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Phase III randomised trial

Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial

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ABSTRACT

Background and purpose: To report the long-term results of a single-institution randomized study comparing the results of breast-conserving treatment with partial breast irradiation (PBI) or conventional whole breast irradiation (WBI).

Patients and methods: Between 1998 and 2004, 258 selected women with pT1 pN0-1mi M0, grade 1–2, non-lobular breast cancer without the presence of extensive intraductal component and resected with negative margins were randomized after BCS to receive 50 Gy WBI ($n = 130$) or PBI ($n = 128$). The latter consisted of either 7×5.2 Gy high-dose-rate (HDR) multi-catheter brachytherapy (BT; $n = 88$) or 50 Gy electron beam (EB) irradiation ($n = 40$). Primary endpoint was local recurrence (LR) as a first event. Secondary endpoints were overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), and cosmetic results.

Results: After a median follow up of 10.2 years, the ten-year actuarial rate of LR was 5.9% and 5.1% in PBI and WBI arms, respectively ($p = 0.77$). There was no significant difference in the ten-year probability of OS (80% vs 82%), CSS (94% vs 92%), and DFS (85% vs 84%), either. The rate of excellent-good cosmetic result was 81% in the PBI, and 63% in the control group ($p < 0.01$).

Conclusions: Partial breast irradiation delivered by interstitial HDR BT or EB for a selected group of early-stage breast cancer patients produces similar ten-year results to those achieved with conventional WBI. Significantly better cosmetic outcome can be achieved with HDR BT implants compared with the outcome after WBI.

Over the last three decades, breast-conserving therapy (BCT) including surgical removal of the primary tumor and whole breast irradiation (WBI) consisting of 5 weeks of external beam radiotherapy (EBRT) with or without an additional 1–2 weeks of boost irradiation to the tumor bed, became the standard of care for the treatment of early-stage breast carcinoma [1–3]. However, the necessity of giving WBI for all patients as a part of BCT has been questioned, and accelerated partial breast irradiation (APBI) has been tested in multiple clinical trials as an alternative treatment option [4–31]. The results of multiple phase I–II trials showed that APBI using interstitial multi-catheter brachytherapy (BT) using adequate patient selection and quality assurance (QA) yields similar results to those achieved with conventional WBI [4,11–14,19,20,23–25,28]. However, two randomized APBI trials conducted in the late eighties showed inferior results with partial breast irradiation (PBI) using less sophisticated EBRT techniques and limited QA procedures [7,15]. Therefore, the hypothesis that PBI produces similar results to those achieved with standard WBI should be proved in prospective randomized trials.

At the Hungarian National Institute of Oncology, a prospective phase III clinical trial comparing PBI with multi-catheter interstitial high-dose-rate (HDR) BT or EBRT with WBI for a selected group of early-stage breast cancer patients was conducted between 1998 and 2004. Five-year results of this study have been published elsewhere, and this is the first report of the ten-year results [18].

Materials and methods

Study design

Between July 1998 and May 2004, 258 patients with stage I–II breast cancer who underwent breast-conserving surgery (BCS) were randomized to receive WBI ($n = 130$) or PBI ($n = 128$). Patients were eligible if they met all the following conditions: wide excision with microscopically negative surgical margins; unifocal tumor; primary tumor size $\leqslant$20 mm (pT1); cN0, pN0, or pN1mi (nodal

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micrometastasis ⩽2 mm) axillary nodal status; and histological grade 1–2. Exclusion criteria included prior breast cancer or other malignancies (except skin basalioma); bilateral breast carcinoma; pure ductal or lobular carcinoma *in situ* (pTis); invasive lobular carcinoma; lymphovascular invasion; or the presence of an extensive intraductal component. Young women aged ⩽40 years were also excluded after a protocol amendment performed in 2001.

Randomization was done by the principal investigator. Patients were randomly allocated to treatment options by a sealed-envelope system in blocks of ten. Blinding of physicians performing treatments and follow-up and of patients was not possible for technical reasons. No stratification was used. The primary endpoint for analysis was the appearance of local recurrence (LR) as a first event. The scientific hypothesis was "non-relevant non-inferiority" of PBI with regard to LR. The difference in LR between the two arms that we considered clinically non-relevant for our sample size calculation was 6% (e.g. 10% after PBI vs 4% after WBI at five years). The 4% figure was considered as the low ceiling of five-year LR rates reported in modern breast-conserving series using WBI. The originally planned sample size ($n = 570$) was calculated to detect this 6% difference in LR rate at five years between the two treatment arms with a statistical power of 80% and at a significance level of 5%. Accrual was stopped prematurely at a sample size of 258 patients, because since June 2004 all eligible patients have been offered to participate in the European multicentric GEC-ESTRO (Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology) phase III APBI trial. One patient in the WBI arm developed distant metastasis before RT and did not receive the assigned treatment. Another patient in PBI arm refused her assigned therapy and underwent mastectomy without RT. However, all patients were analyzed according to the intent to treat policy (Fig. 1). The trial protocol was accepted by the ethics committee of the National Institute of Oncology, Budapest, and informed consent of the patients was required.

Surgery

All patients underwent BCS with axillary dissection ($n = 160$) or sentinel lymph node biopsy ($n = 93$), while surgical axillary staging was omitted in 5 cases, based on the surgeon's preference. During surgery, the boundaries of the excision cavity were marked with titanium clips. All breast specimens were inked and oriented by the pathologist to define microscopic margins. Patient and tumor characteristics are listed in Table 1.

Radiotherapy

Eighty-eight out of 128 (69%) patients in the PBI arm were assigned to be treated with 7×5.2 Gy b.i.d. HDR multi-catheter interstitial BT alone, but the protocol allowed 50 Gy limited-field EB irradiation for patients who were technically unsuitable for interstitial implantation ($n = 40$; 31%). Implantations were performed four to six weeks after BCS under local anesthesia. Patients were treated with HDR remote after-loading equipment using a ^{192}Ir stepping source. The traditional Paris system guidelines were used for the planning of the implant geometry [32]. A preimplant radiograph simulation was performed by using a template placed on the breast to determine the entrance and exit points of the needles from the "needle-eye" view. Planning target volume (PTV) was defined as the excision cavity delineated by the surgical clips plus a margin of 2 cm. However, only a 1–1.5 cm safety margin was applied when excision cavity was close to the skin surface or chest wall. Four to thirteen (median: 9) guide needles were inserted into the tumor bed in a triangular geometry using template guidance. The spacing between the needles was 13 or 15 mm. Then, the guide needles were replaced with flexible plastic catheters, which were fixed with buttons. Single-, double-, triple-, and four-plane implants were performed at 1 (1%), 47 (54%), 38 (44%), and 1 (1%) patients, respectively. The Paris system rules were not used for dose prescription [32]. Our own planning concepts have been established to achieve more conformal coverage of the PTV. The treatment planning was based on a three-dimensional reconstruction of the locations of the catheters, surgical clips, and skin points digitized from two postimplant radiograph films taken with the variable-angle reconstruction technique. The active source positions and reference dose points were defined individually in each catheter, and the optimization of the dwell times to dose points and geometry was performed. The most peripheral active source

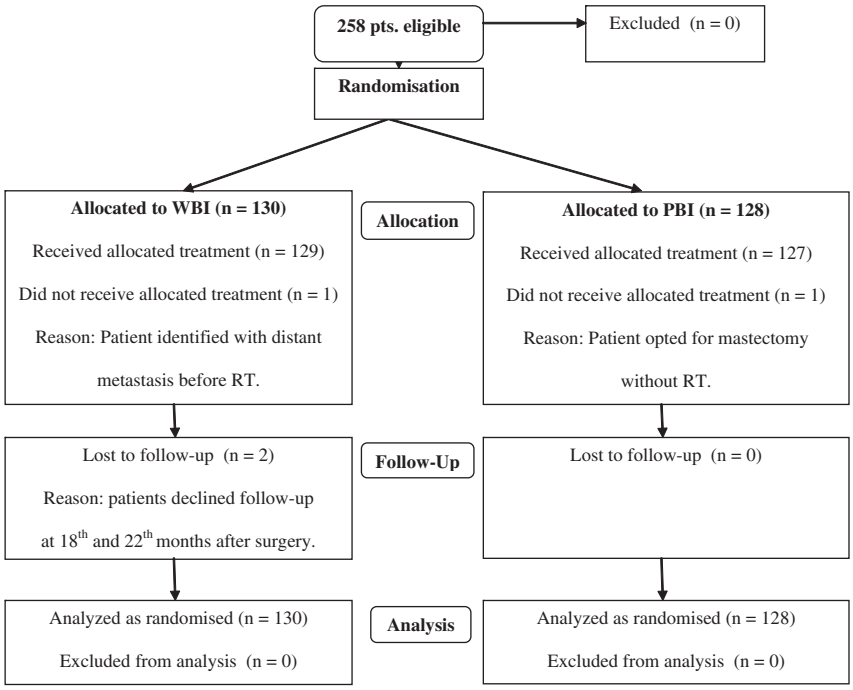

Fig. 1. CONSORT trial flow diagram. *Abbreviations:* WBI – whole breast irradiation; PBI – partial breast irradiation; RT –radiotherapy.