Full-Dose Intraoperative Radiotherapy With Electrons in Breast Surgery

Broadening the Indications

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Hypothesis: Although postoperative fractionated radiotherapy (PFR) remains the standard method for conservative treatment of breast carcinomas, widespread experience in the use of full-dose intraoperative radiotherapy with electrons (ELIOT) merits its application in novel clinical situations, although long-term results of ongoing clinical trials have not been fully reported.

Design: Retrospective case series.

Setting: Division of breast surgery in a comprehensive cancer center.

Patients: From June 1999 to September 2003 ELIOT was used as the sole radiotherapy in 355 patients with unifocal invasive carcinoma who were candidates for breast-conserving surgery and most of whom were participating in an ongoing institutional trial. In a group of patients in whom PFR was not considered safe or feasible (because of previous mantle field irradiation for Hodgkin disease, cosmetic breast augmentation, severe cardiopathy, large hypertrophic scarring from skin burns, vitiligo, and geographic or social obstacles), ELIOT was performed outside of the ongoing trial.

Results: No particular adverse effects, unusual acute reactions, late sequelae, and local or systemic events were noted in these patients after a mean follow-up of 27.3 months.

Conclusions: In appropriated selected patients, when it is critical to perform PFR after breast-conserving therapy, a single dose of ELIOT may be considered to avoid mastectomy, reduce potential treatment toxicity, improve quality of life, and resolve logistic problems. The long-term results of ongoing clinical trials will further delineate patients in whom ELIOT may replace PFR.

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A T THE EUROPEAN INSTITUTE OF ONCOLOGY, MILAN, ITALY, FULL-DOSE INTRAOPERATIVE RADIOThERAPY WITH ELECTRONS (ELIOT) AFTER BREAST-CONSERVING SURGERY (BCS) FOR LIMITED-STAGE BREAST CANCER HAS BEEN EXTENSIVELY INVESTIGATED SINCE 1999 AND APPLIED IN PHASE 1 AND PHASE 2 TRIALS, WITH FAVORABLE PRELIMINARY RESULTS.\(^1\) THE INCREASING SUCCESS OF THE TECHNIQUE LED TO ESTABLISHMENT OF A PHASE 3 CLINICAL TRIAL IN NOVEMBER 2000, IN WHICH ELIOT WAS PROSPECTIVELY COMPARED WITH POSTOPERATIVE FRACTIONATED RADIOTHERAPY (PFR), INCLUDING ELECTIVE TREATMENT OF THE WHOLE BREAST. POSTOPERATIVE FRACTIONATED RADIOTHERAPY REMAINS THE STANDARD TREATMENT FOR BREAST CANCER AFTER BCS, AND ELIOT SHOULD NOT BE USED IN ROUTINE CLINICAL PRACTICE UNTIL THE RESULTS OF LONG-TERM CLINICAL TRIALS HAVE BEEN FULLY REPORTED.\(^2,3\) Nevertheless, with the increased experience gained by radiosurgical teams and the widespread use of the technique, the indications to perform ELIOT are broadening. The objective of this article is to describe the selection criteria of patients receiving ELIOT and the clinical indications for this procedure that have been adopted at the European Institute of Oncology during our first 5 years’ experience.

METHODS

From June 1999 to September 2003 ELIOT was used as the sole radiotherapy in 355 patients with unifocal invasive carcinoma who were candidates for BCS. Nine patients received 1700 rad (17 Gy), and 6 received 1900 rad (19 Gy) as part of the initial dose-finding study. The remaining 340 patients received 2100 rad (21 Gy); 307 patients were prescribed ELIOT at the 90% isodose and 33 patients at the 100% isodose.

Of these 355 patients, 251 were recruited to an ongoing randomized ELIOT trial, with patients assigned to receive standard PFR after BCS (5000 rad [50 Gy] via tangential fields...
followed by 1000 rad (10 Gy) as a boost) or partial-breast irradiation (PBI) (limited to the surgical bed and delivered by a single intraoperative fraction of 2100 rad [21 Gy] prescribed at the 90% isodose). The other 104 patients did not meet the eligibility criteria and were treated outside of the trial. The latter group included patients who received ELIOT before the trial started and were enrolled in the phase 1 and phase 2 investigational ELIOT protocols, those with clinical or logistic problems such that conducting PFR was critical, and those who specifically opted for ELIOT and refused to be randomized for the trial. All patients were fully informed of the experimental nature of the treatment and signed an informed consent form.

Full-dose intraoperative radiotherapy with electrons was delivered using a Novac7 (Hitexys SpA Latina, Aprilia, Italy) mobile linear accelerator delivering an electron beam via a head maneuvered by a robot arm. The accelerator delivers electrons at 3, 5, 7, and 9 MeV (nominal energies) corresponding to 4.5, 5.2, 6.5, and 7.8 MeV of effective energies, respectively, at the phantom surface. Collimation is achieved by a hard-docking system, consisting of 5-mm-thick polymethyl methacrylate (Perspex, Hitexys SpA Latina) round applicators. Flat-ended and beveled (22.5° and 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 electron beam stopper (a trolley-mounted 1.5-cm-thick lead shield) and mobile 1.5-cm-thick lead shields (100 cm long and 150 cm high) are provided.

Eligibility criteria for the ELIOT trial included patients aged 48 to 75 years with unifocal invasive carcinoma with a maximum diameter of 2.5 cm. Exclusion criteria included T3 and T4 tumors, contralateral synchronous or metachronous tumors, noninvasive carcinomas (including Paget disease), breast malignancies other than carcinoma, multifocality or multicentricity of the disease, previous surgical biopsy, and a history of cancer. A breast thickness greater than 3.0 cm was considered a technical contraindication, as ELIOT was unable to deliver more than 9 MeV. No specific tumor locations were exclusion criteria for ELIOT, but close proximity of the tumor to skin and greater pectoral muscle infiltration were considered contraindications to ELIOT, in which case irradiation of the entire breast, including skin and the greater pectoral muscle, is mandatory. Finally, if the tumor was close to the axilla, ELIOT was avoided because of the risk of irradiating the axillary nerves and vessels. Before delivery of ELIOT, tumors are evaluated during surgery by a pathologist to confirm the eligibility criteria and to guarantee safe resection margins.

Thirty-two of the 104 patients who received ELIOT (delivered as already described) outside of the clinical trial had the following clinical conditions: Five patients had previously received mantle field irradiation for Hodgkin disease (HD). One of them received 1700 rad (17 Gy) (prescribed at the 100% isodose) with a 7-MeV electron beam, and the other 4 received 2100 rad (21 Gy) (prescribed at the 90% isodose) with 7-MeV and 9-MeV electron beams. Five other patients had previously undergone cosmetic bilateral breast augmentation and were ineligible for the ELIOT trial because they were younger than 48 years. In each of these patients, a total dose of 2100 rad (21 Gy) (prescribed at the 90% isodose) was delivered. In 12 patients with left breast invasive carcinoma who were scheduled for BCS, severe cardiopathy was detected before surgery, and ELIOT was administered at the classic dose of 2100 rad (21 Gy) at 90% isodose. Four patients presented with skin disorders, 2 with vitiligo and 2 with large pigmented hypertrophic scaric scars due to skin burns from boiling water at a young age. In each of the 4 patients, a total dose of 2100 rad (21 Gy) (prescribed at the 90% isodose) was delivered. Four other patients who received ELIOT were unable to be treated with PFR at a radiation oncology department because of geographic distance, associated comorbidities, or functional status. Finally, 2 patients received ELIOT to treat invasive recurrences 3 and 4 years after BCS and PFR, respectively. In both patients, the recurrence was in an external quadrant of the breast, peripherally and at the border of the previous irradiation field.

The mean follow-up for all patients treated with ELIOT was 27.3 months (range, 9–58 months). Among the 251 patients randomized to the ELIOT trial, adverse effects directly attributable to ELIOT occurred in 3 patients (1.2%). One of them developed severe fibrosis associated with a postsurgical hematoma, which was most evident 6 months after treatment, lasted another 6 months, and slowly disappeared. A second patient developed mild fibrosis in the irradiated area, and the third patient developed moderate skin retractions. Another patient developed ipsilateral breast cancer 17 months after ELIOT and underwent a total mastectomy. Two patients developed contralateral breast cancer 13 and 19 months after ELIOT. Among the 104 patients treated with ELIOT outside of the trial, no particular adverse effects and local or systemic events were noted.

During the past decade, there has been increasing interest in radiation techniques designed to treat only the portion of the breast deemed to be at high risk of local recurrence. These techniques include brachytherapy implants, the MammoSite applicator (Proxima Therapeutics, Inc, Alpharetta, Ga), an intraoperative orthovoltage device, and 3-dimensional conformal or intensity-modulated external radiotherapy (PBI), and all of them have similar indications but different applications. In particular, they differ in the source of radiation (x-ray, iridium, photons, and others) and the breast volume treated. Because of the increasing availability and the ease of use of some of these techniques, widespread and sometimes indiscriminate use of PBI has been observed. Although 5- to 7-year outcome data on patients treated with PBI are becoming available, many issues remain unresolved, including clinical and pathological selection criteria for patients, radiation dose and fractionation and their relation to the standard fractionation for whole-breast irradiation, appropriate target volume, local control within the untreated ipsilateral breast tissue, and overall survival. To provide guidelines and clarify controversial issues, a PBI workshop was held in December 2002. The workshop report outlined variables for clinical trials and emphasized the importance of education and training in PBI. In particular, it was proposed that ELIOT be evaluated in randomized clinical trials as a single, exclusive treatment in limited-stage breast cancer as a possible alternative to standard PFR in selected patients.

We focused our interest on the use of ELIOT in June 1999, and our experience evolved in different phases. Phase 1 and phase 2 investigations defined the maximum tolerated dose in a single fraction, established a biologically equivalent radiation dose, and assessed acute and...
intermediate toxicity, followed by a phase 3 randomized clinical trial that is ongoing. The radiosurgical procedure was described and standardized.4,5

The rationale for PBI is based on the finding that most local relapses (≥85%) occur in the breast area that was operated on.7 The same study noted that, in postmenopausal women undergoing BCS for early unifocal breast cancer, the recurrence rate is significantly lower than in younger patients, independent of whether radiotherapy was performed. In a randomized study8 with 20-year follow-up, the rates of new primary tumors in the ipsilateral breast (far from the primary tumor bed) were similar in patients with and without whole-breast radiotherapy. In addition, the study found that the incidence of new primary tumors in the treated breast was similar to that observed in the contralateral breast.

In a preliminary study9 of intraoperative radiotherapy, the patient selection criteria were restrictive to ensure a homogeneous study group and to eliminate all possible statistical bias. For some conditions that were initially excluded, such as a previous surgical biopsy, history of cancer, and contralateral synchronous or metachronous tumor, ELIOT would now be indicated.10 The widespread experience gained in the use of ELIOT merits its application in novel clinical situations.

Previous radiotherapy, such as mantle field irradiation for HD, is considered a relative contraindication to BCS and to conventional PFR.10 This is based on concern about possible severe sequelae arising after a high total cumulative dose, exceeding normal tissue tolerance, to portions of the breast that had received radiotherapy for lymphoma, although breast modifications occur over time after radiation delivery. Some authors believe that these patients are at significant risk for complications (fibrosis, skin and soft tissue necrosis, rib fractures, and lung and heart toxicities) and do not consider them candidates for BCS and adjuvant radiotherapy.11 In contrast, other reports12,13 support BCS followed by PFR when breast cancer develops many years after radiotherapy for HD. At present, no consensus exists regarding the correct management of breast cancer after mantle field irradiation for HD, and, given the discordant results and the few patients treated with BCS, mastectomy continues to be recommended as the standard treatment. One conservative option is to treat just the tumor bed; irradiation of a small volume of the breast and adjacent structures could minimize the risk of complications.14,17 In the 5 patients in our series who had previously undergone mantle field irradiation for HD, the radiosurgical technique, the dose delivered, and the energy of the ELIOT electron beams that were delivered did not differ from those in the other patients receiving ELIOT.

No increased postoperative complications (pain, seroma, hematoma, or infection) were observed compared with the patients without HD who received ELIOT, and the length of hospitalization was not prolonged. As a result of the complete removal of the skin from the radiation beam, the cosmetic outcome was good in all patients, with no skin erythema observed.18

The surgical treatment of breast cancer in patients who previously have undergone cosmetic breast augmentation is controversial. Questions remain about whether BCS is feasible in this patient population and whether these patients can retain their implants. The compatibility of radiotherapy and implants is of major concern to radiation oncologists. From a dosimetric standpoint, there is no evidence that implants interfere with dose distribution or that standard doses change or damage implants. Clinically, radiotherapy has a negative effect on cosmesis, increasing the rate of complications (contracture, pain, and capsular migration) and implant failure.19 Retaining the implants is not recommended in BCS for most patients with previous augmentation. Mastectomy with immediate reconstruction is advised for these patients. The study concluded that BCS, with explantation and mastopexy, is more appropriate for rare patients with large volumes of native breast tissue. In our series,4 BCS and ELIOT were performed in 5 patients with invasive carcinoma of the breast who had previously undergone augmentation. In 4 of them whose breast implants had been positioned under the greater pectoral muscle, the radiosurgical technique did not differ from the technique described herein. In the fourth patient, the prosthesis was placed under the mammary gland, and protective devices (dedicated lead and aluminum disks, 5 and 4 mm thick, respectively, used to protect the thoracic wall) were positioned between the gland and the capsular plane of the prosthesis after a wide mobilization of the entire mammary gland. In all patients, removal of the prosthesis was avoided, without any immediate or late implant complications and with good cosmetic results.

Although serious treatment-related morbidity of PFR after quadrantectomy is unusual, there is concern that it may lead to an increased risk of cardiac disease because of the inclusion of part of the heart in the irradiated volume. The pathophysiology and clinical manifestations of radiation-induced heart disease, including accelerated coronary disease, have been described, and the risk of cardiac damage correlates with radiation dose volume and fractionation.20 In certain patients, for anatomical reasons, a significant amount of heart disease occurs with high doses. Three-dimensional computed tomographic planning does not always enable complete cardiac sparing without compromise of the target volume coverage, and alternative electron beams with intensity-modulated radiotherapy optimization are not yet commonly available in most radiation facilities. In the 12 patients in our series with invasive carcinoma of the left breast who were candidates for BCS and who had severe cardiopathy, ELIOT was carried out at standard doses. Preoperative and postoperative evaluation of cardiac function by electrocardiography and echocardiography found no cardiac complications related to ELIOT.

Complete radiation-induced depigmentation of the skin is an adverse effect of radiotherapy (Koebner phenomenon),21 due to the loss of melanocytes. To avoid breast skin depigmentation, we used ELIOT in 2 postmenopausal patients in our series, both of whom had small breast carcinoma and severe vitiligo. In 2 other patients in our series, severe skin burns of the thoracic wall had led to hypertrophic skin scarring involving both breasts. Both patients had undergone several plastic surgery procedures in the past, and the thoracic wall skin was weak, thin, and hypovascularized. Because of the high risk of
necrosis,\textsuperscript{22} we did not consider it safe to administer PFR, and ELIOT was used to avoid further injury to the soft tissues and skin of the breasts.

Recent findings indicate that 15\% to 30\% of women treated with BCS for early-stage disease failed to undergo PFR, and older age has been identified as a major determinant of not receiving radiotherapy after BCS.\textsuperscript{23} The traveling distance to a radiation facility may also be a factor in the receipt of PFR. Radiotherapy that follows BCS typically involves daily treatments (weekends excluded) for 5 to 6 consecutive weeks. Long-distance travel may exacerbate the inconvenience or cost of radiotherapy such that treatment is infeasible.\textsuperscript{23} In our series, 4 patients without family support required ELIOT because of logistic difficulties in traveling to a radiation oncology department.

Previous breast irradiation remains an absolute contraindication to reirradiation of the breast or thoracic wall after local recurrence. Rare instances of reirradiation demonstrate that it achieves good and lasting local control with an acceptable rate of acute complications, but it carries a high risk of disabling late sequelae such as severe pain.\textsuperscript{24} Furthermore, there are rare situations in which recurrences occur peripherally in the breast, at the border of the previous irradiation field. In these cases, although mastectomy can be avoided, PFR can be difficult or dangerous to deliver, and ELIOT is a good alternative, permitting BCS. In our series, 2 patients had small invasive recurrences 3 and 4 years after BCS and PFR, respectively. Because of the large size of the residual breast, the peripheral recurrence site, and the small size of the recurrences, new BCS was possible in both patients, and ELIOT was successfully delivered.

CONCLUSIONS

Although PFR remains the gold standard conservative treatment of limited-stage breast cancer, widespread experience with ELIOT invites new indications for its use in BCS to include breast cancer patients who previously had been excluded. The generally accepted criteria in postmenopausal women for PBI, and for ELIOT in particular, are small invasive unifocal carcinomas without an extensive intraductal component and with microscopically negative surgical margins. New indications for ELIOT include prior treatment for HD, cosmetic breast augmentation, severe cardiopathy, large hypertrophic skin scarring from previous burns, and vitiligo. It may also be considered in BCS candidates who for logistic or geographic reasons cannot undergo PFR, enabling them to avoid mastectomy. Long-term results of ongoing clinical trials will further delineate those patients in whom ELIOT may replace PFR.

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REFERENCES