Adjuvant Hypofractionated Radiotherapy with Weekly Concomitant Boost for Women with Early Breast Cancer: The Clinical Experience at Genoa University

RENZO CORVÒ[1,3], FRANCESCO RICCHETTI[1], DANIELA DOINO[3], PAOLO TORIELLI[3], STEFANO AGOSTINELLI[2], FRANCESCA CAVAGNETTO[2], FLAVIO GIANNELLI[1], ALESSIA D'ALONZO[1], STEFANO VAGGE[1], LILIANA BELGIOIA[3] and MARINA GUENZI[1]

[1]*Radiotherapy Department, University and National Institute for Cancer Research, Genoa, Italy;*
[2]*Medical Physics Department, National Institute for Cancer Research, Genoa, Italy;*
[3]*School of Radiotherapy, University of Genoa, Italy*

Abstract. *The aim of this investigation was to evaluate the feasibility of a shortened whole-breast irradiation schedule with a concomitant boost delivered to the tumor bed once-a-week in patients with early breast cancer submitted to conservative surgery. Patients and Methods: Patients with pT1 and pT2 M0 carcinoma of the breast were selected. The basic course consisted of 4600 cGy to the whole breast in 20 fractions, 4 times a week, for 5 weeks. Once a week, a concomitant boost of 120 cGy was delivered to the lumpectomy area. Results: From March 2007 to August 2008, we assessed this radiotherapy schedule in 377 patients. According to the RTOG/EORTC Toxicity Criteria, at treatment completion, 85% of patients showed G0-1, 12% G2 and 3% G3 skin toxicity. At 24 months, late toxicity was G0 in 92%, G1 in 7% and G2 in 1%; cosmesis was excellent or good in 95% of patients. To date, at a median follow-up of 33 months, no patient has yet experienced local relapse. Conclusion: A shortened whole-breast irradiation schedule with a weekly concomitant boost may be an alternative option with acceptable toxicity and excellent cosmesis.*

Adjuvant radiotherapy (RT) has become the standard treatment for stage I-II breast cancer since ultimate locoregional control rates after conservative surgery and radiotherapy proved to be similar to those obtained by radical surgery alone (1, 2). Technical modalities of radiotherapy delivery include external 3-D conformal treatment, interstitial or endocavitary brachytherapy or intraoperative radiotherapy (3, 4). Traditionally, external RT consists of two planned courses: 50 Gy or an equivalent biological dose is delivered to the whole breast (WBI) in 25 fractions over 5 weeks (5 fractions per week) followed by 10-16 Gy delivered in 5-8 fractions over 1-2 weeks to the surgical site of tumor removal (3). In an attempt to intensify treatment especially when RT is delivered sequentially to chemotherapy several months after surgery a simultaneous boost has been introduced in clinical practice by using 3-D conformal radiotherapy or intensity-modulated RT (5,6). Preliminary results from experiences where a boost dose was delivered either daily after WBI (6) or weekly on Saturday as a sixth fraction (7) appear interesting, with a good feasibility in terms of acute toxicity. Since November 2004, we have proposed a concomitant boost technique delivered once a week (W-CB) during a moderately hypofractionated WBI course; compared to the daily-boost regimen (6) this W-CB schedule has practical advantages such as a very limited number of boost delivery sessions in an overall treatment time shortened to 5 weeks. Here we present the results in feasibility obtained at the University of Genoa, National Institute for Cancer Research, from 377 patients with early breast cancer treated with the W-CB schedule; the easy implementation of this RT schedule and relatively low incidence of acute and short-term late toxicity are presented and discussed in detail.

Correspondence to: Francesco Ricchetti, S.C. Oncologia Radioterapica, Istituto Nazionale per la Ricerca sul Cancro, Largo Rosanna Benzi, 10, 16132 Genova, Italy. Tel +39 0105600014, Fax: +39 0105600039, e-mail: francesco.ricchetti@istge.it

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Patients and Methods

Patients. From March 2007 to August 2008, three hundred and seventy-seven consecutive female patients with early breast cancer scheduled to undergo adjuvant external RT after breast-conserving surgery were included in this controlled clinical trial. Eligibility criteria for enrollment were the following: breast carcinoma (ductal, lobular and other histotypes); stage pT1 or pT2, pN0-N3 without

Table I. *Radiotherapy schedule with weekly concomitant boost.*

Week	1							2							3							4							5					
WBI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Dose (Gy)	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	46 Gy
				↑						↑						↑						↑						↑					
W-CB				-						-						-						-						-					
Dose (Gy)				1.2						1.2						1.2						1.2						1.2					6 Gy

WBI: Whole-breast irradiation; W-CB: weekly concomitant boost.

distant metastases (M0) according to UICC-TNM, 2002 version; exclusion criteria were: gross involvement of surgical margins; previous thoracic irradiation; synchronous second primary tumor; age greater than 80 years.

All the patients provided informed consent before starting RT. The RT schedule was planned either immediately after conservative surgery in patients at low-risk of distant failure or sequentially after chemotherapy in patients at high-risk of disease progression. The patients were assigned to different prognostic classes according to the St. Gallen Consensus Conference (8).

Radiotherapy fractionation. The basic course for WBI consisted of 4600 cGy prescribed to the ICRU 50 reference point dose and delivered in 20 fractions, 4 times a week, for 5 weeks. Once a week, immediately after WBI, a concomitant photon boost (W-CB) of 120 cGy was delivered to the lumpectomy area (Table I). The total nominal dose delivered to the tumor surgical bed (considering whole-breast dose and W-CB dose) was 52 Gy in 20 fractions over 5 weeks.

Radiobiological equivalent dose. Using the linear-quadratic cell survival model (9), we calculated the fraction size and total doses for the breast and boost volumes which were biologically equivalent to the total dose delivered in 2-Gy fractions with sequential boost. The biological comparison between the standard adjuvant RT schedule and explored W-CB schedule is shown in Table II. For this purpose, an α/β ratio of 4 Gy for tumor response, an α/β ratio of 10 Gy for acute responding normal tissues, an α/β ratio of 1.7 Gy for late (fibrosis) responding normal tissues and an α/β ratio of 2.5 Gy for vascular tissues were used.

Definition of target volumes and organs at-risk. A planning computed tomography (CT) scan was made for each patient. The patients were positioned on a wing-board with both arms raised above the head. Radiopaque catheters and markers were placed to locate palpable breast and surgical scars. An ink mark was made on the sternum skin to enable patient repositioning during treatment. Patients were scanned from the level of the larynx to the level of the upper abdomen, including both lungs, with a scan thickness and index of 5 mm. The CT data were transferred to the Eclipse Treatment Planning System (Varian, Palo Alto, CA, USA). The whole breast clinical target volume (WB-CTV) included the glandular breast tissue of the ipsilateral breast. The WB-CTV did not extend into the pectoralis major, nor the ribs, and did not include the skin. The whole-breast planning target volume (WB-PTV) was generated by adding a 3-D margin of 5 mm around the breast CTV. A margin of 10 mm was used in the cranial and caudal directions. The definition of the lumpectomy cavity was guided by the presence of surgical clips, as well as by hematoma, seroma and/or other surgery-induced changes considered to be part of the lumpectomy cavity. The CB-CTV was generated by adding a 3-D margin of 10 mm around the lumpectomy cavity. The CB-PTV was generated accordingly by adding a further margin of 5 mm. According to internal department policy, in patients with 4 or more positive nodes in the axilla, a supraclavicular field was added to cover areas at potential risk of microscopic disease in locoregional lymphatic areas: the hemi-field technique was used to match separation between the tangential and supraclavicular beams. The supraclavicular area was irradiated to the same prescription dose as the whole breast (46 Gy in 20 fractions over 5 weeks). Regarding organs at risk (OARs) the heart was contoured to the level of the pulmonary trunks superiorly, including the pericardium and excluding the major vessels. Both lungs were separately contoured, by considering only the ipsilateral lung as an OAR. The inner quadrants of the contra lateral breast were contoured as volume of interest (VOI_s).

Treatment planning. Two opposing tangential beams were planned to conformally cover the WB-PTV. A multi-leaf collimator (MLC) was used to spare OARs according to individual anatomy. The appropriate gantry angles were determined in order to achieve maximal avoidance of the heart, ipsilateral lung and contralateral breast. Subsequently, a boost plan was created conformal to the CB-PTV. It consisted of two or more photon beams with manually selected gantry angles. Wedge and MLC shielding were selected in order to obtain a 95% isodose encompassing the boost PTV. A cumulative dose-volume histogram was created to evaluate dose distribution to WB-PTV, CB-PTV, OARs and VOIs and accept the proposed plan.

Radiation treatment. Generally the RT course started on Monday and ended on Friday. A weekly pause was planned for Wednesday. CB treatment was added each week on Thursday or on Friday. Radiotherapy was performed with 6-MV photon fields. Portal films of WBI and W-CB fields were taken at least once during the first treatment day and quantitatively compared to digitally reconstructed radiographs (DRR) and simulator images to ensure accurate set up.

Follow-up. Clinical evaluations were performed every two weeks during treatment course and at treatment completion. Follow-up evaluations was performed every six months after treatment end. Hormonal treatment, when indicated, was delivered during RT treatment and was not discontinued.

Evaluation of toxicity and cosmesis. Patients were evaluated in order to determine the severity and incidence of acute and late toxicity

Table II. *Characteristics of 377 patients considered for feasibility evaluation.*

Characteristic	Number of patients (%)
Age (years)	
<50	145 (38.5%)
>50	232 (61.5%)
Pathological tumor stage	
p T1a	40 (12.5%)
p T1b	61 (16.5%)
p T1c	180 (47%)
p T2	96 (24%)
Pathological nodal stage	
p N0	243 (64.5%)
p N1	108 (28.6%)
p N2	14 (3.7%)
p N3	8 (2.1%)
p Nx	4 (1.1%)
Histology	
Ductal carcinoma	312 (83%)
Lobular carcinoma	62 (16%)
Other histotypes	3 (1%)
Surgical margins	
Negative	325 (86.2%)
Positive	19 (5%)
Close	33 (8.8%)
Hormonal status	
Positive	294 (78%)
Negative	83 (22%)
Previous chemotherapy	182 (48.3%)
Concomitant hormonotherapy	294 (78%)

with the W-CB technique. Acute toxicity was assessed at RT completion and one month after a treatment course, whereas late toxicity was scored at least six months after the end of treatment. The maximal toxicity was scored using the Common Terminology Criteria (CTC) for Adverse Events, version 3.0 (10), using RTOG/EORTC scale for radiation-related toxicity as reference (11). This resulted in a toxicity score for each patient. Cosmesis was assessed 24 months after treatment end using a cosmetic scale of excellent, good, fair or poor as previously reported by Fowble *et al*. (12).

Results

Patients. At the time of the present report (September 2010), all 377 patients treated with the W-CB RT schedule had achieved the minimum follow-up of 24 months (median follow-up 33 months, range: 24-41 months). All the accrued patients were included in this analysis (by intention-to-treat). Patient characteristics are listed in Table II. A total of 182 (48%) patients received chemotherapy prior to adjuvant RT, and 294 (78%) patients received hormonotherapy concurrently to radiation. All patients completed the planned RT W-CB schedule. Fifteen patients who had four or more pathologically involved lymph nodes at axillary dissection underwent RT on breast and supraclavicular areas. To date, no patient has presented locoregional (breast, axilla and supraclavicular node area) recurrence; twelve patients presented distant disease progression at 18 (n=2), 25 (n=3), 27 (n=8), 28 (n=4) and 32 (n=3) months, respectively. As a consequence, 357 (94.6%) patients are alive and disease free.

Table III. *Assessment of acute skin morbidity and late skin and subcutaneous tissue morbidity and cosmesis in 377 patients treated with W-CB.*

Morbidity score	Time of clinical assessment	Number of patients (%)
RTOG/EORTC Acute toxicity*	At last radiotherapy session	
0		119 (32%)
1		201 (53%)
2		47 (12%)
3		10 (3%)
Skin/subcutaneous late toxicity*	24-Months after radiotherapy completion	
0		349 (92 %)
1		25 (7%)
2		3 (1%)
3		0
Cosmesis score*	24-Months after radiotherapy completion	
Excellent		323 (85%)
Good		37 (10%)
Fair		17 (5%)
Poor		0

*See references 10, 11 and 12.

Assessment of acute and 24-month late toxicity. Two clinical examinations were performed by a group of independent physicians at treatment completion and after 24 months. Locoregional side-effects were evaluated according to RTOG acute/late toxicity criteria (11). As shown in Table III, at the end of radiotherapy, among 377 evaluable patients, 85% showed G0-1, 12% G2 and 3% G3 skin toxicity. At 24 months, late skin and subcutaneous toxicity was assessed with score G0 in 92%, G1 in 7% and G2 in 1% of patients. Cosmesis was assessed and scored at 24 months after radiation completion: 85% of patients had excellent cosmesis, 10% good cosmesis and 5% had fair cosmesis. No patient showed poor cosmesis.

Discussion

In breast cancer management, recent advances have been focused toward the reduction of overall adjuvant RT treatment time (13, 14), by delivering a dose biologically equivalent to the standard schedule consisting of 6 weeks of treatment to a total dose up to 60 Gy. The rationale of

Table IV. *Biological comparison between standard adjuvant radiotherapy schedule and explored W-CB schedule.*

Adjuvant radiotherapy	Basic course and boost delivery	BED			
		Vascular damage (α/β=2.5 Gy)	Fibrosis (α/β=1.7 Gy)	Acute skin effects (α/β=10 Gy)	Cancer clonogen control (α/β=4 Gy)
Standard schedule 60 Gy/30 fx/6 w	WBI basic course: 50 Gy in 25 fx over 5 weeks Sequential boost: 10 Gy in 5 fx over 1 week	108	130	72	90
W-CB schedule 52 Gy/20 fx/5 w	WBI basic course: 46 Gy in 20 fx over 5 weeks WCB: 1.2 Gy, once a week for 5 weeks	108	134	66	87
Difference in dose			+3%	–8.5%	–4%

BED: Biologically effective dose; w: weeks; WBI: whole-breast irradiation; W-CB: weekly concomitant boost; fx: fractions.

delivering the boost dose to the surgical bed during WBI appears particularly appealing: the RT course may be shortened by one or two weeks and a greater dose per fraction is delivered to the area at high risk of residual microscopic disease. We designed an original fractionation schedule consisting of four treatment sessions per week over 5 weeks. The single daily fraction is 2.3 Gy and the total WBI dose is 46 Gy. To avoid a weekly radiation dose superior to 10 Gy, a planned treatment break is scheduled on Wednesdays (see Table I). Once a week, generally before the week-end break, a supplement of 1.2 Gy to the surgical tumor bed is simultaneously given with WBI: when the W-CB is delivered, the total dose delivered to the surgical bed is 3.5 Gy. This daily dose is below the threshold dose of 4 Gy that appeared to be correlated to an increased risk of severe late effects. As shown in Table IV, the nominal total dose administered with our schedule including WBI and W-CB techniques compares favorably with the standard fractionation dose adopted in breast irradiation (respectively, biologically effective dose (BED) for late response with an α/β=1.7 Gy: 134 Gy *vs*. 130 Gy, BED for acute response with an α/β= 10 Gy: 66 Gy *vs*. 72 Gy, BED for clonogen cancer cells response with an α/β= 4 Gy: 87 Gy *vs*. 90 Gy). As shown in Table IV, the two schedules are iso-effective with respect to vascular damage, while the W-CB schedule is less toxic (by 8.5%) than standard schedule regarding acute effects. In the comparison between the two regimens, although slightly less effective with respect to breast tumor control in the linear-quadratic model (by 4%), the biological dose of the W-CB regimen is not significantly different from the one estimated for the standard schedule. In the present report, according to recent investigations, we have assumed an α/β value of 4 Gy for tumor control which is close to that estimated for late responding tissues (15). If this were not the case, the use of an α/β=10 Gy (similar to that for squamous cell carcinoma) would result in a lower BED for tumor control with the W-CB schedule (by 8.5%).

The schedule was adopted for 377 consecutive patients who met the eligibility criteria. The clinical outcomes presented here clearly confirm the feasibility of this schedule in the treatment of patients submitted to RT after conservative surgery. Specifically, all the patients concluded their treatment in the planned overall time of 5 weeks. Twelve months after the end of radiotherapy, only three patients (1%) experienced G2 toxicity according to the RTOG/EORTC classification. Although 10 patients experienced G3 acute toxicity at the end of RT, no patient had G3 late toxicity after 24 months. In the 48 women with G2 toxicity at the last fraction of radiotherapy, local side-effects were not evident in the W-CB area but were frequently observed either in axillary area or in the lower border of the breast. Even if the assessment of cosmesis at 24 months may be considered only a surrogate end-point of long-term cosmesis, at that time an excellent or good score was reported for 85% of patients. To date, no patient has relapsed in the breast or locoregional lymph node areas. A longer follow-up is clearly needed to confirm that this schedule assures excellent locoregional disease control and very good cosmesis.

Conclusion

The proposed 3D conformal W-CB technique appears to be a straightforward technique that has the advantage of providing treatment flexibility, shortening the treatment course. We suggest that this radiation schedule may provide an alternative option to conventional WBI with acceptable acute and late toxicity, good compliance and excellent cosmesis.

References

1 Veronesi U, Cascinelli N, Mariani I, Greco M, Saccozzi R, Luini A, Aguilar M and Marubini E: Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Eng J Med *347*: 1227-1232, 2002.

2 Shafiq J, Delaney G and Barton MB: An evidence-based estimation of local control and survival benefit of radiotherapy for breast cancer. Radioth Oncol *84*: 11-17, 2007.

3 Poortmans P: Evidence-based radiation oncology: breast cancer. Radioth Oncol *84*: 84-101, 2007.

4 Orecchia R, Ciocca M, Lazzari R, Garibaldi G, Leonardi MC, Luini A, Intra M, Gatti G, Veronesi P, Petit JI and Veronesi U: Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. Breast *12*: 483-490, 2003.

5 Guerrero M, Li XA, Earl MA, Sarfaraz M and Kiggundu E: Simultaneous integrated boost for breast cancer using IMRT: a radiobiological and treatment planning study. Int J Radiat Oncol Biol Phys *59*: 1513-1522, 2004.

6 Van der Laan HP, Dolsma W V, Maduro JH, Korevaar EW, Hollander M and Langendijk JA: Three-dimensional conformal simultaneously integrated boost technique for breast-conserving radiotherapy. Int J Radiat Oncol Biol Phys *68(4)*: 1018-1023, 2007.

7 Corvò R, Giudici S, Maggio F, Bevegni M, Sampietro C, Lucido MR and Orsatti M: Weekly concomitant boost in adjuvant radiotherapy for patients with early breast cancer: preliminary results and feasibility. Tumori *94*: 706-711, 2008

8 Primary Therapy of Early Breast Cancer; 9th International Conference, January, 26-29, 2005, St Gallen, Switzerland. Breast *14(suppl 1)*: S1-56, 2005.

9 Joiner MC and van der Kogel AJ: The linear-quadratic approach to fractionation and calculation of isoeffect relationships. *In*: Basic Clinical Radiobiology, 2nd edn. Steel GG (ed.). London: Arnold, pp. 106-122, 1997.

10 National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events. Version 3.0. Available at: http://ctep.cancer.gov

11 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31*: 1341-1346, 1995.

12 Fowble B, Solin LJ and Schultz DJ: Conservative surgery and radiation for early breast cancer. *In*: Breast Cancer Treatment: A Comprehensive Guide to Management. Fowble B, Goodman RL, Glick JH, Rosato EF (eds.). St Louis, MO, Mosby Year Book, pp. 105-149, 1991.

13 Sanders ME, Scroggins T, Ampil FL and Li BD: Accelerated partial breast irradiation in early-stage breast cancer. J Clin Oncol *25(8)*: 996-1002, 2007.

14 Sauer R, Sautter-Bihl A, Budach W, Feyer P, Harms W, Souchan R, Wollwiener D, Kreienberg R and Wenz F: Accelerated partial breast irradiation. Consensus Statement of 3 German Oncology Societies. Cancer *110*: 1187-94, 2007.

15 Owen JR, Ashton A and Bliss JM: Effect of radiotherapy fraction size on tumor control in patients with early-stage breast cancer after local tumor excision. Long-term results of a randomized trial. Lancet Oncol *7*: 467-471, 2006.

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