Abstract. Aim: To evaluate the effectiveness of intra-operative radiotherapy (IORT) in breast cancer in terms of local control, esthetic results and disease-free survival. Patients and Methods: From June 2007 to October 2011, 110 patients with early-stage breast cancer were submitted to quadrantectomy and IORT. A total dose of 21 Gy prescribed at 90-100% isodose was delivered in all cases. Patients were evaluated after surgery for early and late complications. Results: Median follow-up was 27 (range: 2–54) months. In 10 patients (9.1%), breast ultrasound showed liponecrosis. Six patients (5.5%) developed grade 2 fibrosis. Disease-free survival rates at 2 and 3 years were 96.8% and 92.9%. Three patients (2.7%) developed local recurrence, two patients (1.8%) distant metastasis. Two patients died. The 2- and 3-year overall survival rates were 100% and 97.3%, respectively. Conclusion: IORT could be an appropriate therapeutic alternative in selected patients although it remains investigational; longer follow-up to confirm these results is required.

Several randomized trials have established the equivalence of breast-conserving therapy (BCT) to mastectomy in terms of overall survival (1-3). BCT followed by a course of postoperative radiotherapy, is considered the current standard-of-care for patients with operable breast cancer. Routine whole-breast radiotherapy (WBRT) comprises of 50 Gy in daily fractions for five weeks (4). The additional application of an external boost of 10 to 16 Gy to the tumor bed leads to excellent local tumor control, with a local recurrence rate of 6% after a median of 10 years’ follow-up (5). It has been estimated that up to 85% of in-breast recurrences for women undergoing BCT without radiation occur in the region of the segmental mastectomy (6). Because fewer than 15% of the in-breast recurrences occur outside of the segmental mastectomy site, many have hypothesized that irradiation of less than the entire breast would still result in acceptable tumor control rates. Accelerated partial breast irradiation (APBI) aims to deliver radiation to a portion of the breast at a higher dose per fraction over a significantly shorter time frame than standard WBRT. It is hoped that APBI will offer equivalent survival, comparable local control, and improved cosmesis when compared with WBRT (7, 8).

Intraoperative radiotherapy (IORT) is a different technical procedure for partial breast irradiation, and is the application of radiation during a surgical intervention, after the removal of the neoplastic mass. This direct approach potentially improves the ability to localize the tumor bed and subclinical disease. Two important technical advantages of IORT in comparison to the use of external-beam radiotherapy (EBRT) are direct visualization of the target volume with very good dose homogeneity and the possibility of protecting healthy tissues by shielding them from the radiation beam (9). Although the radiation oncologist has full clinical responsibility for prescribing and administering the delivery of radiation, the use of IORT requires multidisciplinary collaboration between surgeons, anesthesiologists, medical physicists, radiation technologists and nurses. The aim of our study was to evaluate the effectiveness of IORT in terms of local control, disease-free survival, overall survival, quality of life and cosmetic results.

Patients and Methods

Between June 2007 to October 2011, we treated 110 women with early-stage breast cancer submitted to quadrantectomy and IORT at the Department of Radiation Oncology, Sant’Andrea Hospital, University of Rome La Sapienza. Inclusion criteria were: tumor size <2.5 cm, age >48 years, post-menopausal status and absence of intra-
ductal component. Diagnosis had to be proven by a biopsy positive for carcinoma. All patients signed an informed consent before surgery. All patients underwent staging tests including chest x-ray, bone scan and liver ultrasonography to rule-out metastatic disease at diagnosis; local evaluation consisted of mammography and breast ultrasonography (magnetic resonance imaging was optional).

As regards to the surgical technique, the IORT procedure does not interfere with the oncological criteria of ‘classic’ breast-conserving surgery in which 1.5-2 cm grossly free-resection margins are required. After tumor removal, the wide mobilization of the mammary gland from the fascia of the pectoralis major and, superficially, from the skin, represents a critical step, permitting for optimal exposure of the ‘target’ to the radiation beam. In keeping with the Quality Assurance program for the use of such dedicated linear accelerators, we implemented an in vivo dosimetry procedure, aimed at controlling the dose delivered to the patient. To minimize the radiation delivered to the chest wall and to guarantee the delivery of the full radiation dose to the gland, a dedicated disc of lead and aluminium, available in various diameters (4, 5, 6 and 8 cm), is used as a protective device. The disc is inserted (lead side down, aluminium side up) in the space between the gland and the pectoralis muscle. To allow for the best protection of the thoracic wall, the disc must be greater in size than the breast target size. The sterile polymethyl methacrylate (Perspex) collimator of the linear accelerator is introduced through the skin incision and placed directly in contact with the breast target. The treatment was delivered using electrons with an energy ranging between 6 and 10 MeV, according to the thickness of breast tissue to be treated. All patients received 21 Gy, prescribed and specified at the depth of the 90-100% isodose line, which was defined as the optimally- and maximally-tolerated dose level. Following IORT, the temporary retaining sutures were removed, the tumor cavity was remodeled and the incision was closed in the conventional fashion. Patients with tumor-involved margins were re-commended to undergo re-excision to tumor-free (<1 mm) margins or mastectomy. In addition, all patients with a tumor-involved sentinel lymph node underwent completion axillary lymph node dissection and underwent either WBRT or a mastectomy. Systematic therapy was recommended independently of the local therapy delivered. Women with estrogen receptor and/or progestone receptor-positive tumors were prescribed an aromatase inhibitor. Follow-up evaluations were performed at one, three, six and 12 months after treatment, and every six months thereafter. During these visits, the radiation oncologist documented disease status, complications and cosmesis. Acute and late side-effects were evaluated according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) late morbidity Scoring Scale (10). Cosmetic results were analyzed by both the doctor’s judgment and the patient’s perspective. The physician rated overall cosmesis using a modified classification based on the classification by Dubois et al.: excellent, no visible effects of therapy in the treated breast; good, minimal but not disturbing effects of therapy (slight skin pigmentation change, mild fibrosis); fair, obvious tissue sequelae (telangiectasia, marked skin alteration, fibrosis with skin retraction); poor=severe side effects with asymmetry and functional disturbances of the treated breast (11).

All statistical analyses were performed using IBM® SPSS® Statistics version (IBM Corporation, Somers, NY). Patient survival was estimated using the Kaplan–Meier method. Univariate analysis was performed to determine significant prognostic factors using the log-rank test. Multivariate analysis was performed using the Cox regression. A \( p \)-value of less than 0.05 was considered statistically significant.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>110</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>111</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>66 (48-87)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>81 (73%)</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>18 (16.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (10.8%)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>50 (45%)</td>
</tr>
<tr>
<td>1-2 cm</td>
<td>45 (40.5%)</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>16 (14.5%)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>28 (25.2%)</td>
</tr>
<tr>
<td>G2</td>
<td>50 (45%)</td>
</tr>
<tr>
<td>G3</td>
<td>33 (29.8%)</td>
</tr>
<tr>
<td>Lymph node status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19 (17.2%)</td>
</tr>
<tr>
<td>Negative</td>
<td>92 (82.8%)</td>
</tr>
<tr>
<td>ER and PR status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>106 (95.5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (23.6%)</td>
</tr>
<tr>
<td>No</td>
<td>84 (76.4%)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>97 (88.2%)</td>
</tr>
<tr>
<td>No</td>
<td>13 (11.8%)</td>
</tr>
</tbody>
</table>

**Results**

Age, menopausal status and tumor-related parameters of size are presented in Table I.

The median follow-up was 27 (range: 2-54) months. The median age was 66 (range: 48-87) years. One patient had a bilateral carcinoma and she underwent bilateral IORT. Out of the 111 tumors 73% were invasive ductal carcinoma. The majority of patients (95/111; 85.6%) had carcinomas ≤2 cm. All patients were post-menopausal. Hormone receptor-positive disease was seen in 95.5% of patients, while 4.5% had triple-negative disease. A total of 75 patients (68.2%) received only endocrine treatment; four patients (3.6%) were treated with chemotherapy-alone, 22 patients (20%) had both treatments and nine patients (8.2%) had no adjuvant medical therapy.

Positive sentinel nodes were found according to the definitive pathology reports in 19 patients (17.3%). Six of these (31.6%) underwent completion axillary lymph node dissection and three patients underwent EBRT to the supraclavicular region.
For close or positive margins, nine patients (8.2%) had a second surgical procedure consisting of re-excision of the breast in five cases and mastectomy in four.

Concerning IORT, the irradiation treatment time depended on the applicator diameter (median=5 mm; range=20-70 mm) and extended the overall time of surgery by 15-35 min. The dose delivered was of 21 Gy with a median of 8 MeV electrons (range=6-10 MeV). Treatment characteristics are shown in Table II. No immediate complications related to the IORT procedure were observed.

Long-term tumor control. Recurrences occurred in four of 110 patients, resulting in a 2 and 3-year disease-free survival rate of 96.8% and 92.9% respectively. Three local recurrences (2.7%) and two cases of distant metastasis (1.8%) were recorded (Figure 1). One patient had local recurrence with a concomitant distant metastasis.

Local tumor recurrences occurred in three of 110 patients, with actuarial local control rates at two and three years of 98.4% and 94.5%, respectively (Figure 2). Local relapses were carefully divided into two different categories: ‘true recurrences’ were considered re-appearances of the carcinoma in the same quadrant as the primary carcinoma and ‘new ipsilateral carcinomas’ the reappearances in other quadrants. We observed two cases of true recurrence (1.8%) occurring 28 and 31 months following IORT; one patient had true recurrence and a new ipsilateral carcinoma 24 months after IORT. These three patients underwent total mastectomy. One patient initially had triple-negative breast cancer and the recurrence was estrogen receptor-positive, progesterone receptor-positive and human epidermal growth factor receptor-2-negative. She underwent a total mastectomy and received chest wall radiation. This patient developed multiple distant metastasis three months after the second operation and she died 45 months after IORT. The other two patients are still alive without evidence of disease.

Two patients developed distant metastases at different times during follow-up (24 and 30 months after the initial treatment). The overall survival of the whole series was very high: two patients died, one of whom from progression of breast cancer and one of other causes. The 2- and 3-year overall survival rates were 100% and 97.3% (Figure 3).

We performed univariate and multivariate analyses of predictors of local events. In univariate analysis, the risk of recurrence was higher in women with tumors with anaplastic
histology \( (p=0.005) \), hormone receptor-negative \( (p=0.001) \), with chemotherapy \( (p=0.05) \) and subsequent EBRT \( (p=0.02) \). In multivariate analysis, there were no independent predictors of local relapse.

**Local side-effects.** No patient developed acute hematoma or postoperative infections in the treated portion of the breast. Six patients (5.5%) presented delay of scarring. One patient developed severe fibrosis with skin retraction (grade 3, RTOG/EORTC scale). An additional 22 patients suffered from mild fibrosis of the irradiated tissue; the development of fibrosis was progressive during the first months after surgery, reaching a peak after 24 months, and thereafter remained stable or slowly regressed without disappearing. At the time of visiting, five patients (4.5%) still have clinical evidence of mild fibrosis in the treated area. Six patients (5.5%) experienced moderate skin retraction, more evident at first follow-up, with tendency to a gradual attenuation.

A limited number of patients experienced a mild postoperative complication defined as ‘liponecrosis’. A localized collection of brown fluid with skin erythema, with no sign of infection, was the clinical manifestation of this complication. We observed 17 (15.5%) cases of liponecrosis 2-4 weeks after surgery. This complication resolved with simple clinical care. This complication appears to be more frequent in patients with a high proportion of fat tissue in the breast. At the time of visiting, 10 patients (9.1%) still have clinical persistence of this fluid layer. Other side-effects were mild edema and occasional pain of the irradiated breast in two patients. The classification of the side effects observed is reported in Table III.

Physicians recorded a good to excellent cosmetic result in 102 (92.8%) out of the 110 evaluated cases; Three patients (2.7%) were scored as having a fair cosmetic result (fibrosis and skin retraction) and five patients (4.5%) as having a poor cosmetic result (asymmetry). Overall cosmesis after breast-conserving surgery and IORT was rated as excellent or good by 102 patients (92.8%), acceptable by five (4.5%), and poor by three patients (2.7%).

**Discussion**

IORT combined with conservative surgery is a promising therapeutic approach for limited-stage breast carcinoma. The argument for such approach is surely of interest due to the fact that partial breast irradiation is going to be a standard treatment for selected patients, but its impact on survival and local control has still to be demonstrated. Several studies on this topic have been published by the group of the European Institute of Oncology in Milan, Italy (12). In a preliminary report on IORT, Veronesi et al. reported that a single fraction of 21 Gy prescribed at the 90% isodose (23.3 Gy at Dmax) can be safely applied intraoperatively and is biologically equivalent to a 60-Gy dose delivered by EBRT in 30 fractions (13).

The first pilot study analyzed 590 patients treated by a single 21-Gy dose after breast-conserving surgery. After a median follow-up of 24 months, three patients developed a local relapse, three ipsilateral carcinoma in another quadrant of the breast, five contralateral breast cancer, and 13 patients distant metastases without local relapse. The toxicity of the intraoperative treatment with electrons was very low. According to the RTOG/EORTC scoring for late effects, grade 2 fibrosis occurred in 3%, while only one patient developed grade 3 fibrosis (14).

Other interesting studies have been published, which aimed at testing the impact of partial breast irradiation on breast cancer treatment; different radiotherapy techniques were used.
for these studies, with controversial results. An early trial at the Christie Hospital showed that whole-breast irradiation was superior in local control when compared to partial-breast irradiation after breast-conserving surgery (10% local recurrences compared to 19.5%, respectively) (15). On the contrary, Reitsamer et al., in a non-randomised study, showed that the boost given with IORT is superior to the breast EBRT (16). Partial-breast irradiation can also be delivered with interstitial brachytherapy and more recently by external sources with three-dimensional radiotherapy (3D-RT) and intensity-modulated radiotherapy (17, 18). A report of a study group convened by the National Cancer Institute in 2002 concluded that partial breast irradiation is a new development in breast cancer radiotherapy which deserves to be encouraged (19). A subsequent consensus statement from the American Society for Radiation Oncology (ASTRO) and assenting reports indicated that accelerated partial-breast irradiation is a new technology that may ultimately demonstrate long-term efficacy and safety comparable to that of whole-breast irradiation for selected patients with early breast cancer (20, 21). ASTRO consensus guidelines recommend cautious consideration of APBI for women less than 60 years old, with tumors >2 cm, and ER-negative disease.

The GEC-ESTRO Breast Cancer Working Group recommends three categories guiding patient selection for APBI: a low-risk group for whom APBI outside the context of a clinical trial is an acceptable treatment option, including patients aged at least 50 years with unicentric, unifocal, pT1–2, pN0, non-lobular invasive breast cancer without the presence of an extensive intraductal component (EIC) and lympho-vascular invasion (LVI) and with negative surgical margins of at least 2 mm; a high-risk group, for whom APBI is considered contraindicated, including patients aged 64 years, having positive margins, and/or multicentric or large (>30 mm) tumors, and/or EIC-positive or LVI-positive tumors, and/or four or more positive lymph nodes or unknown axillary status (pNx); and an intermediate risk group, for whom APBI is considered acceptable only in the context of prospective clinical trials (22).

Out of the many advantages of IORT with electrons, we emphasize on the following: the skin remains intact and plastic surgery may be easily conducted if necessary. A major advantage is the complete change of life for patients living in remote places, far away from radiotherapy centers, who often decide on a mastectomy, even for a tiny carcinoma, due to the differently of undergoing daily post-surgical radiotherapy for six weeks at distant centres (23). In some cases, travel distance to a radiation-treatment facility may influence the receipt of post-operative breast irradiation (24). An additional advantage of IORT is that there is no delay in administering radiotherapy in cases that need adjuvant chemotherapy. There is some evidence that the delay of radiotherapy increases the risk of local recurrence (25, 26). Finally, complete radioprotection abolishes any side-effects in the lung and in the contralateral mammary gland that could occur if conventional whole-breast radiotherapy were administered.

Veronesi et al. reported results of 1,822 patients treated with IORT (27). After a mean follow-up of 36.1 months, 2.3% of patients developed a local recurrence, 1.3% a new ipsilateral carcinoma, 1.4% distant metastases and 2.5% of patients died. Local side-effects were mainly liponecrosis (4.3%) and fibrosis (1.8%).

In the study of Mussari et al., 47 consecutive received conservative surgery followed by IORT with electrons (28). Three different dose levels were used: 20 Gy (seven patients), 22 Gy (20 patients), and 24 Gy (20 patients). After a median follow-up of 48 months, 15 patients developed breast fibrosis (grade 2 in 14 patients, grade 3 in one patient), two patients presented with grade 3 skin changes, one patient developed a clinically relevant fat necrosis, and one patient had breast edema and pain. Two patients developed contralateral breast cancer and one distant metastases; no local relapses occurred. Asymptomatic findings of fat necrosis were observed at mammography in 12 patients (25.5%).

In our study three on 110 patients (2.7%) developed a local recurrence, two patients (1.8%) presented distant metastases and two (1.8%) died. Additionally, no increased postoperative complications (pain, seroma, hematoma, or infection) were observed in 110 patients. The toxicity of IORT is low; there were just five cases (4.5%) of mild fibrosis that resolved spontaneously from their initial observation. The 10 cases (9.1%) of liponecrosis, after a median follow-up of 27 months, represent an issue that further follow-up should clarify; this non-severe complication seems to be unrelated to postoperative infection and mainly involved patients with breast tissue largely represented by fat. Not one patient had any sign of lung fibrosis in the follow-up. Although a longer follow-up is required to properly assess late complications, this finding suggests that the biologically equivalent dose stated for IORT with electrons might have to be considered carefully with regard to late effects on normal tissue.

The side-effects did not cause serious cosmetic impairment. Overall cosmesis after breast-conserving surgery and IORT was rated excellent or good by most patients (92.8%).

Several randomized trials are ongoing comparing APBI with WBRT; if these eventually show equivalent outcomes between APBI and WBRT, the optimal treatment approach will likely remain an unanswered question (29, 30). Even if APBI is found to be inferior to WBRT, the use of IORT to deliver a tumor bed boost at the time of surgery and prior to WBRT, an approach validated in several cohorts, may have both logistical and biological advantages (31, 32).

We recognize several limitations of our study. Our patients numbers were too small for valid multivariate analyses to be performed. With a median follow-up of 27 months, it is still too early to draw firm conclusions regarding the impact of IORT on local control, survival and toxicity. In conclusion,
toxicity of IORT, in our study, was low showing results similar to those available in the literature. The low incidence of toxicity and the short duration of the few manifested collateral effects are consistent with good tolerance. IORT with electron beam in initial stage breast cancer could be an appropriate therapeutic alternative in selected patients, although it remains investigational, and requires longer follow-up to confirm these results.

Conflicts of Interest

All the Authors declare that they have no competing interests.

References


Received January 2, 2013
Revised February 16, 2013
Accepted February 18, 2013

Osti et al: IORT in Breast Cancer