

Clinical Investigation

Accelerated Partial Breast Irradiation Using Only Intraoperative Electron Radiation Therapy in Early Stage Breast Cancer

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Summary

Intraoperative electron radiation therapy was delivered at 21 Gy maximum dose as the only radiation treatment to 226 women with low-risk, early stage breast cancer in a phase II prospective trial. Only 1 case of tumor recurrence was observed after a mean follow-up of 46 months (range, 28-63 months). All patients are alive and free of disease. Toxicity was deemed quite acceptable.

Background: We report the results of a single-institution, phase II trial of accelerated partial breast irradiation (APBI) using a single dose of intraoperative electron radiation therapy (IOERT) in patients with low-risk early stage breast cancer.

Methods and Materials: A cohort of 226 patients with low-risk, early stage breast cancer were treated with local excision and axillary management (sentinel node biopsy with or without axillary node dissection). After the surgeon temporarily reapproximated the excision cavity, a dose of 21 Gy using IOERT was delivered to the tumor bed, with a margin of 2 cm laterally.

Results: With a mean follow-up of 46 months (range, 28-63 months), only 1 case of local recurrence was reported. The observed toxicity was considered acceptable.

Conclusions: APBI using a single dose of IOERT can be delivered safely in women with early, low-risk breast cancer in carefully selected patients. A longer follow-up is needed to ascertain its efficacy compared to that of the current standard treatment of whole-breast irradiation.
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Introduction

Accelerated partial breast irradiation (APBI) is being intensively studied (1-4) to determine whether there are women who might benefit from a shortened course of radiation treatment delivered to a smaller volume, reducing the time required for standard whole-breast irradiation (WBI) from 6-7 weeks to 1 week or less. Several

randomized trials are under way, comparing various APBI approaches to standard WBI, but have not been completed or have not reached sufficient maturity to draw final conclusions. Nevertheless, many thousands of women have been treated with APBI, many outside of clinical trials. American Society for Radiation Oncology (ASTRO) (5) and European Society for Therapeutic Radiology and Oncology (ESTRO) (6) have published guidelines

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for identifying women deemed at sufficiently low risk to be treated with APBI outside of a clinical trial (Table 1) but have specifically excluded intraoperative electron radiation therapy (IOERT) as they had insufficient data for IOERT when the guidelines were established.

If IOERT is proved effective as a single-dose treatment, it could be the ideal APBI approach. IOERT provides a clear view of the tumor bed, eliminating possibility of a geometrical miss. It eliminates all postoperative radiation, increasing the quality of life for the patient and allowing immediate oncoplastic reconstruction. Of the current APBI techniques, it has the most homogeneous dose distribution over the tissue volume at risk (8). Because the dose is delivered subcutaneously, the skin dose is reduced. Finally, because all radiation is delivered at the time of surgery, it does not interfere with any required systemic treatment. This study reports a large cohort of women with low-risk cancer treated with IOERT.

Methods and Materials

From July 2006 to December 2009, 226 patients suitable for breast-conserving therapy (BCT) were enrolled in a phase II study in which IOERT was delivered as radical treatment immediately after surgical resection.

Our inclusion criteria (Table 1) were age ≥ 50 ; tumor size ≤ 3 cm; grade G1-G3; any estrogen receptor (ER) status; unicentric and unifocal disease; histologically proven invasive ductal carcinoma (IDC). Mucinous, medullary, tubular, colloid carcinomas were also allowed, as was associated lobular carcinoma in situ. Lobular carcinoma, ductal carcinoma in situ, and extensive intraductal component were not allowed. Local evaluation consisted of mammography and breast ultrasonography; MRI was optional.

Inclusion criteria, except for nodal evaluation, which is not as relevant for single-dose IOERT as it is for other postoperative APBI methods, does not differ substantially from ASTRO/ESTRO guidelines for APBI (5, 6). Patient characteristics are listed in Table 2.

Statistical methods

This was a single-arm phase II study conducted to test the efficacy of IOERT. The primary endpoint was the rate of true local recurrence, defined as the reappearance of the tumor in the same quadrant; reappearance in another quadrant was defined as new ipsilateral carcinoma. Secondary endpoints were toxicity and cosmesis. We assumed $\alpha = .05$ and power = 0.8. We presented this study to our institutional review board and obtained approval. Patients' informed consent was also obtained.

Surgery

All 226 patients underwent wide local excision (quadrantectomy) plus sentinel node biopsy (SNB). IOERT did not interfere with the criteria for conventional breast-conserving surgery. After sentinel node biopsy determination, the tumor was removed with 1.5-2.0 cm of free margins of resection. After tumor excision, the mammary gland was mobilized from the fascia of the pectoralis major muscle and, superficially, from the skin, and the margins of the tumor bed were temporarily reapproximated to allow IOERT to be delivered. Fifty patients underwent axillary node dissection (AND, 19 in the same surgical session, 31 in a second intervention, after a few weeks).

Table 1 ASTRO and GEC-ESTRO-suitable patient recommendations for APBI outside of clinical trials, compared to the inclusion criteria of our study

Factor	APBI low-risk group by GEC-ESTRO criteria	APBI suitable group by ASTRO criteria	IOERT present study criteria
Age	>50	>60	≥ 50
BRCA 1, 2 mutation	Not present	NA	NA
Tumor size	<3 cm	<2 cm	≤ 3 cm
T stage	T1-2	T1	T1-2
Grade	Any	Any	Any
LVI	Not allowed	Not allowed	NA
ER status	Any	Positive	Any
Multicentricity	Unicentric	Unicentric	Unicentric
Multifocality	Unifocal	Unifocal with total size of <2 cm	Unifocal
Histology	IDC, mucinous, medullary, colloid	IDC, mucinous, tubular, colloid	IDC, mucinous, medullary, tubular, colloid
DCIS	Not allowed	Not allowed	Not allowed
EIC	Not allowed	Not allowed	Not allowed
Associated LCIS	Allowed	Allowed	Allowed
Nodal status	pN0 (by SNB or AND)	pN0 (by SNB or AND)	NA
Neoadjuvant therapy	Not allowed	Not allowed	Not allowed

Abbreviations: AND = axillary node dissection; APBI = accelerated partial breast irradiation; ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; ER = estrogen receptor; GEC-ESTRO = Groupe Européen de Curiothérapie-European Society for Therapeutic Radiology and Oncology; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IOERT = intraoperative electron radiation therapy; LCIS = lobular carcinoma in situ; LVI = lymphovascular invasion; NA = not applicable; SNB = sentinel node biopsy.

Table 2 Patient characteristics (n=226) and follow-up data compared to those of the EIO series of 1822 patients treated only with IOERT

Parameter	Characteristic	Present study (n=226)	EIO series (n=1822)	Fisher's exact test
Mean follow-up (months)		46 (28-63)	36.1 (1-122)	
Age (years)	Median (range)	63 (50-87)	58 (33-83)	Age <50 (<i>P</i> = .006)
	<50	0	368 (20.2%)	
	50-59	49 (21.7%)	665 (36.5%)	
	60+	177 (78.3%)	789 (43.3%)	
Tumor site (quadrant)	Upper inner	76 (33.6%)		
	Lower inner	31 (13.7%)		
	Upper outer	85 (37.6%)		
	Lower outer	34 (15.1%)		
Tumor diameter at pathology	<0.5	13 (5.7%)	108 (5.9%)	
	0.5-1.0	79 (35%)	503 (27.6%)	
	1.0-2.0	104 (46%)	938 (51.5%)	
	2.0-3.0	30 (13.3%)	NR	
	2.0-5.0	30 (13.3%)	261 (14.3%)	
	>5 cm	0	3 (0.2%)	
	Not evaluable	0	9 (0.5%)	
Histology	Ductal Ca	212 (93.8%)	1426 (78.3%)	Lobular carcinoma (<i>P</i> = .04)
	Lobular Ca	0	202 (11.1%)	
	Other	14 (6.2%)	194 (10.6%)	
Grade	G1	48 (21.2%)	467 (25.6%)	
	G2	139 (61.5%)	853 (46.8%)	
	G3	39 (17.3%)	459 (25.2%)	
	Not evaluable	0	43 (2.4%)	
Margins	Negative	193 (85.4%)	1768 (97%)	
	Positive	16 (7.1%)	6 (0.4%)	
	Close	17 (7.5%)	48 (2.6%)	
Estrogen receptor	Positive	207 (91.6%)	1625 (89.2%)	
	Negative	19 (8.4%)	194 (10.6%)	
	Not evaluable	0	3 (0.2%)	
Progesterone receptor	Positive	186 (82.3%)	1420 (77.9%)	
	Negative	40 (17.7%)	398 (21.8%)	
	Not evaluable	0	4 (0.2%)	
Ki-67	<14%	82 (36.3%)	664 (36.4%)	
	>14%	144 (63.7%)	1152 (63.2%)	
	Not evaluable	0	6 (0.3%)	
HER2/neu	Negative	106 (46.9%)	1639 (90.0%)	
	Positive	73 (32.3%)	173 (9.5%)	
	Missing	47 (20.8%)	10 (0.5%)	
Triple negative		11 (4.2%)		
Sentinel node status	Negative	176 (77.9%)		
	Positive	50 (22.1%)		
Total positive nodes	0	176 (77.9%)	1301 (71.4%)	
	1-2	50 (22.1%)	371 (20.4%)	
	3+	0	146 (8.0%)	
	Not evaluated	0	4 (0.2%)	
Oncologic events	True local recurrence	1 (0.4%)	42 (2.3%)	
	New ipsilateral carcinoma	0	24 (1.3%)	
	Regional metastases	0	18 (1.0%)	
	Distant metastases	0	26 (1.4%)	
	Contralateral carcinoma	0	19 (1.0%)	
	Other carcinoma	0	33 (1.8%)	
	Total	1 (0.4%)	162 (8.9%)	
	Deaths due to breast cancer	0	28 (1.5%)	
	Deaths due to other causes	0	12 (0.7%)	
	Total	0	40 (2.2%)	

Abbreviations: EIO = European Institute of Oncology; IOERT = intraoperative electron radiation therapy.

Fisher's exact test was performed to ascertain if the differences in oncologic events between the 2 series could be related to the differences in patient characteristics. Only age and invasive lobular carcinoma were significant.

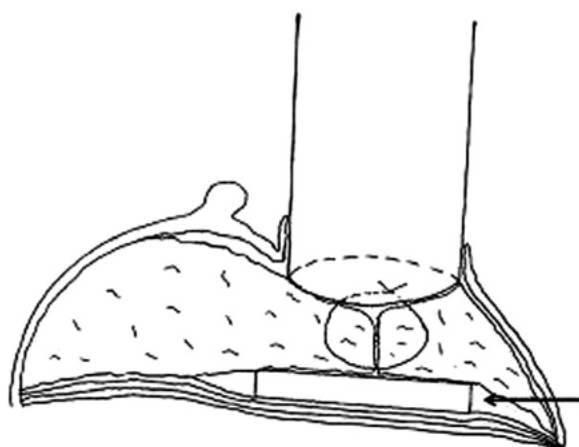


Fig. 1. Schematic of treatment delivery. After tumor resection, the Lucite disk (arrow) is placed between the gland and the pectoralis major muscle. The margins of the gland are placed on the disk and sewed to each other. The Mobetron applicator is introduced through the skin incision and placed in contact with the target.

Radiation therapy

Patients received IOERT with a dedicated mobile linear accelerator (Mobetron, Sunnyvale, CA), which has 4 energy levels: 4, 6, 9, and 12 MeV. On the day of treatment, prior to surgery, quality assurance (QA) for output and energy was performed following the recommendations of the American Association of Physicists in Medicine Task Group report 72 for mobile IOERT accelerators (8).

A 10-mm protective poly methyl methacrylate (Lucite) bolus disk, a standard Mobetron accessory, was placed under the gland to provide another 10 mm of effective tissue (Figs. 1 and 2). The maximum dose transmitted through this protective bolus is 15% of the maximum dose (D_{max}). After the tumor was removed, the surgeon placed the Lucite disk against the pectoralis major muscle

and then put the mammary gland upon the disk and sewed the margins together. We used a mechanical probe to determine the gland thickness for energy selection and also to verify that the disk was in place.

The field size for each patient was selected based primarily on the tumor size, and the applicator was chosen with a diameter that provided a 2-cm margin laterally.

A dose of 21 Gy was delivered to D_{max} ; the prescribed dose to the whole target was the 80% isodose (16.8 Gy). We were aware of the higher dose recommended by the European Institute of Oncology (EIO) studies (ie, 21 Gy to the 90% isodose) (3, 9, 10); nevertheless we believed the dose reduction was justified because, if we assumed the biologically equivalent dose (BED) = $D [1 + d/(\alpha/\beta)]$ (where D is the total dose and d is the dose of a single fraction) and $\alpha/\beta = 4$ Gy for breast cancer (11), the BED for a single dose of 16.8 Gy would be 87.4 Gy, which is comparable to the 75-Gy BED of a standard fractionated treatment of 2 Gy \times 25 fractions. After IOERT, the surgeon cut 1 or more stitches to remove the disk (Fig. 2).

Systemic therapy

Patients were put into risk categories according to St. Gallen Breast Cancer Treatment Consensus Conference criteria (12). Chemotherapy, hormone therapy, and targeted therapy were administered according to those criteria.

Toxicity

Early toxicity was evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Cosmetic evaluation

We used the cosmetic grading system described by Beal et al (13). An assessment of cosmetic outcome was recorded at every

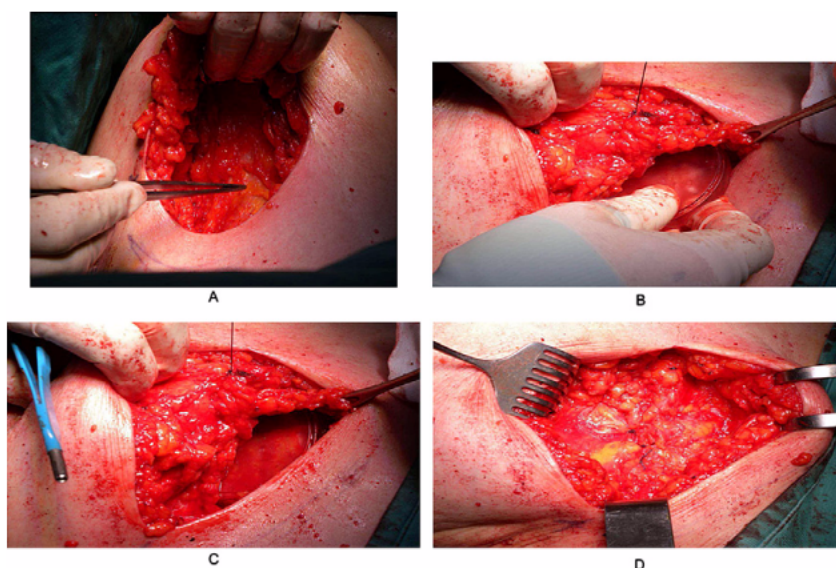


Fig. 2. Positioning of the Lucite disk. (A) Tumor bed after resection. (B and C) Insertion of the Lucite disk under the mammary gland. (D) Gland reconstruction over the disk by sewing the margins together.

Table 3 Treatment-related toxicities (number of patients)

Toxicity	Grade 1	Grade 2	Grade 3
Connective tissue fibrosis	2	-	-
Hematoma	6	-	1
Infections	1	-	-
Soft tissue necrosis	-	-	-
Pain	3	-	-
Transient edema	3	-	-

follow-up examination by grading symmetry, breast edema, discoloration at site, dimpling/local contour change, and scar prominence on score ranging from 0 (no effect) to 3 (severe effects).

Follow-up

Every patient was evaluated at 1, 3, 6, and 12 months after surgery and then every 6 months to ascertain presence of complications. Mean follow-up was 46 months (range, 28-63 months). No patients were lost to follow-up.

Results

Radiation therapy

An energy of 6 MeV was selected for most patients (150 of 226); 66 patients were treated with an energy of 4 MeV and 10 patients with an energy of 9 MeV.

Pathology

A total of 212 patients (93.8%) had IDC. In the remaining 14 (6.2%) cases other histological subtypes (mucinous, tubular,

medullary, colloid) were found. G1 tumors were found in 48 patients (21.2%), while G2 was present in 139 cases (61.5%). The remaining 39 patients (17.3%) had G3 tumors.

Fifty patients (22.1%) had positive SNB results and underwent AND. Of these 50 patients, 38 patients had 1 positive lymph node (after SNB plus AND); 12 patients had 2 positive lymph nodes. No additional WBI was delivered in node-positive patients.

After final postsurgery pathology results, 16 patients (7.1%) had positive resection margins and underwent re-excision and no further treatment. Seventeen patients (7.5%) had close margins (2 mm or less); no further treatment was performed, and they entered follow-up. No further post-IOERT WBI was performed in patients with positive or close margins. The remaining 193 patients (85.4%) had negative margins.

Systemic therapy

A subset of 171 patients (75.7%) received only endocrine treatment; 21 patients (9.3%) were treated with chemotherapy alone; 24 patients (10.6%) had both treatments; and 10 patients (4.4%) had no adjuvant medical therapy.

Side effects and cosmesis

No acute reactions were reported after irradiation. Three patients experienced transient edema. In 7 other patients, a hematoma was observed. We observed no incidence of liponecrosis. Treatment-related toxicities are listed in Table 3.

At 6 months after IOERT, 71 of 226 patients (31.4%) had a score of 2 for symmetry and contour (asymmetry exhibited by one-third or less of breast volume), while 19 of 226 patients (8.4%) had a score of 3 (asymmetry greater than one-third of breast volume). The evolution of cosmetic results over time is shown in Table 4. No breast edema, discoloration at the site, or scar prominence was observed.

Table 4 Evolution of cosmetic results over time

	6 mo (n=226)	12 mo (n=226)	24 mo (n=226)
Grade 0 (no effects)	136	136	136
Grade 1			
Minimal asymmetry	-	-	15
Minimal edema	-	-	-
Mild discoloration at site, notably only with close inspection	-	-	-
Mild dimpling/local contour change, notably only with close inspection	-	-	-
Mild scar prominence, notably only with close inspection	-	-	-
Grade 2			
Asymmetry ($\leq 1/3$ of the gland)	71	71	58
Edema ($\leq 50\%$ of the gland)	-	-	-
Discoloration at site ($\leq 1/3$ of the gland)	-	-	-
Dimpling/local contour change ($\leq 1/3$ of the gland)	-	-	-
Scar prominence (moderate, thickened or raised)	-	-	-
Grade 3			
Asymmetry ($> 1/3$ of the gland)	19	19	17
Edema ($> 50\%$ of the gland)	-	-	-
Discoloration at site ($> 1/3$ of the gland)	-	-	-
Dimpling/local contour change ($> 1/3$ of the gland)	-	-	-
Scar prominence (severe)	-	-	-

Oncological events

One case of true local recurrence at 23 months was reported (0.4%), corresponding to an annual recurrence rate of approximately 0.2%. Recurrence developed in a 55-year-old postmenopausal patient with 2-cm IDC of the left breast; a G2 tumor; pN0 after SNB; HER2-negative; ER-positive; and Progesteron Receptor (PgR) - positive. She was given hormone therapy and did not undergo chemotherapy. Relapse occurred in a quadrant different from that of the primary lesion, so it is debatable whether this was a true recurrence or a second ipsilateral tumor. This patient underwent salvage therapy by mastectomy. All patients of the series are still alive. None have developed distant metastases.

Discussion

There are 3 techniques to provide APBI at the time of surgery: a single high-dose-rate (HDR) treatment using a specially developed HDR breast applicator; 50-kV low-energy X-rays delivered through spherical applicators; and 4- to 12-MeV electron beam treatments from linear accelerators delivered through applicator tubes ranging in diameter from 3 to 10 cm (IOERT).

IOERT generates substantially more uniform dose distributions of electrons than those produced with 50-kV X-rays or brachytherapy, whether the brachytherapy is delivered intraoperatively or as postoperative APBI (7). The other intraoperative approaches do not allow for irradiation of microscopic disease that may extend 1-2 cm beyond the tumor. IOERT offers the advantage of direct visualization of the tumor bed and high sparing of normal tissue, including the skin, because IOERT is administered subcutaneously. IOERT delivers a very high biological dose at the time of the surgery, when residual tumor cells are more rapidly proliferating. IOERT is insensitive to chemotherapy sequencing as all radiation is given during the surgery. IOERT is the only APBI method that lends itself to immediate oncoplastic reconstruction because the target volume receives the full radiation during surgery. Furthermore, mobilization of the breast tissue, required to prepare the target gland for IOERT, is a necessary step in any oncoplastic reconstruction procedure, which shortens the reconstruction. Finally, IOERT as a single-dose treatment is more cost effective than other breast treatments.

Single-dose IOERT was first proposed by the EIO group and has been well described (3, 9). A randomized trial, called "ELIOT," for women >48 years with tumors of <2.5 cm closed in December 2007, compared a single IOERT dose of 21 Gy prescribed to the 90% isodose with 5 weeks of WBI plus a 10-Gy boost given by external beam therapy. Both arms received wide excision surgery. A protective metallic disk inserted below the gland protected the chest wall. Patients with IDC and those with lobular carcinoma were allowed in the study. Results from ELIOT have not yet been reported; nevertheless data for patients treated with the ELIOT approach but outside the trial have been published at various intervals: 590 patients (median follow-up of 20 months; range, 4-57 months) (9) and 1822 patients (mean follow-up of 36 months) (10). These out-trial patients, not subjected to the strict inclusion requirements of the randomized trial, showed ipsilateral recurrence rates of 1.0% and 3.6%, respectively, and true recurrence rates of 0.5% and 2.3%, respectively.

Lemanski et al (14) reported results with a small cohort of 42 patients over the age of 65 with T1N0M0 disease treated with

single-dose IOERT, following the ELIOT dose prescription of 21 Gy to the 90% isodose. With a median follow-up of 30 months (range, 12-49 months), 2 patients had recurrence: a true recurrence at 20 months and a recurrence elsewhere at 24 months. The authors did not observe any acute side effects and offered patients immediate oncoplastic reconstruction, which led to excellent cosmetic outcomes.

Kimple et al (11) reported findings for a series of 53 women with IDC tumors of <3 cm, given IOERT before surgical removal of the tumor, with a prescribed dose of 15 Gy to the 90% isodose line (ie, less than our prescribed dose) and a radial margin of at least 1.5 cm. After a median follow-up of 3 years, 4 patients had invasive ipsilateral breast failure. One patient underwent salvage mastectomy, and the other 3 patients received BCT. Overall survival was 98%, and no patients died of cancer.

When we started our study in 2006, we had the advantage of seeing preliminary data from Veronesi et al (9). We chose to modify both the patient selection criteria and the radiation technique of ELIOT. We restricted single-dose treatment to women with very low-risk cancer: those who were >50 years of age with biopsy proven IDC and tumors <2.0 cm; with N0 and ER+ and PgR+ disease, and lower grade G1/G2 tumors. When ASTRO/ESTRO released their guidelines in 2009 for low-risk cancer patients, we expanded our indications to adhere to their recommendations.

When the ELIOT study started, it was generally believed that an α/β ratio of 10 Gy was a reasonable starting point to obtain a BED for single-dose IOERT. However, soon after the ELIOT trial began, an α/β ratio of 3 or 4 Gy was believed to more accurately represent both tumor control and late toxicity for breast tissue. Even though there is some question whether the α/β model applies to doses in excess of 10 Gy, we thought it prudent to reduce the ELIOT dose slightly to avoid potential late toxicities. We chose to limit the maximum dose to 21 Gy and to ensure that the entire target received at least 80% of the maximum dose.

We recognized the need to protect the chest wall for most patients, but we were uncomfortable using metallic disks as they produce high brehmsstrahlung radiation (which is the electromagnetic radiation produced by a change in the velocity of an electrically charged subatomic particle, such as an electron, as when it collides with another object) when struck by electrons and introduced a backscatter dose uncertainty to the tumor bed. Because we were able to use lower energy to treat our patient population, we were able to use the Lucite disks provided with the Mobetron as protection. These disks introduced zero backscatter and negligible brehmsstrahlung radiation and transmitted, at most, 3.2 Gy, which is of no consequence clinically.

Our absolute recurrence rate of 0.4% and recurrence rate per year of 0.2% are lower than those reported by Veronesi et al (3.6% and 1.2%, respectively) (10). One possible explanation is that, although the mean follow-up was longer in our series, the follow-up in the study by Veronesi et al (10) had many more patients with a longer maximum follow-up, some as long as 122 months. This may partially explain the difference, but if we compare our results to those of the out-trial group at an earlier time (9) or with those of the study by Lemanski et al (14), which had shorter follow-up times than ours, it would appear that a longer follow-up time cannot explain all the differences. To compare patient profiles (Table 2), we ran a simple Fisher's exact test. Age and invasive lobular carcinoma appear to cause significant differences in risk factors in the populations treated. Ki67 and molecular subtype did not reach statistical significance, but showed a trend to significance. The study by Veronesi et al (10) identified within its own

patient population risk factors including age, tumor size, nodal status, and molecular subtype. In that study's multivariate analysis, invasive lobular carcinoma trended toward significance ($P=.09$).

Orecchia (15) reported that when grouping the 1822 patients of the EIO study according to the ASTRO guidelines for patients suitable to be treated outside of a trial, the actuarial 5-year recurrence rate is 1.5%. This corresponds to an annual rate of 0.3%, very close to the 0.2% that we found in our study. It is clear from comparing patient populations and results that only some women are good candidates for single-dose IOERT.

Side effects and cosmesis

In the present study, we did not observe severe acute side effects, apart from transient edema in 3 patients and a hematoma in 7 others. If we compare our toxicity rates with those reported in other studies using a higher dose to the gland (21 Gy to the 90% depth vs the 21 Gy to D_{max} we used), it would appear that the complications we experienced with our patients were lower, which is expected given the lower dose.

In grading symmetry and contour, 31.4% of our patients had a score of 2, and 8.4% of patients had a score of 3. We did not perform oncoplastic reconstruction in this cohort, because we felt it was important to determine the impact of a large single-dose of IOERT on toxicity and cosmesis. Liponecrosis has been reported to occur in 4%-5% of women treated with single-dose IOERT (9, 10). Fat necrosis has also been reported in APBI with mammosite and WBI series (16). Although its absence in our patients seems unusual, Lemanski et al (14) also reported no incidence of liponecrosis.

Concerns

One criticism of IOERT is the management of positive surgical margins found by final histology a few days after surgery. In our series, this finding occurred in 16 (7.1%) patients. For them, we performed a re-excision without any additional radiation therapy. Jobsen et al (17), in a series of 1752 patients treated with conventional BCT, found that for women over 40 years, margin positivity has no influence on recurrence. The radiation technique for IOERT brings all of the margins to the center of the radiation field so that all margins receive at least 18 Gy in a single exposure, which is probably sufficient to sterilize any microscopic residual disease that remains in the margins.

Both ASTRO and ESTRO require pN0 for PBI, using external-beam radiation therapy because the pN status is known. For intraoperative radiation therapy it is not. In our series, we had 38 patients with 1 positive node and 12 women with 2 nodes. In the absence of guidelines, we gave these women no further radiation and systemic therapy according to our institutional protocols.

Another issue is that all of the surgeries were quadrantectomies, the standard surgical approach for breast-conserving surgery in Italy. It is unclear whether the IOERT technique and the dose used in this study were adequate for lesser surgeries. Alternatively, because IOERT lends itself to immediate oncoplastic reconstruction at the time of the breast-conserving surgery, larger surgeries will not compromise cosmesis and could gain wider acceptance of surgeons wishing to provide patients with a single-shot treatment.

Finally, there is question of whether the 21 Gy to D_{max} used in our study is the optimal dose for IOERT. In this low-risk population,

thus far, it appears sufficient to control the disease and produce very low toxicity. There is currently no accepted BED formula for doses above 10 Gy. This is an area that needs further study.

Conclusions

Single-dose IOERT in early stage breast cancer can be delivered safely and with excellent results. Patients at very low risk of local recurrence represent an excellent group to receive a 1-dose procedure and avoid the 5- to 6-week postoperative treatment. Despite our encouraging results, a longer follow-up is needed to compare IOERT efficacy to that of WBI. We recommend that even patients at low-risk as defined by ASTRO and ESTRO criteria be treated only under a strict institutional protocol after institutional review board approval and that patients at higher risk be treated as part of a clinical trial.

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