Background: Local recurrences after breast-conserving surgery occur mostly at the site of the primary carcinoma. The main objective of postoperative radiotherapy is sterilization of residual cancer cells. Whole-breast radiotherapy is the standard of care, but its utility has recently been challenged in favor of radiotherapy limited to the area at highest risk of recurrence. Intraoperative electron radiotherapy (IOeRT) is an innovative technique for accelerated partial breast irradiation (APBI) that is applied to selected patients affected by early breast cancer.

Objectives: To describe our experience with IOeRT at the Rambam Health Care Campus in Haifa since we began utilizing this modality in 2006.

Methods: From April 2006 to September 2010, 31 patients affected by unifocal invasive duct breast carcinoma ≤ 2 cm diameter received wide local resection followed by intraoperative radiotherapy with electrons. Patients were evaluated for early and late complications, and other events, 1 month after surgery and every 3 months thereafter for the duration of the first 2 years.

Results: After a mean follow-up of 38 months, seven patients developed mild breast fibrosis and three suffered from mild postoperative infection. Rib fractures were observed in four patients before routine lead shielding was initiated. Additional whole-breast irradiation was given to four patients. None of the patients developed local recurrences or other ipsilateral cancers. Similarly, no contralateral cancers or distant metastases were observed.

Conclusions: Intraoperative electron radiotherapy may be an alternative to external beam radiation therapy in an appropriate selected group of early-stage breast cancer patients. However, long-term results of clinical trials are required to better evaluate the indications and utility of this technique in the management of breast cancer.
radiotherapy that may overcome these issues but at the same
time provide sound oncological security have been suggested.
One of these options is accelerated partial breast irradiation
[12]. APBI is an approach that treats only the lumpectomy
bed and an additional 1–2 cm margin, rather than the whole
breast. By increasing the radiation fraction size and decreasing
the target volume, this technique allows the treatment to be
accomplished in a significantly shorter time period. The ratio-
nale behind this concept arises from retrospective and pro-
spective studies showing that up to 86% of local recurrences
occur within very close proximity to the tumor bed [7,13,14].
For example, an update of the NSABP B-06 (National Surgical
Adjuvant Breast and Bowel Project Protocol trial) confirmed
this pattern of local recurrence, with 75% of all recurrences
at, or near, the lumpectomy site and other ipsilateral breast
recurrence rates similar to the rates of contralateral second
primary breast cancer [15]. Based on this evidence, it seems
logical to deliver radiation only to the area at highest risk. In
addition, it may be expected that adjacent organs such as the
heart and lungs will receive less radiation. Radiation-induced
lung injury after treatment for WBI, such as pneumonitis, lung
fibrosis, pulmonary function test changes, and an increase in
lung cancer incidence are well documented in the literature
and great benefit may be anticipated by avoiding these poten-
tial complications [16,17].

Intraoperative electron radiation therapy refers to the deliv-
yery of a single fractional dose of electron irradiation directly to
the tumor bed during surgery [12]. The potential advantages
of IOeRT include the delivery of radiation before tumor cells
have a chance to proliferate, and since tissues under surgical
intervention have rich vascularization it makes them more
sensitive to the action of radiation (oxygen effect). In addition,
radiation is delivered under direct visualization at the time of
surgery, which minimizes the chance of missing the target.
IOeRT could also minimize some potential side effects since
skin and the subcutaneous tissue can be displaced during the
procedure, and the spread of irradiation to lung and heart is
significantly reduced [17]. Moreover, IOeRT eliminates the risk
of patients not completing the full course of WBI and allows
radiotherapy to be given without delaying administration of
chemotherapy or hormonal therapy.

Although short-term results show similar results for both
WBI and IOeRT with regard to local recurrence, disease-free
and overall survival (reviewed by Cuncins-Hearn et al. [18]),
the evidence-based data are relatively poor, making definitive
assessment on IOeRT difficult. The largest prospective ran-
domized trial of IOeRT, called ELIOT (electron intraoperative
therapy) began in Italy in 2000 [19]. A single dose of 21 Gy
with energies up to 9 MeV, which are biologically equivalent to
58–60 Gy in standard fractionation, was applied to the tumor bed.

Data are available for 1833 patients treated from January 2000 to
December 2008. Eligible patients included women above the age
of 50 with a single focus of invasive duct cancer < 2.5 cm in larg-
est diameter. Local side effects were mainly liponecrosis (4.2%)
and fibrosis (1.8%). With a mean follow-up of 36.1 months,
42 women (2.3%) developed local recurrence, 24 (1.3%) a new
primary ipsilateral carcinoma and 26 (1.4%) distant metastases
as the first event. Forty-six women died (2.5%), 28 from breast
carcinoma and 18 from other causes. Survival rates at 5 and 10
years were 97.4% and 89.7%, respectively.

In the present report, we describe our experience with
IOeRT at the Rambam Health Care Campus in Haifa since
we began utilizing this modality in 2006.

PATIENTS AND METHODS
The Rambam Health Care Campus inclusion criteria for IOeRT
were based on those suggested by the American Society of
Radiation Oncology [20]. Eligible patients included women
above the age of 50 years with a single tumor of invasive duct
carcinoma ≤ 2.5 cm in largest diameter and clinically nega-
tive lymph nodes (determined by physical examination and
dedicated ultrasound). Patients with multiple tumors, invasive
lobular cancer or extensive DCIS (ductal carcinoma in situ) were
excluded. All patients underwent mammography, breast ultras-
onography, chest X-ray, bone scan, and upper abdominal ultra-
sonography. Informed consent was obtained from all patients.

The surgical procedure was performed under general anes-
thesia in the accelerator suite of the Department of Oncology.
All patients underwent lumpectomy with wide excision mar-
gins and sentinel node biopsy. Frozen section analysis of the
lymph nodes and specimen mammography were obtained
during the operation for all patients. The depth of the lumpec-
tomy cavity was measured to determine the electron energy
to be used (6–12 MeV). Sterile lead shielding was placed above
the pectoralis muscle to protect the ribs and lungs from radia-
tion. The latter procedure was initiated following the detection
of rib fractures in some patients (see Results). The lumpectomy
borders were then mobilized and approximated and the elec-
tron applicator positioned in the surgical wound [Figure 1].
The diameter of the applicators (6–8 cm) was determined by
the lumpectomy cavity and the applicator was attached to an
Elekta Precise accelerator [Figure 2].

After obtaining negative results from specimen radiology
and sentinel node frozen section analysis, a single dose of 21
Gy (calculated at the 90% isodose) was delivered through the
designated applicator. After irradiation the shield was removed
and the cavity and skin were closed in layers. Additional WBI
was provided to some patients at the discretion of the radiation
oncologist in cases of high grade tumor and/or presence of
extensive DCIS in the final pathological report.

APBI = accelerated partial breast irradiation
IOeRT = intraoperative electron radiation therapy
DCIS = ductal carcinoma in situ
Patients were seen for follow-up examinations at 1 week and 1 month after surgery, every 3 months for the duration of the first 2 years, and thereafter every 6 months. Toxicity scoring was measured using the common toxicity criteria version 3.0 scale [21].

**RESULTS**

Between April 2006 and September 2010, 31 patients with early breast cancer were enrolled to BCT and IOeRT after providing informed consent. Patients’ and tumor characteristics are presented in Table 1. The median age of patients was 68 years (range 50–83 years). Initial pathology determined by core biopsy included 28 patients with invasive duct carcinoma and 3 patients with tubular carcinoma. Final pathological reports revealed the presence of DCIS in 20 patients (extensive DCIS in 4 patients). The median tumor size was 1.2 cm (range 0.4–2.2 cm). Ten patients had grade I tumor, 16 patients grade II tumor, and 5 patients grade III tumor. The definitive sentinel lymph node biopsy was negative in 29 patients and lymph node micrometastases were detected in two patients. Negative surgical margins (> 2 mm) were obtained in all definitive pathological reports.

Four patients received postoperative irradiation (40–50.4 Gy, 1.8 Gy/fx) to the whole breast due to grade 3 tumor and/or extensive DCIS. Four patients received adjuvant chemotherapy, including trastuzumab in three of these patients. Adjuvant hormonal therapy was prescribed to all patients.

Clinical outcome of patients is summarized in Table 2. After

<table>
<thead>
<tr>
<th>Table 1. Patient and tumor characteristics</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
</tr>
<tr>
<td>50–60</td>
<td>11 (35)</td>
</tr>
<tr>
<td>61–70</td>
<td>8 (26)</td>
</tr>
<tr>
<td>&gt; 71</td>
<td>12 (39)</td>
</tr>
<tr>
<td><strong>Tumor size (mm)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>14 (45)</td>
</tr>
<tr>
<td>11–20</td>
<td>16 (52)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Invasive duct carcinoma</td>
<td>28 (90)</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>3 (10)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (32)</td>
</tr>
<tr>
<td>II</td>
<td>16 (52)</td>
</tr>
<tr>
<td>III</td>
<td>5 (16)</td>
</tr>
<tr>
<td><strong>DCIS component</strong></td>
<td></td>
</tr>
<tr>
<td>NEDCIS</td>
<td>16 (52)</td>
</tr>
<tr>
<td>EDCIS</td>
<td>4 (13)</td>
</tr>
<tr>
<td>No</td>
<td>11 (35)</td>
</tr>
<tr>
<td><strong>Sentinel lymph node biopsy</strong></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>29 (93)</td>
</tr>
<tr>
<td>Micrometastases</td>
<td>2 (7)</td>
</tr>
<tr>
<td><strong>Receptor status</strong></td>
<td></td>
</tr>
<tr>
<td>ER positive</td>
<td>31 (100)</td>
</tr>
<tr>
<td>PR positive</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Her2-neu positive</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

DCIS = ductal carcinoma in situ, NEDCIS = non-extensive ductal carcinoma in situ, EDCIS = extensive DCIS, ER = estrogen receptor, PR = progesterone receptor
a median follow-up of 36 months (range 10–56) local recurrence was not detected. All patients are alive and free of disease at the time of the last follow-up. Mild breast pain was described in six patients and moderate pain in two patients one week after the operation. Significant postoperative fluid collections (defined as ≥ 5 cm) were seen in two patients. Three patients developed minor wound infections that resolved with antibiotic treatment. Four patients presented with mild and three patients with moderate grade subcutaneous fibrosis after 3 months of follow-up. Overall long-term cosmetic results were determined by the patients as good (n=10) to excellent (n=21). Rib fractures located at the radiation field presenting with pain and radiological changes were seen in 4 of 21 patients after 1 year follow-up. Rib fractures were diagnosed between 6 and 9 months following surgery (median time 8 months). Clinical improvement was achieved in all patients with conservative treatment. No cases of rib fractures were observed after the initiation of lead shielding (3-24 months, median time 14 months).

**DISCUSSION**

Personalized therapy with the aim of providing the minimal yet most effective treatment is the driving principle of modern medicine. The accelerated partial breast irradiation paradigm reflects this principle, with the initial goal of showing its non-inferiority compared to standard whole-breast radiotherapy. However, the utility of APBI is still highly debated within the medical community. Opponents of the technique claim that the current standard of care for early breast cancer works well and is backed by numerous long-term studies and therefore should not be changed. On the other hand, some researchers believe that APBI may have an important role in the clinical management of selected patients with early-stage breast cancer [18]. The potential advantages as described above certainly make this modality attractive. These include a logistically faster, cost-effective, convenient and more accessible method for radiotherapy, as well as a potential improvement in quality of life. Furthermore, this modality may improve accurate-dose delivery by permitting delivery of the radiation directly to the surgical margins. Nevertheless, even the strongest proponents of this concept agree that a few questions have yet to be addressed. The main questions include the appropriate fractionation scheme, the appropriate patient selection criteria, the appropriate technique, and the need for long-term phase II/III clinical trials to establish equivalence or at least non-inferiority compared to WBI. Patient selection seems to be a critical factor for the successful application of APBI [22].

In a recent review it was argued that the relatively poorer results of early APBI studies could be attributed to inadequate patient selection criteria and/or suboptimal treatment technique and lack of appropriate quality assurance [18]. Various organizations have now published recommendations for patient selection criteria, including the American Society of Breast Surgeons, the American Society for Radiation Oncology (ASTRO) and the European Society for Therapeutic Radiology and Oncology (ESTRO) [20,22,]. Generally, young patients (< 50 years) and those who may harbor disease at a significant distance from the edge of the excision cavity or potentially have multicentric disease, such as patients with extensive DCIS or invasive lobular cancer, should not be treated with APBI. Using these criteria, the group from Milan showed a low risk of local recurrence (2.3%) and new primary ipsilateral cancer (1.3%) at a median follow-up of 36.1 months in 1833 cases treated with IOeRT [18]. Our results are consistent with those described by the Milan group, although the cohort of patients in our study is small. The small number of patients enrolled in the present study was due in part to the very strict selection criteria used and in part to the lack of eligible patients undergoing this novel procedure. Neither cases of in-field failure nor new ipsilateral tumors elsewhere were observed at a median follow-up of 36 months. Acceptable rates of mild acute complications were observed and good cosmetic results were achieved. We wish to stress, however, the importance of lead shielding over the chest wall to prevent radiation-induced rib fractures. In the first 21 cases we did not use shielding and observed 4 fractures (19%). Following the initiation of shielding there were no additional fractures.
Four patients received supplementary WBI without boost therapy. The reasons for this practice were poor tumor differentiation or evidence of localized extensive DCIS. Whether this practice was truly needed is not known, emphasizing again the lack of evidence-based data. As with every new technique, great caution is required, which may ultimately prove unjustified when sufficient data become available. Nevertheless, this practice does not cause harm to the patient, and the efficacy of IOERT as an alternative to external boost has been well established [23]. Four patients received adjuvant chemotherapy in addition to hormonal therapy. Reasons included Her-2/neu positivity in three patients and micrometastases in two. These patients had a similar outcome to patients not receiving chemotherapy, in agreement with other studies, suggesting that the addition of chemotherapy should not in itself be a contraindication to IORT.

Interest in APBI is evident from the proliferation of approaches and devices. Nevertheless, data to determine the best modality to deliver APBI are lacking. Studies are therefore required, not only to evaluate the efficacy of APBI but also to assess the safety and toxicity of the various techniques and dosing schedules. Furthermore, it is hoped that future research will determine the strengths and weaknesses of the different techniques, thereby creating a consensus and identifying where each technique may be best applied. Another issue of criticism specific for IOERT is the need for specialized expensive mobile equipment. Although an important concern, especially before this technique receives general acceptance, it can be overcome by performing the operation in the radiation suite as we and others have done [24]. Overall, time consumption is less than that required for performing WBI and the rates of postoperative complications are low, making this practice feasible.

In summary, APBI by means of IOERT in a carefully selected group of early-breast cancer patients seems to be an attractive and safe alternative to whole-breast irradiation. This procedure can be performed using the existing radiation suites and does not need the designated mobile equipment. Further prospective evaluation is needed to include this method in the standard treatment list.

Corresponding author:
Dr. D. Hershko
Dept. of Surgery, Rambam Health Care Campus, Haifa 31096, Israel
Phone: (972-4) 854-2296
Fax: (972-4) 854-1289
email: d_hershko@rambam.health.gov.il

References