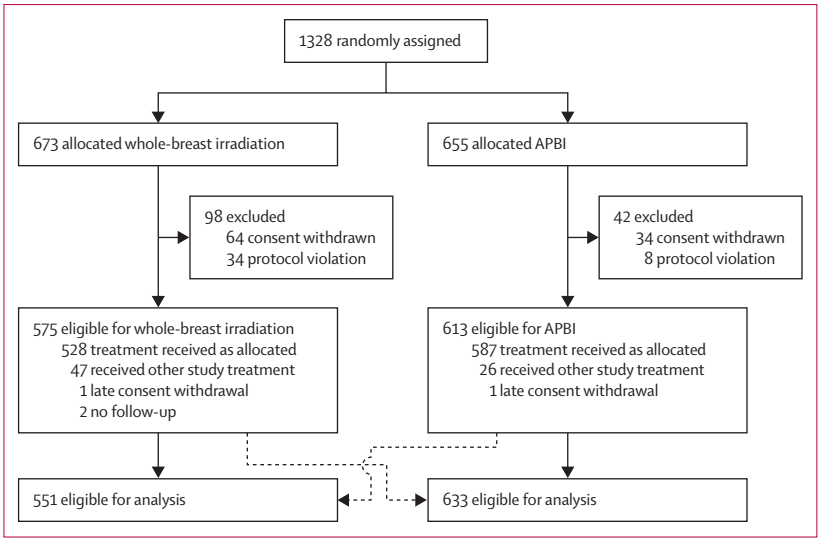

Figure 1: **Trial profile**
APBI=accelerated partial breast irradiation.

disease-free survival), the rate of contralateral breast cancer, and patients' quality of life. We defined time to event as the time from breast-conserving surgery to first diagnosis of the corresponding event. Detailed analyses of early and late side-effects, quality of life, and cosmetic results are not presented here.

The trial is registered with ClinicalTrials.gov, number NCT00402519.

Statistical analysis

The primary endpoint for analysis was the first event of local recurrence within a 5-year observation period. Our scientific hypothesis to be assessed and statistically tested (in a confirmative manner) was non-relevant non-inferiority of the experimental treatment (APBI) with respect to this primary endpoint. Compared with 5-year recurrence with standard treatment (whole-breast irradiation), we judged an absolute increase of up to 3 percentage points under the experimental treatment (APBI) as non-relevant non-inferior. Sample size planning is described in the appendix (p 1). We did the actual assessment of non-inferiority by relating the 95% CI of the difference between treatment groups in local recurrence at 5 years to a predefined acceptable, non-relevant difference, following current recommendations. Addressing non-inferiority, we deliberately did not analyse trial findings based on the intention-to-treat principle, because this approach sometimes introduces bias towards no difference, which is anticonservative in this setting—ie, would exaggerate estimates of equivalence. Instead, we did the primary analysis as treated, including all patients who received treatment according to the study protocol, albeit not necessarily the treatment that was randomly allocated (figure 1). As secondary (sensitivity) analyses, we did both a per-protocol analysis and an intention-to-treat analysis (appendix p 2), to examine consistency of results.

We estimated cumulative incidence by competing-risk analysis and disease-free survival and overall survival as dichotomous outcomes by Kaplan-Meier analysis. We have provided two-sided 95% CIs for differences between treatment groups for primary assessment. For further exploratory statistical testing of secondary outcomes, we used two-sided statistical tests and judged a p value less than 0·05 significant. We used either the log-rank test (for Kaplan-Meier analysis) or Fine and Gray tests (for the effect of group allocation on cumulative incidences). We did analyses with *R* statistical software (version 3.1.3), in particular with the packages *etm* (for generating transition matrices and estimation), *cmprsk* (for Fine and Gray tests), and *coin* (for Monte Carlo approximation of the exact p value of the log-rank test).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 20, 2004, and July 30, 2009, 1328 women with early-stage breast cancer underwent lumpectomy and had corresponding clear resection margins. All patients were randomised to either whole-breast irradiation of 50 Gy with a tumour-bed boost of 10 Gy (n=673) or APBI using multicatheter brachytherapy (n=655). After randomisation, 98 patients allocated whole-breast irradiation and 42 assigned APBI either withdrew their consent or were excluded because of an administrative error. Moreover, after learning the result of the randomisation, a few patients refused the allocated treatment and asked to receive the other study treatment. Therefore, 551 patients were treated with whole-breast irradiation and 633 patients with APBI (figure 1). These 1184 patients were included in the as-treated analyses.

Median follow-up was 6·6 years (IQR 5·8–7·6) and the median age of patients at treatment was 62 years (IQR 54–68). 1124 (95%) patients had invasive carcinoma and in 1015 (86%) women the primary tumour was 2 cm or smaller (pT1). Patients' and tumour characteristics were similar between treatment groups, as was adjuvant treatment with either chemotherapy or hormone therapy (table 1).

541 (98%) of 551 patients who had whole-breast irradiation received the complete prescribed dose of 60 Gy (50 Gy+10 Gy boost), and ten (2%) received between 50 and 60 Gy. All 633 patients in the experimental APBI arm (PDR n=119, HDR with seven fractions n=59, HDR with eight fractions n=451) received the complete prescribed dose. The volume of the reference isodose in APBI-treated patients ranged from 7 cm^3 to 275 cm^3 (median 81 cm^3). Further details will be published elsewhere.

	APBI group (n=633)	WBI group (n=551)
Age (years)		
Median (IQR)	62 (54–67)	62 (54–68)
>40–50	91 (14%)	91 (17%)
>50–60	192 (30%)	162 (29%)
>60–70	256 (40%)	202 (37%)
>70	94 (15%)	96 (17%)
Menopausal status		
Premenopausal	108 (17%)	92 (17%)
Postmenopausal	525 (83%)	459 (83%)
Performance status		
0	604 (95%)	520 (94%)
1–2	26 (4%)	30 (5%)
Unknown	3 (<1%)	1 (<1%)
Tumour size and resection margins		
Tumour diameter (mm)	12 (9–17)	12 (9–17)
Surgical free margins (mm, range)	8 (2–40)	7 (2–25)
T stage		
pTis (DCIS)	36 (6%)	24 (4%)
pT1mi	0	4 (1%)
pT1a	30 (5%)	21 (4%)
pT1b	187 (30%)	182 (33%)
pT1c	313 (49%)	262 (48%)
pT2 (≤3 cm)	67 (11%)	58 (11%)
N stage		
pN0	127 (20%)	118 (21%)
pN0 sn	470 (74%)	408 (74%)
pN1 mi	5 (1%)	5 (1%)
No data	31 (5%)	20 (4%)
Grading		
1	248 (39%)	217 (39%)
2	319 (50%)	288 (52%)
3	57 (9%)	42 (8%)
No data	9 (1%)	4 (1%)
Histological subtype		
Ductal	453 (72%)	424 (77%)
Lobular	85 (13%)	49 (9%)
Tubular	38 (6%)	36 (7%)
Mucinous	14 (2%)	13 (2%)
Papillary	5 (1%)	4 (1%)
Medullary	2 (<1%)	1 (<1%)
Unknown	36 (6%)	24 (4%)
Hormone receptor status		
ER+/PR+	510 (81%)	447 (81%)
ER–/PR+	5 (1%)	6 (1%)
ER+/PR–	69 (11%)	56 (10%)
ER–/PR–	34 (5%)	29 (5%)
Unknown	15 (2%)	13 (2%)
Systemic treatment		
Yes	572 (90%)	505 (92%)
No	59 (9%)	46 (8%)
No data	2 (<1%)	0
Antihormonal treatment		
Yes	549 (87%)	482 (87%)
No	82 (13%)	69 (13%)
No data	2 (<1%)	0
Chemotherapy		
Yes	63 (10%)	65 (12%)
No	568 (90%)	486 (88%)
No data	2 (<1%)	0

(Table 1 continues in next coloumn)

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Data are number (%) or median (IQR), unless otherwise stated. DCIS=ductal carcinoma in situ. ER=oestrogen receptor. PR=progesterone receptor. *p value was calculated for the difference in the distribution of a factor across the two treatment groups (analysed by treatment as received), using Wilcoxon's test and Fisher's exact test, as appropriate.

Table 1: **Patient, tumour, and adjuvant treatment characteristics**

At 5-year follow-up, five of 551 women treated with whole-breast irradiation and nine of 633 who received APBI had a local recurrence. The cumulative incidence of local recurrence at 5 years was 0·92% (95% CI 0·12–1·73) with whole-breast irradiation versus 1·44% (0·51–2·38) with APBI (difference 0·52%, 95% CI –0·72 to 1·75; p=0·42; figure 2). As a sensitivity analysis, a per-protocol analysis of all patients receiving treatment as randomly allocated was done (n=525 whole-breast irradiation, n=586 APBI). 5-year local recurrence was 0·97% (95% CI 0·12–1·81) in patients assigned whole-breast irradiation and 1·38% (0·43–2·33) in those allocated APBI (difference 0·41%, 95% CI –0·86 to 1·69; p=0·53), which was consistent with the as-treated primary analysis. Further supplemental analyses are presented in the appendix (pp 1–2).

At 5-year follow-up, regional recurrences were reported in one of 551 women who had whole-breast irradiation and three of 633 who had APBI, and distant metastases occurred in five and five patients, respectively. The cumulative incidence of regional (lymph node) recurrence at 5 years was 0·18% (95% CI 0·00–0·54) with whole-breast irradiation and 0·48% (0·00–1·02) with APBI (difference 0·30%, 95% CI –0·35 to 0·95; p=0·39). The cumulative incidence of distant metastases at 5 years was 0·93% (95% CI 0·12–1·74) with whole-breast irradiation and 0·80% (0·10–1·50) with APBI (difference –0·13%, 95% CI –1·20 to 0·94; p=0·81). 5-year disease-free survival was 94·45% (95% CI 92·54–96·4) with whole-breast irradiation and 95·03% (93·34–96·75) with APBI (difference 0·58%, 95% CI –2·00 to 3·16; p=0·79; figure 3). At the time of analysis, 32 (6%) of 551 patients who received whole-breast irradiation had died compared with 27 (4%) of 633 patients who received APBI. Breast cancer-related mortality did, hitherto, not differ between groups (four events *vs* four events; p=0·84). 5-year overall survival was 95·55% (95% CI 93·82–97·31) with whole-breast irradiation versus 97·27% (96·00–98·56)

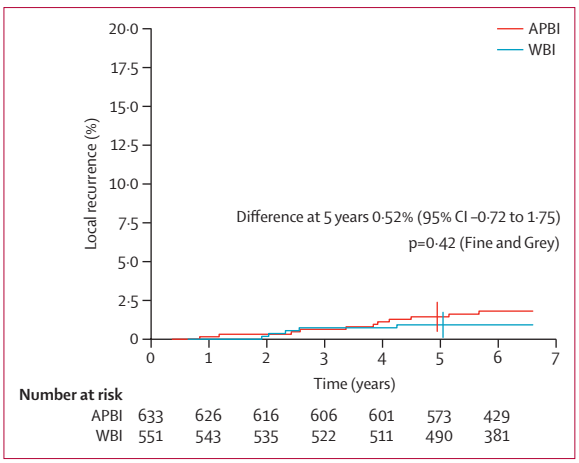

Figure 2: **Ipsilateral breast tumour recurrence**
APBI=accelerated partial breast irradiation. WBI=whole-breast irradiation.

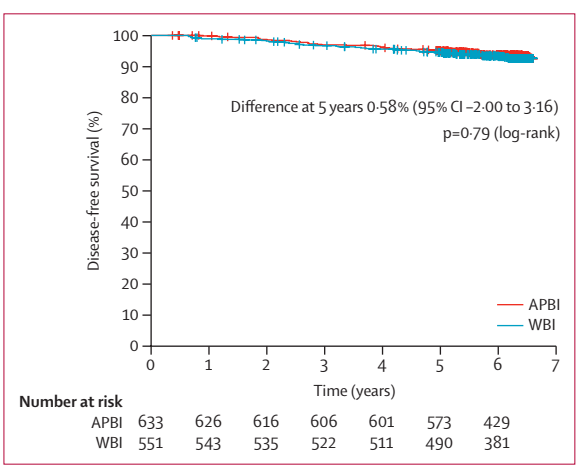

Figure 3: **Disease-free survival**
APBI=accelerated partial breast irradiation. WBI=whole-breast irradiation.

with APBI (difference 1·72%, 95% CI −0·44 to 3·88; p=0·11; figure 4).

The absolute risk of ipsilateral breast tumour recurrence and of overall recurrence was not associated with age (table 2), and this finding remained after stratification by treatment (data available on request). However, overall survival was reduced for older patients, possibly because of age-related comorbidities, whereas breast cancer-related death was not associated with age at inclusion (p=0·35). Overall, at 5-year follow-up, of 14 ipsilateral breast tumour recurrences, eight occurred in the primary tumour bed, two arose close to the edge of the tumour bed (so-called marginal miss), and four were outside the original tumour bed (so-called elsewhere failure).

At 5-year follow-up, five of 551 patients who had whole-breast irradiation and five of 633 who received APBI had a second primary tumour in the contralateral breast, and 13 and 27 patients, respectively, had a second tumour at a site other than the breast. The cumulative

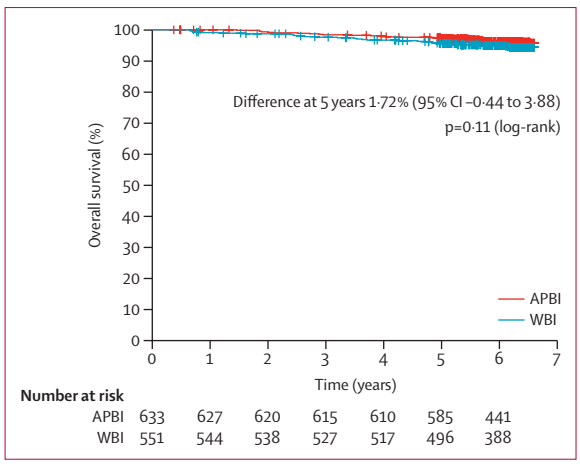

Figure 4: **Overall survival**
APBI=accelerated partial breast irradiation. WBI=whole-breast irradiation.

incidence of a second primary contralateral tumour was 0·96% (95% CI 0·12–1·79) with whole-breast irradiation and 0·81% (0·10–1·51) with APBI (difference −0·15%, 95% CI −1·24 to 0·94; p=0·81). The cumulative incidence of a second primary tumour at sites other than the breast was 2·47% (95% CI 1·14–3·79) with whole-breast irradiation and 4·36% (3·79–4·36) with APBI (difference 1·89%, 95% CI 0·19–3·97; p=0·778). Second primary ipsilateral breast cancers (different histology compared with the primary tumour) arose in four of 551 patients who received whole-breast irradiation and three of 633 who had APBI. The cumulative incidence of a second primary ipsilateral tumour was 0·75% (95% CI 0·02–1·49) with whole-breast irradiation and 0·49% (0·00–1·04) with APBI (difference −0·27%, 95% CI −1·18 to 0·65; p=0·56).

At 5 years, mastectomy as initial salvage treatment for ipsilateral breast tumour recurrence was done for one of 633 patients who received APBI but none who received whole-breast irradiation. The cumulative incidence of salvage mastectomy at 5 years was thus 0% (95% CI 0·00–0·60) with whole-breast irradiation and 0·16% (0·00–0·47) with APBI (p=0·35). Lumpectomy was the salvage treatment for four of 551 patients who had whole-breast irradiation and two of 633 who received APBI (including women who also had chemotherapy or antihormonal therapy and those who had excision of secondary tumours of the ipsilateral and contralateral breast). The cumulative incidence of lumpectomy at 5 years was, thus, 0·76% (95% CI 0·02–1·50) with whole-breast irradiation and 0·33% (0·00–0·78) with APBI (difference −0·43%, 95% CI −1·30 to 0·44; p=0·31). Systemic chemotherapy or hormone therapy was used as salvage treatment in four (1%) of 551 patients who received whole-breast irradiation and four (1%) of 633 who had APBI. The cumulative incidence of salvage chemotherapy or hormone therapy at 5 years was 0·54% (95% CI 0·01–1·84) with whole-breast irradiation and

	Events (n)	Incidence (95% CI)	p value
Local recurrence			
Age <50 years	3	2·26% (0·00–4·78)	0·2348
Age ≥50 years	11	1·07% (0·44–1·69)	..
Age 50–70 years	9	1·07% (0·37–1·76)	0·4937
Age >70 years	2	1·06% (0·00–2·52)	..
Overall recurrence			
Age <50 years	4	2·99% (0·10–5·87)	0·6236
Age ≥50 years	24	2·33% (1·41–3·25)	..
Age 50–70 years	20	2·37% (1·34–3·40)	0·8717
Age >70 years	4	2·13% (0·06–4·19)	..
Overall survival			
Age<50 years	2	98·50% (96·45–100)	0·2142
Age ≥50 years	39	96·21% (95·05–97·38)	..
Age 50–70 years	22	97·39% (96·31–98·47)	<0·0001
Age >70 years	17	90·92% (86·88–95·13)	..

Whole study population (n=1184).

Table 2: **5-year cumulative incidence of ipsilateral breast tumour recurrence, overall recurrence (local, regional, or distant metastasis), and overall survival, by age**

0·32% (95% CI 0·01–1·61) with APBI (difference –0·22%, 95% CI –1·15 to 0·71; p>0·99). No information about salvage treatment for ipsilateral or contralateral secondary breast tumours was available for one patient who received whole-breast irradiation and three who had APBI.

No grade 4 late side-effects were recorded during the follow-up period. At 5-year follow-up, data for late side-effects were available for 969 patients (n=442 whole-breast irradiation, n=527 APBI). Grade 2–3 late side-effects of the skin were recorded in 25 (6%) women who had whole-breast irradiation and 17 (3%) who received APBI, and grade 2–3 subcutaneous tissue effects were noted in 28 (6%) and 40 (8%), respectively. The risk of grade 2–3 late skin side-effects at 5 years was 5·66% with whole-breast irradiation versus 3·23% with APBI (difference –2·43%, 95% CI –5·06 to 0·20; p=0·0807). With respect to grade 2–3 late subcutaneous tissue effects at 5 years, the risk was 6·33% with whole-breast irradiation versus 7·59% with APBI (difference 1·26%, 95% CI –1·94 to 4·46; p=0·5281). Severe (grade 3) fibrosis was reported in one woman who had whole-breast irradiation and in none of those who received APBI. The risk of grade 3 fibrosis at 5 years was 0·23% with whole-breast irradiation and 0% with APBI (difference –0·23%, 95% CI –0·67 to 0·21; p=0·4561). Grade 2–3 breast pain was reported in 14 women who had whole-breast irradiation and six of those who received APBI. The risk of grade 2–3 breast pain was low in both treatment groups (3·17% after whole-breast irradiation and 1·14% after APBI; difference –2·03%, 95% CI –3·90 to –0·16; p=0·0389). Detailed analyses on late side-effects, including cosmesis, will be published separately.

Discussion

Our findings show that local recurrence was equivalent between the standard treatment (whole-breast irradiation) and the experimental treatment (APBI). The difference in 5-year cumulative incidence between groups was 0·52% (95% CI –0·72 to 1·75; p=0·42). With respect to the prespecified acceptable absolute increase of local recurrence by 3 percentage points, the 95% CI does not include this threshold criterion. Hence, non-inferiority with respect to the 5-year rate of local recurrence has been confirmed.

Adjuvant radiation therapy after breast-conserving surgery reduces the risk of local recurrence in the ipsilateral breast by about 70%,[1,16,17] accompanied by a substantial improvement in breast cancer-specific and overall survival at 15 years.[1] Despite these well-known facts, oncologists are often faced with underuse of adjuvant external-beam radiation therapy.[3] The reasons include, but are not restricted to, patients' lack of acceptance of the inconvenience caused by the prolonged course of external beam irradiation. Other concerns include the slightly increased risk of death after adjuvant whole-breast irradiation due to radiation-induced heart disease (relative risk 1·27; p=0·001)[1,17] and that exposure of the heart to ionising radiation amplifies the subsequent risk of ischaemic heart disease by 7·4% per Gy (95% CI 2·9–14·5; p<0·001) with no apparent threshold.[18] Accordingly, at least fourfold higher doses of radiation to the heart have been reported with advanced whole-breast irradiation techniques, compared with multicatheter brachytherapy.[4] These reasons could be why gynaecologists and medical oncologists, in particular, are reluctant to use adjuvant radiation therapy after breast-conserving surgery. Moreover, adjuvant whole-breast irradiation slightly raises the risk of secondary malignant disease (eg, sarcomas and lung cancer),[19] and the higher risk seemingly correlates with the irradiated volume of organs at risk. Subsequently, several approaches to deliver adjuvant radiation therapy for breast cancer have been developed to reduce cardiac and lung dose,[17] including the prone-position technique, intensity-modulated and breathing-adapted image-guided radiation therapy, and APBI. APBI offers the largest reduction in radiation dose to surrounding healthy tissues. Since the pioneering investigations of King and colleagues in the 1990s,[20,21] several groups have investigated different techniques of APBI, mostly with promising results.[7–10] During the past 10–15 years, several phase 3 randomised trials of different APBI techniques have been done, and some long-term results have been published.[11,22–27] Finally, some trials have tested the possibility of omitting radiation therapy altogether for patients with low-risk breast cancer who were aged 65–70 years or older.[28–30]

To date, two randomised clinical trials (the ELIOT and TARGIT trials) have investigated the use of intraoperative radiotherapy for delivery of APBI.[7,11] Unfortunately, because no final pathology report was available at the

time of intraoperative radiotherapy, no strict and clear selection criteria for patients could be used in these trials. This drawback could account for the significantly higher proportion of recurrences at 5 years with intraoperative radiotherapy than with whole-breast irradiation in the ELIOT trial (4·4% *vs* 0·4%; hazard ratio 9·3).[11] The confusing design of the TARGIT trial (allowing optional use of whole-breast irradiation in the APBI arm after intraoperative radiotherapy), and the use of a low-energy (50 kV) x-ray device attenuating steeply to a very low total dose of 5 Gy at 1 cm distance from the tumour bed, raised concerns about this APBI technique.[7] Perhaps as a result, in the TARGIT trial, the criterion for non-inferiority of recurrence has not been met (3·3% [95% CI 2·1–5·1] after intraoperative radiotherapy *vs* 1·3% [0·7–2·5] after whole-breast irradiation; p=0·042), but follow-up is still very short (median 2·4 years).[7,12]

Use of external beam radiation therapy for delivery of APBI seems to be very attractive, because this technique is broadly available and easy to do. Unfortunately, until now, the reported results of phase 3 APBI trials using external beam radiation therapy either are disappointing or have low statistical power. Olivotto and colleagues[23] reported that APBI with three-dimensional conformal external beam radiation therapy (3D-CRT) significantly increased the rates of adverse cosmetic results and late side-effects. After median follow-up of 36 months, adverse cosmesis at 3 years was higher among patients treated with 3D-CRT APBI compared with whole-breast irradiation, as assessed by trained nurses (29% *vs* 17%; p=0·0001) and by patients (26% *vs* 18%; p=0·002). Cumulatively, 1·4% of 3D-CRT APBI patients had a grade 3 adverse event compared with none of those allocated whole-breast irradiation.[23] By contrast, in a very small randomised trial (n=105), Rodriguez and colleagues[25] reported similar efficacy, side-effects, and cosmesis for patients treated with either 3D-CRT APBI or whole-breast irradiation, but this trial must probably be regarded as under-powered to detect relevant differences between the treatment arms. In the recent clinical trial of Livi and co-workers,[27] 520 patients were randomised and treated with APBI using intensity-modulated external beam radiation therapy or whole-breast irradiation with boost and, after median follow-up of 5 years in both treatment groups, recurrence was reported in 1·5% of patients, with significantly better results with respect to acute (p=0·0001), late (p=0·004), and cosmetic outcomes (p=0·045) in the APBI arm. However, the statistical power of this study with respect to the proof of non-inferiority of recurrence was also limited.

Use of multicatheter interstitial brachytherapy for APBI has been tested, until now, in only one single-institution phase 3 trial. Polgar and colleagues[22] randomised 258 patients with early-stage invasive breast cancer to receive either 50 Gy whole-breast irradiation (n=130), APBI with multicatheter HDR brachytherapy (n=88), or APBI with electron beam irradiation (n=40). After median follow up of 10·2 years, the proportion of patients with local recurrence at 10 years was 5·9% (95% CI 1·6–10·2) after APBI and 5·1% (1·1–9·1) with whole-breast irradiation (p=0·767). The proportion of women with excellent-to-good cosmetic results was 81% with APBI and 63% with whole-breast irradiation (p<0·01). However, similar to the trials of Rodriguez and colleagues[25] and Livi and co-workers,[27] the number of patients randomised in the study by Polgar and colleagues[22] limited the statistical power of the trial to confirm non-inferiority.

Omission of adjuvant whole-breast irradiation for low-risk tumours has been investigated in some phase 3 trials.[28–30] Pötter and co-workers[30] reported, in patients with favourable early breast cancer, not only a higher proportion of local recurrence with no radiation therapy (5·1% *vs* 0·4%; hazard ratio 10·2; p=0·0001) and lower 5-year disease-free survival (hazard ratio 3·48; p=0·002) but also no significant difference in 5-year overall survival (96·2% *vs* 97·9%). Hughes and colleagues[28] randomly allocated patients aged 70 years or older with stage I breast cancer to receive either tamoxifen plus radiation therapy, or tamoxifen alone. At 10-year follow-up, 98% of patients were free from local and regional recurrences with tamoxifen plus radiation therapy compared with 90% with tamoxifen alone. Time to distant metastasis, breast cancer-specific survival, and overall survival did not differ between groups. Similar results have been reported by Kunkler and colleagues[29] in patients aged 65 years or older with early breast cancer (up to 3 cm). After median follow-up of 5 years, ipsilateral breast tumour recurrence was 1·3% in women assigned whole-breast irradiation and 4·1% in those assigned no radiation therapy (p=0·0002), whereas no differences were recorded between groups with respect to regional recurrences, distant metastases, and overall survival.

By contrast, in our trial, we noted few local recurrences at 5 years in both study groups (about 1% in both groups) and a low incidence of all serious, late side-effects (around 3% in both groups). Thus, we were able to confirm non-inferiority of APBI using multicatheter brachytherapy to conventional whole-breast irradiation. Because of the very low proportion of recurrences in both study groups, we believe our chosen selection criteria are appropriate. However, the very low number of recurrences in both groups is also a limitation of our study. At the present stage (median follow-up 6·6 years), the low number of events has precluded subgroup analyses with sufficient statistical power (eg, in patients younger than 50 years, those with lobular carcinoma, individuals with DCIS, or patients with grade 3 tumours). Substantially longer follow-up (eg, 10 years) and more events will be necessary to evaluate the role of APBI in these subgroups of patients. Since a rapid improvement in local recurrence for early breast cancer in recent years is obvious, the power calculation at the start of a trial more than 10 years ago becomes less representative.

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Another limitation of our trial was the lack of central pathology review. However, exact values of margins of the surgical specimen were recorded for all patients at every participating centre, and the 5-year cumulative risk of local breast cancer relapse as a first event was not significantly affected by either the histological type of the primary tumour (eg, lobular carcinoma *vs* all others) or the width of free surgical margins. In this context, findings of the largest randomised trial of APBI to date (the ongoing NSABP B-39/RTOG 0413 trial), including more than 4000 patients, will hopefully give further important information about the efficacy of APBI in different prognostic subgroups of patients. However, most patients (about 80%) in the APBI group have been treated with 3D-CRT, and only a few (about 15–20%) have received different techniques of brachytherapy. Therefore, it remains to be seen how various techniques of APBI affect the results.

In conclusion, our phase 3 APBI trial is the first trial designed and implemented to judge the value of APBI using multicatheter brachytherapy alone. Our results confirm that adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery is as effective as adjuvant whole-breast irradiation for carefully selected patients with early breast cancer. Moreover, at least during the first 5 years of follow-up, efficacy is independent of a patient's age and tumour characteristics. Although availability of multicatheter APBI expertise is scarce in some countries, we believe that our positive results that prove non-inferiority of multicatheter APBI to whole-breast irradiation (by contrast with those of the ELIOT and TARGIT trials that failed to prove non-inferiority of intraoperative radiotherapy) will at least partly change clinical practice, and that more radiation oncologists will consider interstitial brachytherapy as a valid option for the treatment of breast cancer patients.

Contributors

VS, CP, WU, TM, and OJO designed the study. GH, DK-D, HK, JL, JLG, JD, CGM, PS, MA, KL, BP, GK, A-RF, TGW, RF, MH, AR, AK, LA, PN, FG, AS, and RP recruited patients and obtained data. WU, CG, and MM analysed data. VS, CP, OJO, CG, and WU interpreted data and wrote the first draft. All authors revised the report and approved the final submitted version.

Declaration of interests

VS declares a grant from German Cancer Aid during the conduct of the study and consultation fees from Nucletron Operations BV, an Elekta Company, outside the submitted work. All other authors declare no competing interests.

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References

1 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366:** 2087–106.

2 Bartelink H, Maingon P, Poortmans P, et al, on behalf of the European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015; **16:** 47–56.

3 Showalter SL, Grover S, Sharma S, Lin L, Czerniecki BJ. Factors influencing surgical and adjuvant therapy in stage I breast cancer: a SEER 18 database analysis. *Ann Surg Oncol* 2013; **20:** 1287–94.

4 Lettmaier S, Kreppner S, Lotter M, et al. Radiation exposure of the heart, lung and skin by radiation therapy for breast cancer: a dosimetric comparison between partial breast irradiation using multicatheter brachytherapy and whole breast teletherapy. *Radiother Oncol* 2011; **100:** 189–94.

5 Polgar C, Major T, Fodor J, et al. Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. *Radiother Oncol* 2010; **94:** 274–79.

6 Strnad V, Hildebrandt G, Potter R, et al. Accelerated partial breast irradiation: 5-year results of the German-Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2011; **80:** 17–24.

7 Vaidya JS, Wenz F, Bulsara M, et al, on behalf of the TARGIT trialists' group. 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.

8 Khan AJ, Arthur D, Vicini F, et al. Six-year analysis of treatment-related toxicities in patients treated with accelerated partial breast irradiation on the American Society of Breast Surgeons MammoSite Breast Brachytherapy registry trial. *Ann Surgl Oncol* 2012; **19:** 1477–83.

9 Offersen BV, Overgaard M, Kroman N, Overgaard J. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: a systematic review. *Radiother Oncol* 2009; **90:** 1–13.

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

11 Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; **14:** 1269–77.

12 Hepel J, Wazer DE. A flawed study should not define a new standard of care. *Int J Radiat Oncol Biol Phys* 2015; **91:** 255–57.

13 Gilleard O, Goodman A, Cooper M, Davies M, Dunn J. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. *World J Surg Oncol* 2008; **6:** 61.

14 Rubin P, Constine LS, Fajardo LF, et al. Late effects consensus conference: RTOG/EORTC. *Radiother Oncol* 1995; **35:** 5–7.

15 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

16 Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005; **97:** 116–26.

17 Lee LJ, Harris JR. Innovations in radiation therapy (RT) for breast cancer. *Breast* 2009; **18** (suppl 3)**:** S103–11.

18 Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med* 2013; **368:** 2527.

19 Kirova YM, Gambotti L, De Rycke Y, Vilcoq JR, Asselain B, Fourquet A. Risk of second malignancies after adjuvant radiotherapy for breast cancer: a large-scale, single-institution review. *Int J Radiat Oncol Biol Phys* 2007; **68:** 359–63.

20 King TA, Bolton JS, Kuske RR, Fuhrman GM, Scroggins TG, Jiang XZ. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg* 2000; **180:** 299–304.

21 Vicini FA, Chen PY, Fraile M, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. *Int J Radiat Oncol Biol Phys* 1997; **38:** 301–10.

22 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.

23 Olivotto IA, Whelan TJ, Parpia S, 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.

24 Dodwell DJ, Dyker K, Brown J, et al. A randomised study of whole-breast vs tumour-bed irradiation after local excision and axillary dissection for early breast cancer. *Clin Oncol* 2005; **17:** 618–22.

25 Rodriguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2013; **87:** 1051–57.

26 Polgar C, Strnad V, Kovacs G. Partial-breast irradiation or whole-breast radiotherapy for early breast cancer: a meta-analysis of randomized trials. *Strahlenther Onkol* 2010; **186:** 113–14.

27 Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015; **51:** 451–63.

28 Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013; **31:** 2382–87.

29 Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015; **16:** 266–73.

30 Pötter R, Gnant M, Kwasny W, et al. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. *Int J Radiat Oncol Biol Phys* 2007; **68:** 334–40.