


# Ten-year results of accelerated hypofractionated adjuvant whole-breast radiation with concomitant boost to the lumpectomy cavity after conserving surgery for early breast cancer

Domenico Cante<sup>1</sup> · Edoardo Petrucci<sup>2</sup> · Piera Sciacero<sup>1</sup> · Cristina Piva<sup>1</sup> ·  
Silvia Ferrario<sup>1</sup> · Silvia Bagnera<sup>3</sup> · Sebastiano Patania<sup>3</sup> · Guido Mondini<sup>4</sup> ·  
Massimo Pasquino<sup>2</sup> · Valeria Casanova Borca<sup>2</sup> · Giorgio Vellani<sup>5</sup> ·  
Maria Rosa La Porta<sup>1</sup> · Pierfrancesco Franco<sup>6</sup> 

Received: 13 July 2017 / Accepted: 31 July 2017 / Published online: 3 August 2017  
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**Abstract** Accelerated hypofractionated whole-breast radiotherapy (WBRT) is considered a standard therapeutic option for early breast cancer (EBC) in the postoperative setting after breast conservation (BCS). A boost to the lumpectomy cavity may further increase local control. We herein report on the 10-year results of a series of EBC patients treated after BCS with hypofractionated WBRT with a concomitant photon boost to the surgical bed over 4 weeks. Between 2005 and 2007, 178 EBC patients were treated with a basic course of radiotherapy consisting of 45 Gy to the whole breast in 20 fractions (2.25 Gy daily) with an additional boost dose of 0.25 Gy delivered concomitantly to the lumpectomy cavity, for an additional dose of 5 Gy. Median follow-up period was 117 months. At 10-year, overall, cancer-specific, disease-free survival and local control were 92.2% (95% CI 88.7–93.4%), 99.2% (95% CI 96.7–99.7%), 95.5% (95% CI 91.2–97.2%) and 97.3% (95% CI 94.5–98.9%), respectively. Only eight patients recurred. Four in-breast recurrences, two axillary

node relapses and two metastatic localizations were observed. Fourteen patients died during the observation period due to other causes while breast cancer-related deaths were eight. At last follow-up,  $\geq$ G2 fibrosis and telangiectasia were seen in 7% and 5% of patients. No major lung and heart toxicities were observed. Cosmetic results were excellent/good in 87.8% of patients and fair/poor in 12.2%. Hypofractionated WBRT with concomitant boost to the lumpectomy cavity after BCS in EBC led to consistent clinical results at 10 years. Hence, it can be considered a valid treatment option in this setting.

**Keywords** Breast cancer · Hypofractionated radiotherapy · Adjuvant whole-breast radiation · Hypofractionation · Local control · Concomitant boost

## Introduction

The standard treatment option for early-stage breast cancer (EBC) comprises conservative surgery, radiotherapy, chemotherapy, and hormone therapy, differently combined according to patient and tumor characteristics [1]. Breast-conserving surgery (BCS) and subsequent adjuvant whole-breast radiotherapy (WBRT) showed equivalent outcomes compared to mastectomy in this subset of patients [2–4]. A total dose of 45–50 Gy, given with conventional fractionation (1–2 Gy daily) over 5 weeks, is generally delivered for WBRT. A subsequent 10–16 Gy boost dose to the lumpectomy cavity can be added sequentially to reduce the rate of local relapse, over 1–2 adjunctive weeks of treatment [5]. To optimize patient and healthcare system resources, hypofractionated regimens (radiation delivered with higher dose per fraction given over a shorter treatment period) were implemented [6]. Clinical results of

✉ Pierfrancesco Franco  
pierfrancesco.franco@unito.it

<sup>1</sup> Radiotherapy Department, Ivrea Community Hospital, ASL TO4, Ivrea, Italy  
<sup>2</sup> Medical Physics Department, Ivrea Community Hospital, ASL TO4, Ivrea, Italy  
<sup>3</sup> Diagnostic Imaging Department, Ivrea Community Hospital, ASL TO4, Ivrea, Italy  
<sup>4</sup> Breast Surgery Department, Ivrea Community Hospital, ASL TO4, Ivrea, Italy  
<sup>5</sup> Medical Oncology Department, Ivrea Community Hospital, ASL TO4, Ivrea, Italy  
<sup>6</sup> Department of Oncology – Radiation Oncology, University of Turin, Via Genova 3, 10126 Turin, Italy

hypofractionated WBRT were found to be consistent, especially if the total nominal dose is lowered compared to conventionally fractionated schedules [7–13]. Prospective randomized studies contributed to create clinical evidence in this setting [14–16]. Thus, we started treating EBC patients with WBRT after BCS, employing a 20 fraction schedule delivered over 4 weeks with a concomitant boost to the lumpectomy cavity [8]. We implemented this approach in several settings including both invasive and in situ disease and results at 5 years have already been reported [17–19]. We herein present 10-year results in terms of local control, survival, toxicity profile and cosmetic results.

## Methods and materials

Data of 178 EBC patients were retrieved from the medical records of our institution hospital and reviewed. Those patients were treated with WBRT at the Ivrea Hospital between March 2005 and May 2007.

### Cohort characteristic

Patients had a histologically proven diagnosis of breast adenocarcinoma, received prior conservative surgery (lumpectomy or quadrantectomy) with negative surgical margins and pathological stage pT1 or pT2, pN0-N1 according to America Joint Committee-Union Internationale Contre le Cancer staging system (6th Edition 2002).

### Setup, simulation and target definition

All the 178 patients were positioned on a wingboard with both arms raised above the head and radiopaque markers placed along the clinical borders of the breast. Subsequently, 5-mm slice thickness axial images were acquired from the lower aspect of the mandible to the bases of the lung. An isocenter was then found in virtual simulation using the CT-simulation software Oncentra Masterplan v 3.0 (Nucletron, Veendhal, The Netherlands). The whole-breast clinical target volume (WB-CTV) encompassed the palpable remaining glandular tissue of the breast, with a superior and inferior border delimited within the extent of the radiopaque catheters, which marked the palpable breast gland. Moreover, a uniform limit of 5 mm separated the WB-CTV from the skin surface and the thoracic wall. The whole-breast planning target volume (WB-PTV) was generated by adding a 5-mm isotropic margin around the WB-CTV and subsequently refined to account for the skin and thoracic surface and organs at risk. The definition of the lumpectomy cavity was driven by the position of radiopaque clips placed at time of surgery. The concomitant

boost clinical target volume (CB-CTV) was generated by adding a 5-mm isotropic margin around the lumpectomy cavity, while the concomitant boost planning target volume (CB-PTV) required a further margin of 5 mm around the CB-CTV. The heart and ipsilateral lung were separately contoured as organs at risk; particularly, the heart was outlined up to the level of the pulmonary trunk superiorly, with the inclusion of the pericardium and the exclusion of the major vessels.

### Treatment schedule and delivery

The basic course for WBRT consisted of 45 Gy, prescribed to the ICRU reference point dose and delivered to the whole breast in 20 fractions with 2.25 Gy per fraction with two opposing 6 MV tangential fields. An additional boost dose of 0.25 Gy was concomitantly delivered, on a daily basis, to the lumpectomy cavity (CB-PTV), for a total additional dose of 5 Gy, using 2–3 adjunctive 6 MV-photon fields. The cumulative nominal dose was 50 Gy. Finally, the isocenter and the dose normalization point were identical either for the breast or for the boost plan. For setup verification purposes, tangential fields portal images were taken before the first treatment session and quantitatively compared with digitally reconstructed radiographs (DRRs) obtained from planning computed tomography.

### Follow-up, toxicity and cosmesis

During follow-up time, patients were examined at 3 and 6 months after the end of WBRT and twice a year afterward. Surveillance for disease recurrence at any site included a clinical examination at every time point, plan chest X-ray and mammography once a year, complete blood cell count and serological markers twice a year. Acute toxicity was assessed at the completion of treatment and after 3 months; conversely, late toxicity was scored starting from 6 months after the end of the treatment course. The maximal detected toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3.0, using the RTOG/EORTC toxicity scale associated with radiation as Refs. [20, 21]. Cosmetic results were assessed at the end of the radiation course and thereafter at 3 and 6 months of follow-up time, using a cosmetic evaluation scale consisting of different categories, namely excellent, good, fair or poor in agreement with the Harvard criteria [22]. At each follow-up examination, patients were asked to judge the cosmetic appearance of the irradiated breast as follows: “excellent,” designating little or no change; “good,” minimal but noticeable change; “fair,” significant change; “poor,” severe change. Similarly, physicians were asked to judge the cosmetic results as follows: an “excellent” cosmetic

result score was assigned when the treated breast looked essentially the same as the contralateral breast; a “good” cosmetic score was assigned for minimal but identifiable radiation effects of the treated breast; a “fair” score meant significant radiation effects were readily observable; a “poor” score was used for radiation-induced severe late effects of breast tissue.

### Statistical analysis

Descriptive statistical analysis was provided for all 178 patients. Overall (OS), cancer-specific (CSS), disease-free (DFS) survival and local control (LC) were assessed. Disease recurrence was defined as local (LR) if occurring in the ipsilateral breast or overlying skin, as regional (RR) if involving the ipsilateral axillary, supraclavicular or internal mammary lymph nodes and as systemic with distant metastasis (DM) if arising at other sites. Local relapse, RR and DM were evaluated to calculate the disease-free survival (DFS). Multivariate analyses were also performed on the available dataset. Cox proportional hazard model was used to develop a regression model for survival based on pretreatment characteristics, and Kaplan–Meier estimate was used to evaluate survival. Groups were compared with the log-rank test. A  $p$  value  $<0.05$  between groups was considered significant. Time was calculated starting from the end of WBRT. Deaths from disease recurrence were considered as an event for disease-specific mortality, while the others were censored. In descriptive statistics, mean values, standard deviation and statistical range were reported for numerical variables, while for ordinal and categorical variables data were arranged as rates. In multivariate analysis, tumor and nodal stage, grading, estrogen/progesterone receptor status, Ki-67, histology, age, chemotherapy, hormonal therapy and surgery were included. Kaplan–Meier analysis was stratified according to these variables and plotted against overall and disease-free survival. All statistical analyses were performed using IBM SPSS® Statistical Software, version 20.0.

### Results

Baseline characteristics of all 178 patients are reported in Table 1. Almost 92% were aged  $>50$ ; most represented pathological stages were pT1b/pT1cN0. Up to 23% of the patients received adjuvant chemotherapy, while up to 91% was given hormonal therapy. The most common surgical approach was quadrantectomy and sentinel lymph node biopsy (66.3%), while almost 22% of the patients received also axillary dissection. All patients completed the planned radiotherapy program, with no interruptions needed. In Table 2, the average PTV and boost volumes and average

**Table 1** Tumor and treatment characteristics

Parameter	N°	%
T-stage		
pT1	137	76.9
pT2	41	33.1
N-stage		
pN0	142	79.8
pN1	35	19.7
pN2	1	0.5
Histology		
IDC	130	73.0
ILC	18	10.1
Mixed IDC/ILC	24	13.5
Papillary	3	1.7
Mucinous	3	1.7
Grading		
1	30	16.8
2	118	66.4
3	30	16.8
Estrogen receptor		
Negative	20	11.2
$\leq 80\%$	44	24.7
$>80\%$	114	64.1
Progesterone receptor		
Negative	36	20.2
$\leq 80\%$	87	24.7
$>80\%$	50	61.6
Surgery		
QUAD	21	11.8
QUAD + SLNB	118	66.3
QUAD + AD	16	9.0
QUAD + SLNB + AD	26	12.9
Axillary dissection		
Yes	39	21.9
No	139	78.1
Chemotherapy		
Yes	137	76.9
No	41	23.1
Hormonal therapy		
Yes	162	91.0
No	16	9.0

*T-stage* tumor stage, *N-stage* nodal stage, *N°* number, *IDC* infiltrative ductal carcinoma, *ILC* infiltrative lobular carcinoma, *QUAD* quadrantectomy, *SLNB* sentinel lymph node biopsy, *AD* axillary dissection

doses to ipsilateral lung and heart (for left-sided tumors) are reported. With a median follow-up of 117 months (range 4–140), 10-year OS, CSS, DFS and LC were 92.2% (95% CI 88.7–93.4%), 99.2% (95% CI 96.7–99.7%), 95.5% (95% CI 91.2–97.2%) and 97.3% (95% CI

**Table 2** Technical and dosimetric aspects

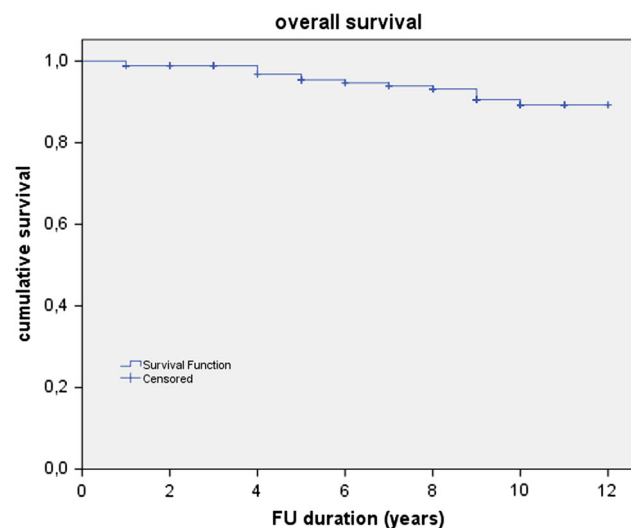
Parameter	Mean	SD	Range
PTV whole breast (cm <sup>3</sup> )	715	±428	202–3071
PTV boost (cm <sup>3</sup> )	50	±37	7–220
Mean heart dose (Gy)—left-sided tumors	2.46	±1.08	0.14–6.13
Ipsilateral mean lung dose (Gy)	10.94	±7.77	2.15–19.2

*PTV* planning target volume, *SD* standard deviation, *Gy* gray

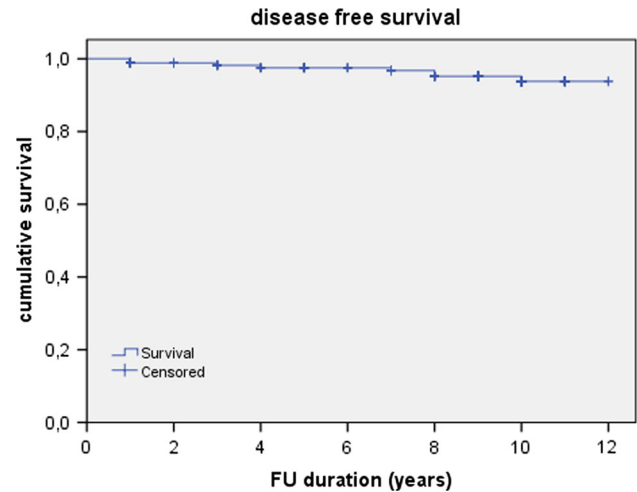
94.5–98.9%), respectively (Figs. 1, 2). Only eight patients experienced disease recurrence during the observation period with four in-breast recurrences, two axillary node relapses and two metastatic localizations. Fourteen patients died during follow-up due to other causes while breast cancer-related deaths were seen in eight patients; among the latter, four LR, two RR and two DM were seen. At last follow-up examination, ≥ G2 fibrosis and telangiectasia were 7% and 5%, respectively. No major lung and heart toxicities could be detected. Cosmetic results were scored as excellent/good in 87.8% of patients and fair/poor in 12.2%. Cox multivariate analysis was performed on the pretreatment with respect to DFS (T, N, G, PGR, ER, KI67, histology, age, chemotherapy, hormone therapy and surgery). As seen in Table 3, nodal stage and estrogen receptor status had a significant correlation with DFS ( $p = 0.037$  and  $p = 0.026$ , respectively).

**Discussion**

Hypofractionation, with the delivery of a daily dose per fraction higher than 1–8–2 Gy, is a valid option to treat EBC patients in a postoperative setting after breast conservation, shortening the overall treatment time [23]. Long-



**Fig. 1** Overall survival



**Fig. 2** Disease-free survival

**Table 3** Correlation between clinical factors and disease-free survival

Parameter	$\beta$	SE	Wald	p value	HR
T-stage	0.657	0.655	1.009	0.315	1.930
N-stage	1.415	0.679	4.349	0.037	4.118
Grading	-0.298	0.878	0.115	0.734	0.742
PgR	0.004	0.014	0.063	0.802	1.004
ER	-1.556	0.701	4.931	0.026	0.211
Ki-67	0.005	0.024	0.039	0.844	1.005

*T-stage* tumor stage, *N-stage* nodal stage, *PgR* progesterone receptor, *ER* estrogen receptor, *SE* standard error, *HR* hazard ratio

term follow-up data coming from randomized phase III trials confirmed consistent clinical results for hypofractionated schedules in this setting [24, 25]. Concerning the UK studies, the START-A trial employed 41.6 or 39 Gy in 13 fractions over 5 weeks, while the START-B trial used a regimen of 40 Gy in 15 fractions over 3 weeks, as experimental arms [15, 16]. Conversely, the Canadian trial used a pragmatic regimen of 42.5 Gy in 16 fractions over 22 days, in a similar manner as the START-B study [14]. These reported relapse rates of 3.5% (START-A for the 41.6 Gy/13 fraction schedule), 2% (START-B) and 2.8% (Canadian trial) at 5 years and of 4.3% (START trials) and

6.2% (Canadian study) at 10 years. [14–16, 24, 25]. In the Canadian study, no patients received a boost dose to the lumpectomy cavity [14]. In the UK trials, the boost strategy was left to discretion of enrolling institutions, outside the study protocol. Notably, in the START-B study, almost 44% of the enrolled patients received a boost [16]. In our series of patients, LC rate was 97.3% (95% CI 94.5–98.9%), with a percentage of local relapse below 3% (namely 2.7%). This is reasonable, considering the low-risk profile of our cohort where most of the tumors were below 2 cm (76.9%), pN0 (79.8%), G1–G2 (83.2%), with expression of estrogen receptor (88.8%). These findings are consistent with clinical series available in the literature [26]. A positive nodal status and a negative estrogen receptor status were found as significantly correlated with the likelihood to develop tumor recurrence. These clinical and biological factors are well-established prognostic variables for breast cancer patients [1]. In our series, we employed a boost to the lumpectomy cavity, in order to provide a further potential benefit in terms of LC. The EORTC “boost vs no boost” trial demonstrated a 10-year cumulative incidence of local relapse of 10.2% for the boost arm compared to 6.2% for the no boost arm [27]. The largest absolute risk reduction (23.9 vs 13.5%;  $p = 0.0014$ ) was seen for patients ages  $\leq 40$  [27]. Risk factors for local relapse were young age ( $\leq 50$  years) and high-grade invasive ductal carcinoma. A 16 Gy sequential boost dose to the surgical bed significantly reduced the rate recurrence (19.4 vs 11.4%; HR 0.51;  $p = 0.0046$ ; 18.9 vs 8.6%; HR 0.42;  $p = 0.01$ ) [27]. Hence, not all cases do benefit from an additional dose to the surgical bed, but only a subset of patients stratified according to clinical characteristics and tumor features. In general, the boost dose to the lumpectomy cavity can be delivered after the WBRT phase, employing a sequential approach or incorporated within the irradiation of the whole breast with a concomitant boost or simultaneous integrated boost strategy [28, 29]. Incorporating the boost dose in the whole-breast phase can shorten the overall treatment time, with a further acceleration of treatment [30]. Moreover, dosimetric advantages in terms of normal tissue avoidance and dose homogeneity and conformity within the lumpectomy cavity can be seen [26]. The role of boost integration within a hypofractionated WBRT schedule is being explored in few prospective trials. In the USA, the RTOG 1005 trial was launched as a phase III prospective study exploring accelerated WBRT for EBC, comparing standard RT (50 Gy/25 fractions) (with the option of 42.7/16 fr; 2.67 Gy daily) followed by a sequential boost of 12–14 Gy/6–7 fractions vs an hypofractionated accelerated WBRT schedule of 40 Gy/15 fractions (2.67 Gy daily) with a concomitant boost of 3.2 Gy to the tumor bed (up to 48 Gy/15 fractions) [26]. This trial has terminated accrual, and results are awaited. In

the UK, the IMPORT High trial tested dose escalated RT delivered with IMRT in early breast cancer patients with higher than average risk of local recurrence, with the primary end-point of palpable induration inside boost volume of irradiated breast [26]. The standard arm comprised 40.5 Gy/15 fractions (2.7 Gy daily) and a sequential tumor bed boost of 16 Gy/8 fractions for adjunctive 1.6 weeks (23 fractions for total of 4.6 weeks). Two different experimental arm were chosen: in addition to 2.4 Gy  $\times$  15 fractions to the whole breast and 2.67 Gy  $\times$  15 fractions to the index quadrant, the first arm received 3.2 Gy  $\times$  15 fractions (up to 48 Gy), while the second arm got 3.5 Gy  $\times$  15 fractions (up to 53 Gy) to the tumor bed. These schedules were calculated (considering an  $\alpha/\beta$  ratio = 3 Gy for tumor control) as isoeffective to 60 and 69 Gy, respectively [26]. The planned global sample size has been reached, and results are awaited. Since the first results of the aforementioned trials have yet to be published, our data provide long-term evidence on the clinical consistency in terms of local control, survival toxicity profile and cosmetic results of hypofractionated WBRT after BCS for EBC delivered with a concomitant boost to the lumpectomy cavity. This approach can be safely implemented in routine clinical practice.

**Acknowledgments** The Authors would like to thank all the professionals involved in the Breast Unit of the Ivrea Community Hospital and ASL Torino 4, Italy.

#### Compliance to ethical standards

**Conflict of interest** We declare that we do not have any conflict of interest.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Ethical standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Ethical Approval** The present study has been reviewed and approved by the Ethical Review Board of Ivrea Community Hospital, ASLTO4, Ivrea, Italy.

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