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CLINICAL INVESTIGATION **Breast**

PRELIMINARY RESULTS OF ELECTRON INTRAOPERATIVE THERAPY BOOST AND HYPOFRACTIONATED EXTERNAL BEAM RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY IN PREMENOPAUSAL WOMEN

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Purpose: To report the acute and preliminary data on late toxicity of a pilot study of boost with electron intraoperative therapy followed by hypofractionated external beam radiotherapy (HEBRT) of the whole breast.

Methods and Materials: Between June 2004 and March 2007, 211 women with a diagnosis of early-stage breast cancer were treated with breast-conserving surgery. During surgery, an electron intraoperative therapy boost of 12 Gy was administered to the tumor bed. Adjuvant local treatment was completed with HEBRT, consisting of a course of 13 daily fractions of 2.85 Gy to the whole breast to a total dose of 37.05 Gy. Acute toxicity of the breast was evaluated at the end of HEBRT and at 1 month of follow-up. Late toxicity was recorded at 6 and 12 months of follow-up.

Results: We report the data from 204 patients. The maximal acute skin toxicity was observed at the end of HEBRT (182 patients evaluable) with 7 (3.8%) Grade 3, 52 (28.6%) Grade 2, 123 (67.6%) Grade 1, and no Grade 0 or Grade 4 cases. A total of 108 patients were evaluated for late toxicity. The recorded late skin toxicity was Grade 4 in 1 patient (0.9%), Grade 3 in 1 patient, and Grade 2 or less in 106 patients (98.2%).

Conclusions: The results of this study have shown that electron intraoperative therapy followed by HEBRT allows for the delivery of a high dose to the tumor bed and an adequate dose to the whole breast. This treatment is feasible, compliance is high, and the rate of acute toxicity and the preliminary data on chronic toxicity seem acceptable. **© 2008 Elsevier Inc.**

Electron intraoperative therapy, Intraoperative radiotherapy, Breast cancer, Hypofractionation, Breast-conserving surgery.

INTRODUCTION

Breast-conserving surgery (BCS) followed by adjuvant radiotherapy (RT) has been shown to be equivalent to mastectomy for the treatment of early-stage breast cancer (1–3).

The standard course of whole breast RT last for 5–7 weeks, causing logistical problems in terms of time and travel difficulties for the patients. However, in young women, breast tumors generally present with aggressive biologic behavior and require intensive treatment (4, 5).

In patients who require adjuvant chemotherapy, it is difficult to define the optimal sequence between RT and chemotherapy that will minimize the risk of local recurrence and distant metastases (5). Many studies have significantly correlated young age with poorer local control and local relapse-free survival rate (4, 5). In the ''conservative surgery alone'' arm of the Milan III trial, 85% of local failures developed in the scar area, with a rate two times greater in women <45 years old than in patients 46–55 years old (6). The European Organization for the Research and Treatment of Cancer trial 22881/10882 demonstrated that a greater radiation dose to the primary tumor area significantly reduced the rate of local recurrence at 5 years, with the largest clinical benefit achieved in women <40. These data suggest the need for a supplemental dose of irradiation to the surgical bed, especially in younger women. Moreover, most trials have shown that, particularly in premenopausal women, the rate of development of breast tumors outside the area of the initial primary tumor, is not negligible (≤42%) (7). A recent meta-analysis

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Table 1. RTOG cutaneous acute radiotherapy toxicity score

Grade	Description
0	No change over baseline
1	Follicular, faint, or dull erythema; epilation, dry desquamation, or decrease in sweating
2	Tender, bright erythema; patchy, moist desquamation or moderate edema
3	Confluent, moist desquamation other than skin folds; pitting edema
4	Ulceration, hemorrhage, necrosis

Abbreviation: RTOG = Radiation Therapy Oncology Group.

has shown that whole breast radiotherapy reduces local recurrence by a factor of four (with boost by a factor of eight), indicating that whole breast radiotherapy has an effect on the total breast, and not only on the tumor bed (8).

At the European Institute of Oncology, 21-Gy full-dose intraoperative radiotherapy with electrons (ELIOT) after BCS for limited-stage breast cancer has been extensively investigated since 1999 (9). On the basis of this experience, we designed a trial for premenopausal women in which hypofractionated external beam radiotherapy (HEBRT) to the whole breast follows the ELIOT boost to further reduce the total time of adjuvant RT. A major potential benefit of this treatment schedule would be the possibility to complete EBRT in 13 daily fractions, enabling systemic therapy to start within a few weeks of surgery.

This preliminary report presents the feasibility and safety in terms of acute toxicity and the preliminary data on chronic toxicity and patient compliance.

METHODS AND MATERIALS

The eligible patients were premenopausal women <49 years old with invasive breast cancer, clinical Stage T1-T2 and clinical minimal axillary involvement (N0-N1), who were candidates to undergo conservative surgery. All patients underwent bilateral mammography and/or breast ultrasonography for staging purposes. On the basis of our experience with the sentinel node technique, which showed a sensitivity of 95.6% and specificity of 100%, clinical Stage N0 patients underwent sentinel node biopsy only, followed by complete axillary dissection, in the case of positive sentinel nodes (10). Clinically node-positive patients underwent complete axillary dissection.

The exclusion criteria were clinical Stage T4 disease, multicentric disease, pregnancy or lactating, severe nonmalignant disease (*e.g.,* cardiovascular or pulmonary disease), connective tissue disorder (*e.g.,* lupus erythematosus, scleroderma), and the presence of psychiatric disorders that would preclude informed consent or adherence to the program.

Acute toxicity of the breast was evaluated during HEBRT, at the end of HERBT, and at 1 month after the end of the treatment using the Radiation Therapy Oncology Group scale (Table 1) (11). The irradiated area was divided into six regions (medial, lateral, areola, sulcus, axilla, and boost area). Late toxicity was evaluated using the Subjective Objective Management Analytic Late Effect of Normal Tissue criteria (Table 2), at 6 and 12 months of follow-up (12). For the subjective assessment, the patients were asked to assign

Table 2. LENT-SOMA criteria for breast

Criteria	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal, hypersensation, pruritus	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective				
Edema	Asymptomatic	Symptomatic	Secondary dysfunction	
Fibrosis/fat necrosis	Barely palpable increased density	Definite increased density and firmness	Very marked density, retraction and fixation	
Telangiectasia	<1/cm^2	1–4/cm^2	>4/cm^2	
Lymphedema, arm (circumference)	2–4-cm increase	>4–6-cm increase	>6-cm increase	Useless arm, angiosarcoma
Retraction/atrophy	10–25%	>25–40%	>40–75%	Whole breast
Ulcer	Epidermal only, ≤1 cm^2	Dermal, >1 cm^2	Subcutaneous	Bone exposed, necrosis
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Edema			Medical intervention	Surgical intervention/ mastectomy
Lymphedema, arm		Elevate arm, elastic stocking	Compression wrapping, intensive physiotherapy	Surgical intervention/ amputation
Atrophy				Surgical intervention/ mastectomy
Ulcer		Medical intervention	Surgical intervention, wound debridement	Surgical intervention/ mastectomy
Analytic				
Photographs	Photographic assessment of skin changes			Yes/no, date
Tape measure	Assessment of breast size and arm diameter			Yes/no, date
Mammography	Assessment of skin thickness and density			Yes/no, date
CT/MRI	Assessment of size, fat atrophy, fibrosis			Yes/no, date

Abbreviations: LENT-SOMA = late effects of normal tissue–subjective, objective, management, and analytic; CT = computed tomography; MRI = magnetic resonance imaging.

a score for the treated breast with respect to itching, pain, and burning during EBRT, at the end of treatment, and at every follow-up visit. For this purpose, a 0–10 numeric rating scale, with endpoints marked as no symptoms (score 0) and worst severity ever experienced (score 10), was adopted (13). We arbitrarily divided the reported symptom scores into four groups: 0, 1–3, 4–7, and 8–10. A digital photograph of the irradiated breast was taken at each visit.

Treatment protocol

Quandrantectomy and sentinel node biopsy with or without Level I, II, and III axillary dissection were performed. Thereafter, an electron-anticipated RT boost was administered to the tumor bed, with one of the two dedicated mobile intraoperative radiotherapy accelerators (Liac and Novac). A round Plexiglas applicator tube with a 4–10-cm diameter collimated the electron beam with 3–9-MeV energies. The energy of the electron beams was selected according to the measured thickness of the reconstructed gland. Protection of the thoracic wall and underlying critical structures was achieved using aluminum and lead discs placed between the gland and the pectoral muscle.

The dose, prescribed to the 90% reference isodose, was 12 Gy in a single fraction (equivalent to 13.33 Gy to the depth of the maximal dose). Patients were required to start HEBRT in the fourth week after surgery, and to undergo an ELIOT boost, consistent with the stage of wound healing. Three-dimensional EBRT was delivered with two opposed tangential fields of 6-MV photons to the whole breast. The beam axes were angled anteriorly to set the coplanar posterior edges. The total prescribed dose was 37.05 Gy delivered in 13 daily fractions of 2.85 Gy (biologically equivalent, for α/β ratio of 10, to 47.6 Gy delivered in 2 Gy/fraction), using an isocentric technique.

Patients were treated in a breast board in the supine position, with both arms abducted above their head. Cutaneous radiopaque markers were placed to outline the palpable ipsilateral breast tissue and surgical bed. Contiguous 5-mm computed tomography axial images were obtained, including the entire breast and lungs. The data set was then transferred to a three-dimensional treatment planning workstation for treatment planning: the clinical target volume of the whole breast, ELIOT boost volume, contralateral breast, both lungs, and the heart were contoured on each slice. The tumor bed/ELIOT boost volume was usually defined according to the four surgical clips placed intraoperatively to trace the site of excision. In the few cases in which the surgical clips were not present, the boost volume was outlined according to the pretreatment imaging, description of the surgical procedure, and visible area of architectural distortion/postoperative edema at computed tomography simulation. The planning target volume was shaped by applying 1.5-cm margins to the clinical target volume in craniocaudal directions using the Beam Eye View (BEV) images. A dose distribution was computer generated on every slice, correcting for lung inhomogeneity. A specific analysis was performed of the dose distribution with particular care with the ELIOT boost volume to avoid any overdosage in that volume. The treatment plans were normalized at the International Commission on Radiation Units and Measurements (ICRU) reference point. Wedges were used to optimize the dose homogeneity to the planning target volume of −5% and +7%, as recommended by ICRU report 50 (14). Dose–volume histogram analysis was performed routinely for all surrounding critical structure (contralateral breast, heart, and ipsilateral lung). In each plan, the central lung distance and, for left-sided breasts, the maximal heart distance, were measured. The organ at risk constraints were as follows: 5% of the heart and 20% of the lung were kept to <50% of the prescribed dose and no point of the contralateral breast could receive >15% of the prescribed dose.

If regional node RT was needed, it was postponed until after chemotherapy and was given as a conventional fractionation of 2 Gy to a total dose of 50 Gy.

Biologically effective dose: radiobiologic considerations

To compare the conventional treatment of 50 Gy in 25 fractions with the altered treatment of 37.05 in 13 fractions to the whole breast, a conversion to a biologic effective dose (BED) using the linear quadratic equation was performed (15). To make the calculations, an α/β ratio of 10, as reported for both carcinoma cell lines and skin (considering early reactions), was used. For late reactions (lung and skin), an α/β ratio of 3 was used.

A dose of 37.05 Gy administered in 13 fractions is equivalent to 47.6 Gy using a BED of 10 and 72.2 Gy using a BED of 3, and 50 Gy in 25 fractions is equal to 60 Gy using a BED of 10 and 83.3 Gy using a BED of 3.

We took into consideration the 2.5-week difference in overall time for the two schedules. However, before calculating the time correction, we first calculated the equivalent EQD2 values for the hypofractionated scheme, using the following equation: $EQD2 = D[d + (\alpha/\beta)]/[2+ (\alpha/\beta)] = 39.7$ Gy, where D is the altered schedule total dose, d is the altered daily dose, and α/β for tumor = 10. applying the equation for time correction, $EQD2,T = EQD2,t - (T - t) \times D_{prolif}$, where D_{prolif} is the dose recovered daily owing to proliferation (assumed to be about 0.7 Gy/d for most tumors), T is the overall time of the altered schedule (17 days), t is the overall time of the conventional schedule (33 days), the magnitude of the time effect is quantified by $EQD2 = 39.7 + (16 \times 0.7) = 51$ Gy. Thus, correcting for differences in overall time, 37.05 Gy delivered within 17 days is biologically equivalent to 51 Gy in 2-Gy fractions.

Considering the early reactions, a D_{prolif} of 0.12 is applicable for skin erythema and 0.54 for lung pneumonitis, resulting in a correction for the overall treatment time that can be quantified by the two corresponding equations: $EQD2 = 39.7 + (16 \times 0.12) = 41.6$ Gy and $EQD2 = 39.7 + (16 \times 0.54) = 48.3$ Gy. In contrast, the influence of the overall treatment time on late effects can be neglected.

RESULTS

Between June 2004 and March 2007, 211 patients were enrolled in the study. Of the 211 patients, 7 underwent surgery and ELIOT but did not complete the planned treatment with HEBRT. Of these 7 patients, 4 underwent mastectomy after their primary surgery because of positive margins on final pathologic examination, 1 with positive cytology for malignant cells did not require additional treatment because no tumor was found on the final pathologic assessment, 1 had metastatic disease detected just before beginning HEBRT, and 1 had liponecrosis of the surgical area and a long-lasting delay in wound healing that did not allow for the delivery of HEBRT.

We analyzed the data from the 204 patients (median age, 41 years; range, 24–49) who completed the whole planned treatment scheme. Up to March 2007, the median follow-up for radiation toxicity was 11 months (range, 6–14.6). No patient was lost to follow-up. Table 3 lists the demographic and tumor characteristics (16).

A few patients, 14 (6.8%), had large breasts (>1,000 cm^3); for most, 122 (59.8%), the breast size was 400–1,000 cm^3

Table 3. Patient characteristics (n = 204)

Characteristic	Value
Age (y)	
Median	41
Range	24–49
Histologic type	
IDC	175 (85.7)
ILC	11 (5.3)
Mixed IDC and ILC	4 (2.0)
Other	11 (5.5)
DCIS	3 (1.5)
pT stage	
pT1mic	2 (1.0)
pT1a	8 (3.9)
pT1b	33 (16.2)
pT1c	106 (52)
pT2	49 (24)
pT3	1 (0.5)
pTis	3 (1.5)
ypTX	1 (0.5)
ypT0	1 (0.5)
Tumor diameter (cm)	
Median	1.5
Range	0.2–5.5
Grade	
1	24 (11.7)
2–3	167 (81.9)
Not evaluable/missing	13 (6.4)
AJCC stage	
0	4 (2)
I	94 (46)
IIA	73 (35.8)
IIB	18 (8.8)
IIIA	11 (5.4)
IIIC	4 (2)
Focality	
Single nodule	186 (91.2)
Multifocality	18 (8.8)
Sentinel lymph node biopsy only	127 (62.3)
Sentinel lymph node biopsy and axillary dissection	62 (30.3)
Axillary dissection	77 (37.7)

Abbreviations: IDC = infiltrating ductal carcinoma; ILC = infiltrating lobular carcinoma; DCIS = ductal carcinoma *in situ*; y = classification after initial therapy; AJCC = American Joint Commission on Cancer (2003 staging system).

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

(medium size); 68 patients (33.3%) had a breast volume of <400 cm^3 (small size).

Internal mammary chain biopsy was performed in 20 patients (9.8%) who had presented with an inner quadrant tumor. The resection margins were clear of tumor in all but 1 patient. Three patients who clinically had Stage T1 at presentation were found to have pTis at the final pathologic examination.

Systemic therapy

Eleven patients (5.4%) underwent neoadjuvant treatment with either chemotherapy alone or combined with hormonal therapy. The final pathologic assessment of 1 of the 11 patients reported only microfoci of infiltrating ductal carcinoma, which was therefore classified as Stage ypTX, and in another patient, no cancer cells were found and was therefore classified Stage ypT0.

Of the 204 patients, all but 4 (98%), received adjuvant therapy. Of the 200 patients, 30 (14.7%) received chemotherapy alone, 105 (51.4%) hormonal therapy alone, and 65 (31.9%) underwent both chemotherapy and hormonal therapy. Table 4 lists the details of the systemic adjuvant therapy. To administer systemic therapy as soon as possible, it was often started concomitantly with the last period of HEBRT. The association of radiotherapy and anthracycline-based regimen was rarely performed to avoid any excessive local and systemic toxicity.

Treatment compliance

A 12-Gy ELIOT anticipated boost was administered to all patients. The dose was always prescribed at the 90% isodose with a median depth of 1.5 cm (range, 0.7–2.8) using 4–6-cm diameter collimators. Of the 204 patients, 99.5% completed the whole treatment schedule, including the HEBRT. Only 1 patient (0.5%) was unable to receive HEBRT because of liponecrosis of the surgical area and a long-lasting delay in the wound healing.

The median interval between surgery plus the ELIOT boost and the first day of HEBRT was 22 days (range, 15–80); 88.3% patients started HEBRT within 4 weeks, in accordance with the protocol, 10.8% started within 6 weeks, and 1% started HERBT after 6 weeks. During this interval, 9 patients (4.4%) developed liponecrosis of the treated quadrant. For these 9 patients, the liponecrosis did not cause a relevant delay in beginning HEBRT; in fact, the mean interval between surgery and HEBRT for this subgroup was 24 days (range, 15–35). HEBRT did not start within the 4 weeks required by the protocol mainly because of a delay in wound healing.

Radiotherapy parameters

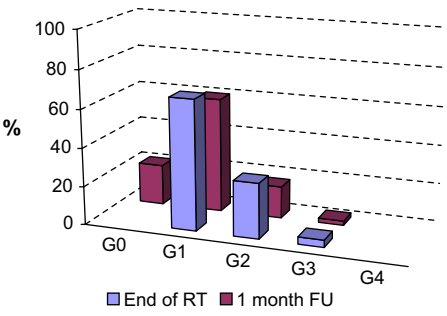
ELIOT boost. The mean gland thickness measured to set the beam energy was 1.5 cm (range, 0.7–2.8). The two energies most used were 5 and 7 MeV, and the collimator diameter used most was 4 cm.

HEBRT dose distribution. Dis-homogeneity within the planning target volume was maintained within the ICRU 50 recommendations. We ensured that the boost area was distant from any hot spots resulting in a mean dose of 100.4%

Table 4. Systemic adjuvant chemotherapy (n = 95)

Chemotherapy regimen	n	%
AC × 4 ± CMF × 3	75	36.8
CEF	6	1.9
CMF × 3/6	4	2
Other	10	5

Abbreviations: A = adriamycin; C = cyclophosphamide; E = epirubicin; F = 5-fluorouracil; M = methotrexate.



	End of RT		1 month FU	
	%	N	%	N
G0	0	0	21.2	28
G1	67.6	123	59.8	79
G2	28.6	52	16.7	22
G3	3.8	7	2.3	3
G4	0	0	0	0

Fig. 1. Radiation Therapy Oncology Group acute skin toxicity at end of hypofractionation external beam radiotherapy (RT) and at 1 month of follow-up (FU).

(range, 96–104%). The extent of the boost area was always defined according to the diameter of the ELIOT applicator; therefore, it was not significantly different when outlined with or without using the surgical clips.

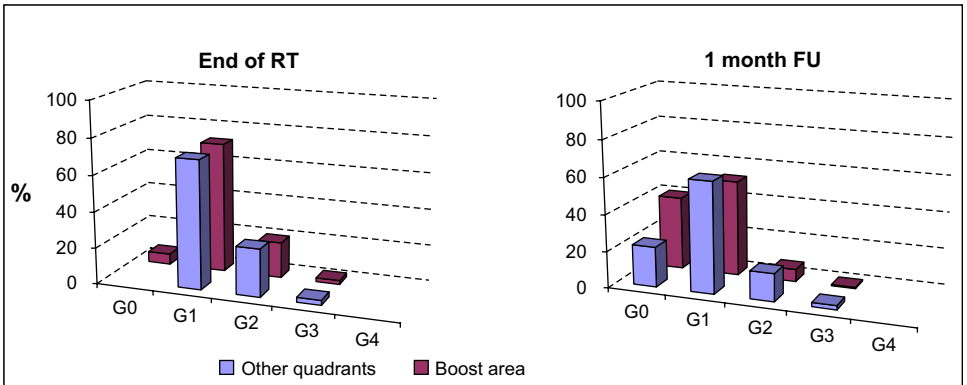
The mean central lung distance was 2 cm (range, 1.2–2.8), with a mean lung volume of 9.2% included in the 50% isodose. For the 108 left-sided breasts, a mean heart volume of 0.8% and 3.6% was included in the 50% and 25% isodose, respectively. The mean maximal heart distance was 0.5 cm (range, 0.1–1.5).

Toxicity

Acute toxicity. The peak incidence of severe skin reaction occurred at the end of treatment. Acute skin toxicity is summarized in Fig. 1. The boost area was not affected by a greater rate of acute skin toxicity, with 4 patients (2.2%) having Grade 3 toxicity at the end of HERBT; 2 had Grade 3 confined to the boost area only. At 1 month of follow-up, no patient had Grade 3 toxicity confined to the boost area only (Fig. 2). Patients with large breasts did not have a greater rate of acute skin toxicity than patients with small or medium breasts (Table 5).

Table 6 details the frequencies of the scores on the numeric rating scale for clinical symptoms of radiation dermatitis at the end of the treatment and at 1 month of follow-up.

Chronic toxicity. A total of 108 patients were evaluable for late subjective and objective toxicity, with a minimal follow-up of 6 months (median, 11; range, 6–14.6) from the end of HEBRT. In 1 patient who had received anthracycline-based chemotherapy starting 2 weeks after the end of HEBRT, Grade 4 skin toxicity was recorded at 6 months follow-up because of liponecrosis of the scar area that developed late. It took 7 months of clinical care and two session of plastic surgery for complete wound healing. Of the 108 patients, 55 (51%) reported Grade 1-2 toxicity and 53 (49%) did not report any pain (Table 7).



RTOG Grading	End of RT		1 month FU	
	Other quadrants	Boost area	Other quadrants	Boost area
G0 (%)	0	6	22	40.2
G1 (%)	70.9	72	60.6	52.3
G2 (%)	26.4	19.8	15.2	6.8
G3 (%)	2.7	2.2	2.3	0.7
G4 (%)	0	0	0	0

Fig. 2. Radiation Therapy Oncology Group (RTOG) acute skin toxicity at end of hypofractionated external beam radiotherapy (RT) and at 1 month of follow-up (FU) for boost area only vs. other quadrants (boost area excluded).

Table 5. Correlation between breast volume and acute skin toxicity at end of HEBRT and at 1 month of follow-up

	At end of HEBRT (%)				At 1-mo of follow-up (%)			
Breast volume (cm^3)	G0	G1	G2	G3	G0	G1	G2	G3
Small (<400)	0	76.7	21.7	1.6	33.3	55.6	11.1	0
Medium (400–1,000)	0	64.2	30.3	5.5	17.6	61.2	17.6	3.5
Large (>1,000)	0	53.8	46.2	0	18.2	54.5	27.3	0

Abbreviations: HEBRT = hypofractionated external beam radiotherapy; G = grade.

Outcome

At a median follow-up of 8.9 months (range, 0.8–32.4), we observed five recurrences: two axillary lymph node metastasis (one Rotter lymph node), two liver metastases, and one liver metastasis associated with a lower neck node metastasis. No patients developed an intrabreast tumor recurrence.

DISCUSSION

A number of randomized trials comparing BCS and whole breast RT with mastectomy have shown the same survival rates, with satisfactory local control (1–3, 8, 15). Many different fractionation schedules have been tested and proved to be effective and comparable to conventional fractionation in randomized studies (17–23). The results of the UKCCR START trial B on hypofractionation are pending (24).

Several studies have significantly correlated young age with poorer local control and local relapse-free survival, but a clear definition of ''young age'' has not yet been defined. For this study, we considered women ≤49 years old as a generalized categorization of premenopausal status (25).

The treatment schedule we used included an ELIOT boost to the tumor bed. Intraoperative RT with high-energy electrons for breast cancer was initially exploited by Dubois (26), Dobelbower and Abe (27), Merrick *et al*. (28), and Dubois *et al*. (29), with good results in terms of local control and cosmesis. Recently, the Montpellier study group reported updated encouraging long-term results in terms of local control and toxicity in 50 women who had received 10 Gy intraoperatively, followed by 50 Gy as postoperative whole breast EBRT (30). Also, interesting results have been reported from a sequential intervention study conducted by Reitsamer *et al*. (31), who treated 188 women with a 12-Gy postoperative electron boost and 190 with an intraoperative electron boost of 9 Gy, and all patients received 51–56.1 Gy of postoperative whole breast RT. The 4-year actuarial rates of local recurrence were 4.3% in the first group and 0% in the second (31).

We previously reported our experience with patients treated with an ELIOT boost dose of 10 and 15 Gy, followed by whole breast EBRT to 44 and 40 Gy, respectively, using conventional fractionation (32). At a mean follow-up of 42 months, 4 of the 25 patients reported mild fibrosis at the boost area (Grade 1 and 2 according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late morbidity scale) (32). Almost no study of hypofractionation in BCS used a boost to the tumor bed because of concerns of possible major toxicity. Nonetheless, the results from the EORTC 22881/10882 trial (8) should be considered, because they demonstrated the benefit of a 16-Gy boost, especially in patients <50 years, who represented the population included in our study.

To further reduce the total treatment duration, we investigated the feasibility of hypofractionation to the whole breast in 13 fractions within a 2.5-week period. The choice of such a fractionation schedule was somewhat empirical. The dose equivalence of this schedule compared with conventional treatment (50 Gy to the whole breast in 2-Gy fractions daily plus a 10-Gy boost dose to the tumor bed in 2-Gy fractions

Table 6. Distribution of patient symptoms according to numeric rating scale at end of HEBRT and 1 month of follow-up

	NRS score (%)			
Symptom	0	1–3	4–7	8–10
Pain				
At end of HEBRT	53.3	18.7	26.4	1.6
At 1-mo follow-up	47.0	22.7	26.5	3.8
Itching (%)				
At end of HEBRT	59.3	22.0	18.2	0.5
At 1-mo follow-up	62.9	16.7	18.2	2.3
Burning (%)				
At end of HEBRT	75.3	12.1	12.6	0.0
At 1-mo follow-up	88.6	6.0	3.9	1.5

Abbreviations: NRS = numeric rating scale; RT = hypofractionated external beam radiotherapy.

Table 7. Chronic toxicity (6–12 months of follow-up) according to SOMA-LENT criteria (n = 108)

Toxicity	G0	G1	G2	G3	G4
Symptom					
Pain	49	40.8	10.2	0	0
Edema	72.2	22.2	5.6	0	0
Fibrosis	34.3	46.3	18.5	0.9	0
Sign					
Telangiectasia	88	7.4	4.6	0	0
Lymphedema arm	94.5	4.6	0.9	0	0
Retraction/atrophy	63.9	28.7	7.4	0	0
Ulcer	99.1	0	0	0	0.9

Abbreviations: SOMA-LENT = late effects of normal tissue–subjective, objective, management, and analytic; G = grade.
Data presented as percentage of patients.

daily) was established using the linear quadratic model. This model could be subject to some criticism, because it was validated for daily fractions of 1.5–4 Gy. Assuming the previous statements to hold true, for an α/β value of 10 Gy for tumors, the BED for the tumor bed would be 72 Gy for conventional fractionation but 74 Gy for a combined ELIOT boost plus hypofractionated whole breast EBRT. For the whole breast, considering a dose of 37.05 Gy administered using a hypofractionated scheme compared with a conventional dose of 50 Gy (2 Gy in 25 fractions), the BED for an α/β ratio of 10 is 48 Gy vs. 60 Gy, neglecting the influence of the overall treatment time. Thus, the biologic effect of our hypofractionated approach on the potential residual tumor foci in the breast outside the original tumor area would be slightly less than the conventional 50 Gy (2 Gy in 25 fractions). How the reduction in the total dose in terms of the BED will affect local control is unknown. Therefore, many factors were considered in designing this schedule: the short gap between surgery and RT, the contribution of the anticipated ELIOT boost in terms of toxicity and effectiveness, and the risk of late normal tissue toxicity because of the large dose per fraction with the EBRT. The Sydney study adopted a lower whole-breast dose (45 Gy in 25 fractions) for women receiving a boost of 16 Gy in eight fractions, aiming to maintain a good cosmetic result (33). Correcting for overall treatment time and assuming that the EQD2 of 37.05 Gy in 13 fractions is 39.7 Gy and a recovery factor (K) of 0.7 Gy/d, the biologic effectiveness of the hypofractionated scheme would increase up to about 51 Gy. On the basis of these considerations, we consider the dose delivered to the entire breast adequate to ensure control of microscopic disease. Additional evaluation is needed, and a randomized trial would be worthwhile.

The best interval between the ELIOT boost and whole breast EBRT is unknown but theoretically should be as short as possible. Our EBRT begins as soon as possible after surgery plus ELIOT and shortens the standard course of whole breast RT to 2.5 weeks. Patients have the great advantage of avoiding a delay in the initiation of systemic treatment, and controversies regarding the sequence of local treatment and chemotherapy are prevented. This trial was not designed to treat patients with locally advanced tumors, who, in our institution, usually undergo preoperative chemotherapy. When locally advanced disease was reported at pathologic examination, nodal RT was performed at the end of systemic treatment with conventional fractionation to avoid the risk of brachial plexopathy. We are now trying to refine our preoperative staging using magnetic resonance imaging to identify and exclude from this treatment schedule those patients with a greater probability of having more advanced disease.

Recht *et al.* (34) suggested that for high-risk patients it is better to administer adjuvant chemotherapy before RT, because it results in fewer distant metastases than does RT followed by adjuvant chemotherapy. Huang *et al.* (35), as did several other investigators, reported an increased risk of local recurrence when RT was initiated after adjuvant chemotherapy. These data are controversial (35).

The patients in our study were able to complete adjuvant RT within a short time after quandrantectomy. Simultaneous delivery of chemotherapy with the hypofractionated scheme has not been routinely performed because of concerns over increased toxicity. Our patients' compliance to the treatment was high: all but 1 were able to complete the planned RT. In 180 (88.2%) of the 204 patients, the surgical wound had healed, allowing them start HEBRT within 4 weeks after surgery. To avoid an excessive delay, 7 patients received their first chemotherapy cycle concomitantly with HEBRT. Of these 7 patients, 4 received anthracycline-based chemotherapy, 2 of whom had early Grade 3 toxicity. However, none had severe toxicity at their last follow-up examination.

The early toxicity, consisting mainly of erythema and dry desquamation, was mild for most patients (67.6%). Although at 1 month of follow-up, the inflammatory signs had decreased compared with the end of HEBRT, a worsening of symptoms was noted. This pattern of evolution of subjective toxicity can be explained by the hypofractionation of the EBRT regimen.

A preliminary assessment of late complications was available for 108 patients with a minimal follow-up of 6 months and for 64 patients with a follow-up of 12 months. The latter group was not the subject of this report because of the limited number of patients.

At a median follow-up of 11 months, 6 patients complained of symptomatic edema. Of these 6 patients, 2 presented with significant thickening and indurations at the ELIOT boost area, that in 1 patient was associated with severe liponecrosis. In one-third of the patients, no increased density was noted in the whole breast. The 5.5% telangiectasia recorded was actually more identifiable as dermal capillary dilation around the ELIOT boost area. It is unknown whether it will degenerate to true telangiectasia, which usually appears later in the follow-up period.

In 9 patients (4.4%), liponecrosis of the surgical area developed within the fourth week after surgery. Liponecrosis, a localized collection of necrotic fluid with skin erythema, was diagnosed clinically and radiologically by ultrasonography. In all cases, it was managed with fine needle aspiration of the necrotic collection and a few sessions of clinical care without surgical curettage and did not cause a significant delay in beginning HEBRT. In only 1 patient liponecrosis developed later and degenerated to Grade 4 toxicity with fat tissue necrosis. That patient had also received adjuvant chemotherapy and was obese, and it can partially explain the greater probability of developing late liponecrosis, a phenomenon known to occur more frequently in patients with a greater proportion of fat tissue in the breast.

The use of 2-Gy fractions in breast cancer is based on the assumption that a larger fractionation size causes a steeper increase in the rate of late adverse effects. A randomized clinical trial in the United Kingdom was designed to test the hypothesis that fewer larger fractions would be at least as effective as a standard fractionation of 2 Gy, with late effect endpoints. The trial generated an estimated α/β ratio of 3.6 (95% confidence interval 5.4–8) for late changes in breast

appearance and 3.1 Gy (95% confidence interval 1.8–4.4) for moderate or substantial breast indurations (36). In our study, great care was taken not to exceed the recommended daily dose of 3 Gy to avoid poor cosmetic results. At daily fractions of 2.85 Gy, an 8% hot spot (off-axis dose or near the entrance of the beam) would result in a daily dose of 3 Gy/d. At the last follow-up examination, Grade 1 fibrosis, according to the Subjective Objective Management Analytic Late Effects of Normal Tissue criteria, was observed in 46.3% of our patients.

Studies of long-term normal tissue toxicity after breast RT have shown a variable effect on the incidence of ischemic heart disease. In a retrospective cohort study, Paszat *et al.* (37) observed a 1% increase in the rate of fatal myocardial infarction at 10 years with a fraction size of >2 Gy/fraction for left-sided breast RT. In our study, the percentage of heart volume receiving 50% of the total dose was kept to <5%. Acute pneumonitis did not occur in any of our patients, but lung fibrosis was not explored using computed tomography scans. To draw accurate conclusions regarding the incidence and severity of side effects, longer follow-up is needed, because such side effects have been observed to increase with longer follow-up.

CONCLUSIONS

The results of our study have shown that after BCS, an ELIOT boost followed by HEBRT allows for a high dose to be delivered to the tumor bed and an adequate dose to the whole breast within a short overall treatment time, with a potential gain in the radiobiologic effect. Although longer follow-up is necessary to draw conclusions on the rate of late side effects and the final cosmetic outcome to establish the efficacy and safety of this schedule, we can state that the treatment is feasible, compliance was high, and the incidence and severity of the acute side effects were low and acceptable.

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