European Journal of Cancer (2015) **51**, 451–463

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial

Lorenzo Livi [a], Icro Meattini [a,*], Livia Marrazzo [b], Gabriele Simontacchi [a], Stefania Pallotta [b], Calogero Saieva [c], Fabiola Paiar [a], Vieri Scotti [a], Carla De Luca Cardillo [a], Paolo Bastiani [d], Lorenzo Orzalesi [e], Donato Casella [e], Luis Sanchez [e], Jacopo Nori [f], Massimiliano Fambrini [g], Simonetta Bianchi [h]

[a] *Department of Radiation Oncology, University of Florence, Florence, Italy*
[b] *Medical Physics Unit, University of Florence, Florence, Italy*
[c] *Molecular and Nutritional Epidemiology Unit, ISPO (Cancer Research and Prevention Institute), University of Florence, Florence, Italy*
[d] *Radiotherapy Unit, Azienda Sanitaria 10, University of Florence, Florence, Italy*
[e] *Department of Surgery, University of Florence, Florence, Italy*
[f] *Diagnostic Senology Unit, University of Florence, Florence, Italy*
[g] *Gynecologic and Obstetrics Unit, University of Florence, Florence, Italy*
[h] *Division of Pathological Anatomy, Department of Medical and Surgical Critical Care, University of Florence, Florence, Italy*

Received 5 September 2014; received in revised form 13 October 2014; accepted 22 December 2014
Available online 17 January 2015

KEYWORDS
Accelerated partial breast irradiation
Whole breast irradiation
Intensity-modulated radiotherapy
IMRT
Phase 3 trial

Abstract ***Background:*** Accelerated partial breast irradiation (APBI) has been introduced as an alternative treatment method for selected patients with early stage breast cancer (BC). Intensity-modulated radiotherapy (IMRT) has the theoretical advantage of a further increase in dose conformity compared with three-dimensional techniques, with more normal tissue sparing. The aim of this randomised trial is to compare the local recurrence and survival of APBI using the IMRT technique after breast-conserving surgery to conventional whole-breast irradiation (WBI) in early stage BC.

Methods: This study was performed at the University of Florence (Florence, Italy). Women aged more than 40 years affected by early BC, with a maximum pathological tumour size of 25 mm, were randomly assigned in a 1:1 ratio to receive either WBI or APBI using IMRT. Patients in the APBI arm received a total dose of 30 Gy to the tumour bed in five daily

* *Corresponding author at:* Department of Radiation Oncology, University of Florence, Largo G. A. Brambilla 3, 50134 Florence, Italy. Tel.: +39 055 7947719; fax: +39 055 4379930.
E-mail address: icro.meattini@unifi.it (I. Meattini).

http://dx.doi.org/10.1016/j.ejca.2014.12.013

fractions. The WBI arm received 50 Gy in 25 fractions, followed by a boost on the tumour bed of 10 Gy in five fractions. The primary end-point was occurrence of ipsilateral breast tumour recurrences (IBTRs); the main analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT02104895.

Findings: A total of 520 patients were randomised (260 to external WBI and 260 to APBI with IMRT) between March 2005 and June 2013. At a median follow-up of 5.0 years (Interquartile Range (IQR) 3.4–7.0), the IBTR rate was 1.5% (three cases) in the APBI group (95% confidence interval (CI) 0.1–3.0) and in the WBI group (three cases; 95% CI 0.0–2.8). No significant difference emerged between the two groups (log rank test $p = 0.86$). We identified seven deaths in the WBI group and only one in the APBI group ($p = 0.057$). The 5-year overall survival was 96.6% for the WBI group and 99.4% for the APBI group. The APBI group presented significantly better results considering acute ($p = 0.0001$), late ($p = 0.004$), and cosmetic outcome ($p = 0.045$).

Interpretation: To our knowledge, this is the first randomised study using the IMRT technique for APBI delivery. No significant difference in terms of IBTR and overall survival was observed between the two arms. APBI displayed a significantly better toxicity profile.

1. Introduction

The standard treatment for early breast cancer (BC) patients is based on breast conservative surgery (BCS) followed by whole-breast irradiation (WBI) [1,2]. The majority of early breast recurrences occur at the site of the original primary tumour, regardless of whether radiotherapy (RT) has been administered or whether the margins are involved [3,4].

Accelerated partial breast irradiation (APBI) has been introduced as an alternative treatment method for selected patients with early stage BC [5]. Potential advantages of APBI include shorter treatment time, improved cosmesis because of the decreased volume of breast tissue treated, and a cost reduction compared with standard fractionation [6]. Recently, many techniques have been tested in an attempt to administer adjuvant RT while reducing the burden for patients and RT departments [7,8].

There are currently little randomised controlled trial data confirming that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity [9].

As the oncology community awaits results from NSABP B-39/RTOG 0413, the largest randomised trial of WBI versus APBI, to provide more conclusive data, many academic and private radiation oncology practices are utilising APBI off protocol [10]. Although the ideal patient profile for APBI is not clearly identified, the American Society for Radiation Oncology (ASTRO) [11] and the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) [12] have suggested selection criteria for 'suitable patients' for APBI outside of clinical trials.

We present the results of a randomised trial comparing local recurrence and survival of APBI using the IMRT technique after BCS to conventional WBI in early stage BC.

2. Methods

2.1. Study profile and patients

This single-institution study was conceived and performed at the Radiation-Oncology Department of University of Florence (Florence, Italy).

Between 11th March, 2005, and 18th June, 2013, a randomised phase 3 clinical trial was conducted to compare conventional (tangential field) WBI and APBI using the IMRT technique. Eligible patients, as previously described [13], were women aged more than 40 years with early BC (maximum diameter 2.5 cm) suitable for BCS. Enrolled patients had to be able to complete prescribed treatments and to adhere to trial follow up programme. Angiovascular invasion, ductal carcinoma in situ (DCIS), and axillary lymph node positive status were not considered exclusion criteria.

Exclusion criteria were: previously diagnosed solid tumours; left ventricular ejection fraction (LVEF) <50% as measured by echocardiography or a history of active angina, myocardial infarction, or other cardiovascular disease; forced expiratory volume in 1 s (FEV_1) <1 L/m; extensive intraductal carcinoma; multiple foci cancer; final surgical margins <5 mm; and the absence of surgical clips in tumour bed.

The local Ethics Committee (Azienda Ospedaliero-Universitaria Careggi, Florence, Italy) gave permission to perform the present study, which was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice. All patients provided full written informed consent. The trial profile is summarised in Fig. 1.