ORIGINAL ARTICLE

Full-Dose Intraoperative Radiotherapy With Electrons During Breast-Conserving Surgery

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Hypothesis: The current standard treatment for early breast cancer includes conservative surgery followed by entire breast radiotherapy (RT). Recent study findings show that most local recurrences are in the scar tissue area suggesting that whole-breast RT may not always be necessary. If the volume of breast tissue to be irradiated is limited, RT may be performed intraoperatively. Intraoperative RT delivered with electrons at the total isodose of 2100 rad (21 Gy) could in principle substitute the currently used radiation course of external RT after breast-conserving surgery in selected cases.

Patients and Methods: We report our findings on intraoperative RT using a specially designed mobile linear accelerator delivering 4 energy levels of electrons (3, 5, 7, and 9 MeV) via a head maneuvered by a robot arm. We applied this technique to 237 patients with breast cancer (mean age, 59 years; age range, 33-80 years) with tumors smaller than 2 cm in maximum diameter (T1); most underwent wide resection and an axillary sentinel node biopsy.

Results: After a median follow-up of 19 months (range, 7-33 months), the rate of posttreatment complications is very low. Four patients (1.7%) developed breast fibrosis—mild in 3 patients and severe in 1 patient—that resolved in 24 months. Three patients (1.4%) developed ipsilateral breast cancer—2 (1.0%) contralateral breast cancer, 1 (0.5%) supraclavicular node metastasis, and 1 (0.5%) distant metastases.

Conclusions: Intraoperative RT with electron beams reduces irradiation to the skin, subcutaneous tissue, and contralateral breast and lung. It appears to be a promising method for irradiating conservatively treated breasts and it avoids the long period of postoperative RT that may not be easily accessible to all patients.

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BREAST-CONSERVING surgery followed by radiotherapy (RT) is accepted as a standard treatment option for most women with clinical stage I/II invasive breast cancer.[1,2] The recently introduced technique of sentinel node biopsy makes it possible to conserve the axillary lymph nodes in many patients with breast cancer.[3,4] These 2 techniques combined constitute a minimally mutilating approach to breast cancer that achieves local control rates indistinguishable from those of mastectomy and is expected to have a highly favorable effect on the patient's quality of life.

The current standard RT for patients receiving breast-conserving surgery is whole-breast irradiation. A question that has remained unanswered, however, is whether the entire breast needs to be irradiated following conservative surgery, or whether it is sufficient to treat a more limited volume of tissue surrounding the tumor bed, considering the recent data showing that 85% local recurrences develop in the scar tissue area.[5]

If a single session of RT could produce the same outcome as the normal 6-week course of whole-breast irradiation, this would substantially improve the patients' quality of life and greatly ease the difficulties of those who have to contend with long waiting lists for RT or who live a long way from an RT center. Equally important is the fact that this logistically simpler and quicker treatment will cost less than conventional RT for patients with breast cancer. We report our experience at the European Institute of Oncology, Milan, Italy, using full-dose intraoperative RT with electrons (ELIOT) in patients with breast cancer.

METHODS

From January 4, 2000, to February 28, 2002, 237 patients with breast cancer (mean age, 59

Table 1. Patients Who Received Full-Dose Intraoperative Radiotherapy With Electrons Between January 4, 2000, and February 28, 2002

Treatment Year	Isodose, rad	No. of Patients
2000	1700	9
	1900	6
	2100	82
2001	2100	118
2002 (January and February)	2100	22
Total		**237**

SI conversion factor: To convert the isodose to gray, divide by 100.

Table 2. Characteristics of 237 Patients With Breast Cancer Who Received Intraoperative Radiotherapy With Electrons

Characteristics	No. of Patients
Age, y	
≤50	33
51-60	120
61-70	84
Tumor site	
Upper external quadrant	141
Upper internal quadrant	36
Lower external quadrant	28
Lower internal quadrant	22
Central quadrant	10
Tumor diameter, mm	
≤5	13
>5≤10	55
>10≤15	93
>15	76
Histologic finding	
Ductal invasive carcinoma	178
Lobular invasive carcinoma	26
Other histology	32
Ductal carcinoma in situ	1

years; age range, 33-80 years) received intraoperative electron beam therapy as sole RT. Nine patients received 1700 rad (17 Gy) and 6 received 1900 rad (19 Gy) as part of the initial dose-finding study. The remaining 222 patients received 2100 rad (21 Gy) prescribed at the 90% isodose. All were fully informed of the experimental nature of the treatment and signed an informed consent. A description of our ELIOT cases in the interval described is given in **Table 1**.

The primary tumor was ductal invasive carcinoma in 178 patients, lobular invasive carcinoma in 26 patients, and other types in 33 patients. Patient characteristics are summarized in **Table 2**.

Most patients (182) underwent wide excision with sentinel node biopsy; 55 patients underwent wide excision with axillary dissection. Among patients who underwent sentinel node biopsy, 134 (74%) had a negative sentinel node and axillary dissection was not performed; 48 (26%) had sentinel node metastasis and underwent total axillary dissection. Among the 55 patients who had a total axillary dissection without sentinel node biopsy, 36 (65%) had positive axillary nodes.

The details of the surgical RT procedure have been published.[6] Briefly, the breast gland that is going to receive ELIOT is prepared by separating it from the subcutaneous tissue and the underlying pectoralis muscle and by restoring the continuity of the surgical breach, after having protected the thoracic wall by lead and aluminium disks to optimize the delivered isodose. The skin is moved out of the radiation field by dedicated devices we developed in our Division of Senology and the collimator is placed under the direct control of the operator to delimit the target.

To deliver ELIOT we use a mobile linear accelerator (Novac7; Hitesys SpA Latina, Aprilia, Italy) delivering an electron beam via a head maneuvered by a robotic arm. The linear accelerator delivers electrons at 3, 5, 7, or 9 MeV (nominal) corresponding to 4.5, 5.2, 6.5, and 7.8 MeV of effective energy, respectively, at the phantom surface. Collimation is achieved by a hard-docking system, consisting of 5-mm-thick, high-quality polymethyl methacrylate (Perspex; Hitesys SpA Latina) round applicators. Flat-ended (22.5°-) and beveled (45°-) applicators of 4-, 5-, 6-, 8-, and 10-cm diameter are available. The nominal source to surface distance is 100 cm for the 10-cm applicator and 80 cm for the others. For radiation protection a primary beam stopper (a trolley-mounted 15-cm-thick lead shield) and mobile 1.5-cm-thick lead shields (100 cm long and 150 cm high) are provided.

RESULTS

The mean follow-up is 19 months (range, 7-33 months). Two patients developed acute hematoma and 2 patients developed a postoperative infection in the treated part of their breast. Adverse effects directly attributable to ELIOT have occurred in 6 patients (2.5%). One patient who received 2100 rad (21 Gy) developed severe fibrosis according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer's Late Radiation Morbidity Scoring Scheme, associated with postsurgical hematoma. The fibrosis was most evident 6 months after treatment, lasted a further 6 months, then slowly disappeared.

Three patients developed mild fibrosis in the irradiated area and 2 patients had moderate skin retractions. Three patients developed ipsilateral breast carcinoma 9, 14, and 17 months after being treated with ELIOT.

The first patient developed a second primary carcinoma out of the radiation field 9 months after being treated with ELIOT (1900 rad [19 Gy]). The field of ELIOT during follow-up was identified by checking the radiopaque markers we leave after radiation delivery during surgery. The tumor had different histological characteristics than the primary neoplasm treated with ELIOT. She underwent a mastectomy.

The second patient developed a multifocal breast carcinoma out of the radiation field 13 months after being treated with ELIOT (1700 rad [17 Gy]) with histological characteristics similar to the primary tumor. This patient underwent a partial resection, but the report of extensive multifocality of the disease indicated a subsequent mastectomy.

In the third patient the new manifestation of breast disease was an invasive ductal carcinoma that appeared out of the radiation field 17 months after being treated with ELIOT (2100 rad [21 Gy]). She also underwent a mastectomy.

Two patients (1%) developed contralateral breast cancer, both 13 months after being treated with ELIOT.

One patient (0.5%) developed bone metastases 16 months after being treated with ELIOT and is receiving anastrazole therapy. Another patient (0.5%) developed ipsilateral supraclavicular node metastasis 25 months after RT and received 3 cycles of an anthracycline antineoplastic antibiotic agent. Three patients (1.4%) developed an ipsilateral second breast carcinoma 9, 14, and 17 months after being treated with ELIOT.

COMMENT

After we pioneered conservative surgery[3] and developed sentinel node biopsy to spare unneeded axillary dissections,[4] our next priority has been to reduce the RT field after conservative surgery for limited-stage breast cancer. In fact, our randomized trial findings on the role of postoperative RT after breast-conserving surgery[5] showed, after 12 years of follow-up, that in patients who did not receive postoperative RT 85% of local relapses occurred in the operated on area of the breast. In the remaining 15% the recurrences were in other quadrants and were considered new ipsilateral carcinomas. These results suggested that the main role of RT should be to destroy residual cancer cells in the operating field. To achieve this objective the radiation field can be reduced and RT may be concentrated on this area.

One method to reach this objective is interstitial brachytherapy, an established method of boosting the isodose to a circumscribed area. In 2001, Baglan et al[7] reported on 37 patients with 38 stage I/II breast cancers whose sole RT after surgery was an interstitial high-dose rate implant radiolabeled with iridium Ir 192 to the lumpectomy cavity. A minimum isodose of 3200 rad (32 Gy) was delivered on an outpatient basis in 8 fractions of 400 rad (4 Gy) to the entire lumpectomy cavity with an additional 1- to 2-cm margin over 4 consecutive days. After a median follow-up of 31 months, 1 ipsilateral breast carcinoma recurrence was observed (crude failure rate, 2.6%); there were no regional or distant failures. Wound healing was not impaired. Three minor breast infections occurred and all resolved with oral antibiotic therapy. The cosmetic outcome was described as "good to excellent" in all patients.

The results of a study conducted by the National Institute of Oncology, Budapest, Hungary, also indicated that a reduced radiation field is effective.[8] One hundred twenty-six patients with T1 breast cancer were randomized to whole-breast irradiation (5000 rad [50 Gy] in 25 fractions in 63 patients) or partial-breast irradiation (7×520-rad [5.2-Gy] high-dose rate interstitial brachytherapy in 46 patients, or 5000 rad [50 Gy] in 25 fractions using wide electron fields in 17 patients). After a median follow-up of 30 months, no local or regional recurrences were observed. No significant differences were noted in the 2 arms of the study for the development of fibrosis, fat necrosis, or telangiectasia.

The results of a large trial conducted in the period 1982 through 1987 at Christie Hospital, Manchester, England, indicated that some caution was required when reducing the extent of breast RT. The trial randomized 708 patients to irradiation to the entire breast and regional lymph nodes without a boost (4000 rad [40 Gy] in 15 fractions over 21 days, using a 4-MV linear accelerator) or to treatment of the tumor bed only (4000-4250 rad [40-42.5 Gy] in 8 fractions over 10 days, using 10-MeV electrons to an average field size of 8×6 cm, at the 100% isodose line).[9,10] After a median follow-up of 65 months, the incidence of tumor recurrence in the operated on breast (first event) was 7% in the whole-breast RT arm and 14% in the tumor bed irradiation arm. The 5-year actuarial local recurrence rates were 8% and 17%, respectively, and the 7-year rates were 11% and 20%, respectively. However, the survival rates were identical in the 2 arms. Histological analysis indicated that the difference was largely because of patients with infiltrating lobular microanatomy. The respective 7-year actuarial recurrence rates in these patients were 8% and 34% (whole-breast and tumor bed RT) vs 11% and 15% in patients with infiltrating ductal microanatomy. Furthermore, among patients who received partial breast RT, 64% of those with invasive ductal carcinoma had local failures in the same quadrant as the primary neoplasm compared with only 38% in patients with invasive lobular carcinoma.

A recent interesting review by Vicini et al[11] underlined the importance of partial-breast irradiation in selected cases of breast carcinoma and described the use of brachytherapy in this setting. A randomized trial on partial-breast irradiation is ongoing in London, England.[12] This compares the Targit (targeted intraoperative RT) treatment with a conventional 6-week RT course after breast-conserving surgery.

We began clinical research on ELIOT in 1999. Our first task was to estimate the single dose of electrons biologically comparable to standard fractionated RT for breast cancer. To do this we used a linear-quadratic surviving fraction model, otherwise known as a multitarget surviving fraction model, which indicated that a single isodose in the range 2000 to 2200 rad (20-22 Gy) is equivalent to 6000 rad (60 Gy) delivered in 200-rad (2-Gy) daily fractions 5 days a week over 6 weeks (the isodose required to control microscopic residual disease after breast resection). We decided to err on the side of caution initially and began with intraoperative isodoses lower than this level and then increased them. The results we got from our preliminary experience both in terms of treatment tolerance and control of disease are encouraging and reinforce our effort in testing ELIOT.[13]

In terms of costs, time saved, and patient quality of life, ELIOT has notable advantages over conventional postoperative RT. First, it offers the prospect that many patients, particularly those with a negative axillary sentinel node, can receive definitive treatment for their disease in just 1 day. In Italy, and probably other areas too, many women still undergo mastectomy for breast cancer because they do not have access to the postoperative RT necessary to ensure adequate local control after conservative surgery. The main reason for this is that the RT center is often geographically distant from the patient's and the costs of travel and accommodation are prohibitive. An analysis by Athas et al[14] based on a geographic information system used to measure actual patient travel distances to RT facilities clarified the relationship between travel distance and receipt of RT after breast-

conserving surgery. In this analysis, the likelihood of receiving RT following breast-conserving surgery decreased significantly with increasing travel distance to the nearest RT facility.

A second advantage of ELIOT is that the delay in administering RT in patients given adjuvant anthracycline antineoplastic antibiotic agents can be avoided; there is evidence that the delay increases the risk of local recurrences.[15]

Because the sensitivity of cells to RT is increased by high oxygen levels and because it is easy to saturate the blood with oxygen during general anesthesia, we intend to investigate the influence of oxygenation on the breast response to ELIOT although no data are available on the local oxygenation of the breast during intraoperative RT.

One area of concern in the use of ELIOT is the management of positive surgical margins as positivity is discovered at final histological examination, a few days after undergoing surgery and after having received intraoperative RT. The adoption of an extensive breast resection as a standard procedure in breast-conserving surgery keeps the incidence of positive surgical margins to very low rates. Moreover, data from our randomized Milan II trial show that margin positivity did not influence the rate of local recurrences if effective RT is delivered.[16]

CONCLUSIONS

Full-dose intraoperative RT with electrons is easy to perform in settings characterized by close cooperation between surgeons, radiotherapists, and medical physicists. The required time for the treatment is about 20 minutes. If a sentinel node biopsy with intraoperative pathological examination is being performed, this period is amply contained within the 40 to 50 minutes required for the pathologist's report. A final advantage is that ELIOT markedly reduces radiation exposure to the skin, lung, and subcutaneous tissues, contributing to a low incidence of radiation-induced sequelae. Our preliminary results with this new technique are highly encouraging.

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