



Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial

Csaba Polgár, Oliver J Ott, Guido Hildebrandt, Daniela Kauer-Dorner, Hellen Knauerhase, Tibor Major, Jaroslaw Lyczek, José Luis Guinot, Jürgen Dunst, Cristina Gutierrez Miguelez, Pavel Slampa, Michael Allgäuer, Kristina Lössl, Bülent Polat, György Kovács, Arnt-René Fishedick, Rainer Fietkau, Alexandra Resch, Anna Kulik, Leo Arribas, Peter Niehoff, Ferran Guedea, Annika Schlamann, Richard Pötter, Christine Gall, Wolfgang Uter, Vratislav Strnad, on behalf of the Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO)

Summary

Background We previously confirmed the non-inferiority of accelerated partial breast irradiation (APBI) with interstitial brachytherapy in terms of local control and overall survival compared with whole-breast irradiation for patients with early-stage breast cancer who underwent breast-conserving surgery in a phase 3 randomised trial. Here, we present the 5-year late side-effects and cosmetic results of the trial.

Methods We did this randomised, controlled, phase 3 trial at 16 centres in seven European countries. Women aged 40 years or older with stage 0–IIA breast cancer who underwent breast-conserving surgery with microscopically clear resection margins of at least 2 mm were randomly assigned 1:1, via an online interface, to receive either whole-breast irradiation of 50 Gy with a tumour-bed boost of 10 Gy or APBI with interstitial brachytherapy. Randomisation was stratified by study centre, menopausal status, and tumour type (invasive carcinoma *vs* ductal carcinoma in situ), with a block size of ten, according to an automated dynamic algorithm. Patients and investigators were not masked to treatment allocation. The primary endpoint of our initial analysis was ipsilateral local recurrence; here, we report the secondary endpoints of late side-effects and cosmesis. We analysed physician-scored late toxicities and patient-scored and physician-scored cosmetic results from the date of breast-conserving surgery to the date of onset of event. Analysis was done according to treatment received (as-treated population). This trial is registered with ClinicalTrials.gov, number NCT00402519.

Findings Between April 20, 2004, and July 30, 2009, we randomly assigned 1328 women to receive either whole-breast irradiation ($n=673$) or APBI with interstitial brachytherapy ($n=655$); 1184 patients comprised the as-treated population (551 in the whole-breast irradiation group and 633 in the APBI group). At a median follow-up of 6·6 years (IQR 5·8–7·6), no patients had any grade 4 toxicities, and three (<1%) of 484 patients in the APBI group and seven (2%) of 393 in the whole-breast irradiation group had grade 3 late skin toxicity ($p=0\cdot16$). No patients in the APBI group and two (<1%) in the whole-breast irradiation group developed grade 3 late subcutaneous tissue toxicity ($p=0\cdot10$). The cumulative incidence of any late side-effect of grade 2 or worse at 5 years was 27·0% (95% CI 23·0–30·9) in the whole-breast irradiation group versus 23·3% (19·9–26·8) in the APBI group ($p=0\cdot12$). The cumulative incidence of grade 2–3 late skin toxicity at 5 years was 10·7% (95% CI 8·0–13·4) in the whole-breast irradiation group versus 6·9% (4·8–9·0) in the APBI group (difference –3·8%, 95% CI –7·2 to 0·4; $p=0\cdot020$). The cumulative risk of grade 2–3 late subcutaneous tissue side-effects at 5 years was 9·7% (95% CI 7·1–12·3) in the whole-breast irradiation group versus 12·0% (9·4–14·7) in the APBI group (difference 2·4%; 95% CI –1·4 to 6·1; $p=0\cdot28$). The cumulative incidence of grade 2–3 breast pain was 11·9% (95% CI 9·0–14·7) after whole-breast irradiation versus 8·4% (6·1–10·6) after APBI (difference –3·5%; 95% CI –7·1 to 0·1; $p=0\cdot074$). At 5 years' follow-up, according to the patients' view, 413 (91%) of 454 patients had excellent to good cosmetic results in the whole-breast irradiation group versus 498 (92%) of 541 patients in the APBI group ($p=0\cdot62$); when judged by the physicians, 408 (90%) of 454 patients and 503 (93%) of 542 patients, respectively, had excellent to good cosmetic results ($p=0\cdot12$). No treatment-related deaths occurred, but six (15%) of 41 patients (three in each group) died from breast cancer, and 35 (85%) deaths (21 in the whole-breast irradiation group and 14 in the APBI group) were unrelated.

Interpretation 5-year toxicity profiles and cosmetic results were similar in patients treated with breast-conserving surgery followed by either APBI with interstitial brachytherapy or conventional whole-breast irradiation, with significantly fewer grade 2–3 late skin side-effects after APBI with interstitial brachytherapy. These findings provide further clinical evidence for the routine use of interstitial multicatheter brachytherapy-based APBI in the treatment of patients with low-risk breast cancer who opt for breast conservation.

Funding German Cancer Aid.

Lancet Oncol 2017

Published Online
January 13, 2017
[http://dx.doi.org/10.1016/S1470-2045\(17\)30011-6](http://dx.doi.org/10.1016/S1470-2045(17)30011-6)

See Online/Comment
[http://dx.doi.org/10.1016/S1470-2045\(17\)30011-3](http://dx.doi.org/10.1016/S1470-2045(17)30011-3)

Center of Radiotherapy, National Institute of Oncology, Budapest, Hungary (Prof C Polgár MD, T Major PhD); Department of Radiation Oncology, University Hospital Erlangen, Erlangen, Germany (Prof V Strnad MD, O J Ott MD, Prof R Fietkau MD); Department of Radiation Oncology, University Hospital Leipzig, Leipzig, Germany (Prof G Hildebrandt MD, A Schlamann MD); Department of Radiation Oncology, University Hospital Rostock, Rostock, Germany (Prof R Fietkau, H Knauerhase MD, Prof G Hildebrandt); Department of Radiation Oncology, University Hospital AKH Wien, Vienna, Austria (D Kauer-Dorner MD, A Resch MD, Prof R Pötter MD); Brachytherapy Department, Centrum Onkologii—Instytut im Marii Skłodowskiej, Warsaw, Poland (J Lyczek MD, A Kulik MD); Podkarpacki Hospital Cancer Center Brzozów, Brzozów, Poland (J Lyczek); Department of Radiation Oncology, Valencian Institute of Oncology, Valencia, Spain (J L Guinot MD, Prof L Arribas MD); Department of Radiation Oncology, University Hospital Kiel, Kiel, Germany (Prof P Niehoff MD, Prof J Dunst MD); Department of Radiotherapy, Sana Hospital

Offenbach, Offenbach, Germany (Prof P Niehoff); Department of Radiation Oncology, Catalan Institute of Oncology, Barcelona, Spain (Prof C Gutierrez Miguelez MD, Prof F Guedea MD); Department of Radiation Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic (Prof P Slampa MD); Department of Radiation Oncology, University Hospital Bern, Inselspital, Switzerland (K Lössl MD); Department of Radiation Oncology, Hospital Barmherzige Brüder, Regensburg, Germany (M Allgäuer MD); Interdisciplinary Brachytherapy Unit, University of Lübeck/Universitätsklinikum Schleswig-Holstein Campus Lübeck, Lübeck, Germany (Prof G Kovacs MD); Department of Radiation Oncology, Clemens Hospital, Münster, Germany (Prof A R Fishedick MD); Department of Radiation Oncology, University Hospital Würzburg, Würzburg, Germany (B Polat MD); and Department of Medical Informatics, Biometry and Epidemiology, University Erlangen-Nuremberg, Erlangen, Germany (Prof W Uter MD, C Gall DSc)

Correspondence to: Prof Csaba Polgár, Center of Radiotherapy, National Institute of Oncology, Budapest 1122, Hungary
polgar@oncol.hu

See Online for appendix

Research in context

Evidence before this study

We searched PubMed and MEDLINE for any prospective studies published in English and ClinicalTrials.gov for studies that were ongoing or completed, in which late side-effects and cosmetic results of accelerated partial breast irradiation (APBI) were investigated after breast-conserving surgery. The date of our final search was Aug 10, 2016. Our search terms were “early breast cancer”, “radiation therapy”, “accelerated partial breast irradiation”, “APBI”, “brachytherapy”, “three-dimensional conformal radiotherapy”, “3D-CRT”, “intraoperative radiotherapy”, “IORT”, “late toxicity”, “late side-effects”, “cosmetic results”, and “adjuvant therapy”. We identified only six phase 2 trials, and one small phase 3 study with mature results, mostly showing a favourable late toxicity profile, and good to excellent cosmetic results after breast-conserving surgery and accelerated partial breast irradiation with interstitial brachytherapy. However, uncertainty remained regarding the safety of APBI with interstitial brachytherapy with respect to long-term toxicities and cosmetic results. Data for late side-effects and cosmetic outcomes with other techniques of APBI, including intraoperative radiotherapy with high-energy electrons, and 50-kV photons and external beam irradiation, were premature or controversial. Therefore, we initiated a randomised trial to investigate the value of interstitial brachytherapy for APBI as sole adjuvant radiotherapy for selected patients with early stage (stage 0, I, and IIA) breast cancer. Our aim was to prove the non-inferiority and safety of

APBI with interstitial brachytherapy compared with conventional whole-breast irradiation.

Added value of this study

Our 5-year results show that APBI with interstitial brachytherapy is not only as effective as adjuvant whole-breast irradiation for selected patients with early stage breast cancer, but also provides at least equivalent cosmetic outcomes and significantly fewer late skin side-effects compared with conventional whole-breast irradiation. When we consider the negative results of phase 3 trials of intraoperative radiotherapy APBI trials with respect to local tumour control and the controversial late toxicity data obtained from phase 3 external beam APBI trials, our findings provide further clinical evidence to support the routine use of interstitial multicatheter brachytherapy-based APBI in the treatment of patients with low-risk breast cancer who opt for breast conservation.

Implications of all the available evidence

To our knowledge, this trial is the first phase 3 study that shows similar late toxicity profiles and cosmetic outcomes, and significantly fewer late skin side-effects of APBI with interstitial brachytherapy compared with whole-breast irradiation for selected patients with early stage breast cancer. On the basis of our findings, APBI with interstitial brachytherapy can be regarded as a valid alternative treatment option after breast-conserving surgery, and can be offered for all patients with low-risk breast cancer as part of routine clinical practice.

Introduction

Breast-conserving surgery followed by a 5-week course of whole-breast irradiation with or without an additional 1–2 weeks of boost irradiation to the tumour bed was the standard of care for early-stage breast cancer for the past four decades.^{1,2} A randomised trial³ published in 2011, also justified the routine use of a 3-week course of modestly hypofractionated whole-breast radiotherapy. However, in the past 15 years, accelerated partial breast irradiation (APBI) has been gradually accepted as an alternative radiotherapy option, at least for the treatment of selected patients with low-risk breast cancer.^{4–6} Initially, the results of several phase 2 trials^{7–9} and one single-institution phase 3 clinical trial¹⁰ showed that outcomes of APBI with interstitial brachytherapy, with appropriate quality assurance for patients who were strictly selected, were similar to those of conventional whole-breast irradiation. In 2016, we reported the 5-year results of the phase 3 GEC-ESTRO trial¹¹ of APBI, which showed that APBI with interstitial brachytherapy after breast-conserving surgery in patients with early-stage breast cancer was non-inferior to whole-breast irradiation for 5-year local control, disease-free survival, and overall survival. The trial also reported favourable preliminary findings for treatment-related late side-

effects.¹¹ We did the present analysis to assess the effectiveness of APBI with sole multicatheter brachytherapy compared with whole-breast irradiation in terms of late side-effects and cosmetic results in patients with low-risk invasive carcinoma and low-risk ductal carcinoma in situ of the female breast after breast-conserving treatment. Early toxicity results and patients' compliance have recently been reported elsewhere.¹²

Methods

Study design and participants

We did the multicentre, phase 3, randomised, controlled GEC-ESTRO trial at 16 medical centres in seven European countries (Austria, Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland; appendix p 4).

We reported the eligibility criteria in detail in our previous publication.¹¹ Briefly, women were eligible if they were aged 40 years or older with ductal carcinoma in situ (pTis) or invasive breast carcinoma up to a diameter of 3 cm (pT1–2a), with pN0 or pN1mi axillary status (stage 0, I, and IIA) who had undergone local excision of the breast tumour with microscopically clear resection margins of at least 2 mm. We excluded patients if they had multiple tumour foci, lymphovascular invasion, an

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات