



# Intraoperative Electrons

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**Intraoperative radiotherapy (IORT) has been used for many years for treating patients with various locally-advanced malignancies, usually combined with external-beam radiation therapy (EBRT). Long-term results confirm that IORT improves local control, which is generally associated with increased survival. Recently, electron-beam IORT has been used as the sole treatment for patients with earlier-stage cancers, especially for breast tumors, with extremely promising results. Most of this work has been done at the European Institute of Oncology in Milan. We report the rationale and techniques of the use of electron intraoperative treatment (ELIOT) and the results of our different clinical studies. In our opinion, ELIOT may be an excellent alternative to EBRT for the treatment of patients with early-stage breast cancer. However, intensive long-term follow-up is needed to fully evaluate local control and possible side effects.**

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**I**ntraoperative radiotherapy (IORT) refers to the application of a single dose of radiation during a surgical intervention, after the removal of the neoplastic mass. This direct visualization potentially improves the ability to localize the tumor bed and subclinical disease. Modern IORT is performed with electron beams (IOERT) produced by a linear accelerator. The most widely used approach for IOERT is to transport the patient from the operating room to the shielded radiotherapy facility in the middle of surgery and then return him/her to the operating room after the treatment.<sup>1</sup> Recently, miniaturized mobile-linear accelerators have been designed that can be placed in the operating room, avoiding the disadvantages of transferring an anesthetized patient; they can also be placed in any operating room without requiring undue structural modifications. These accelerators have a variable spectrum of electron energies (from 3 to 12 MeV).

Two important technical advantages of IOERT in comparison to the use of external-beam radiotherapy (EBRT) are direct visualization of the target volume and the possibility of protecting healthy tissues by moving them away from the path of the radiation beam. The use of electron beams allows the administration of a homogeneous dose to a selected layer of tissues surrounding the removed tumor or, less frequently, unresectable or residual gross disease.

Although the radiation oncologist has full clinical respon-

sibility for prescribing and administering the delivery of radiation, the use of IOERT requires multidisciplinary collaboration between surgeons, anesthesiologists, medical physicists, radiation technologists, and nurses.

IOERT has been used in the treatment of various malignancies, particularly those that are locally advanced or recurrent, usually combined with EBRT.<sup>2,3</sup> Several clinical studies have been performed of its role in treatment of cancers of the stomach, pancreas, rectum, and retroperitoneal sarcomas, for which local recurrence is one of the main causes of failure. Local control has always been very high and toxicity generally low. The long-term results of these nonrandomized series suggest that the improvement in local control achieved with IOERT increases survival rates.

More recently, IOERT has been used as the sole form of radiation treatment for patients with early-stage diseases, especially for those with breast tumors. Most of this work has been done at the European Institute of Oncology in Milan, with extremely promising results. This article will discuss the rationale for such a treatment approach, its technical aspects, and the results of treatment so far.

## **Rationale of the Use of IOERT in Breast Cancer**

### **Radiobiology**

The probability of tumor control for a given absorbed dose decreases with an increase in the initial number of malignant cells (assuming no differences in cellular radiosensitivity). Therefore, the greater the tumor volumes, the higher the dose required to achieve the same control rate. From this point of

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view, IOERT offers an important theoretical advantage in comparison to conventional postoperative EBRT. In the latter case, the time between surgical removal of the tumor and the start of radiotherapy allows repopulation from the neoplastic clones present in microscopic residual disease. Indeed, after surgery, there can be “accelerated repopulation,” during which the first phases of neoplastic cellular growth follow an exponential course. Thus, giving IOERT immediately after surgery (either as a boost or as the sole treatment) may avoid this problem.

The dose-response relationship can be analyzed by various mathematical models, with the linear-quadratic model most commonly used (although the validity of this model is better for fraction sizes smaller than 6-8 Gy). By giving a large dose in a single fraction, the same amount of tumor-cell killing can be achieved with a total dose only one half to one third as large as that needed when conventional fractionated treatment is given.<sup>4</sup> Assuming that the alpha-beta ratio of tumor cells is equal to 10, giving single-dose treatment of 12 Gy (as a boost) or 21 Gy (as the sole treatment) should result in the same local control as conventionally fractionated doses of 26 and 56 Gy, respectively. However, there may be a higher risk of late effects (such as fibrosis) in late-responding tissues (which have alpha-beta ratios of 3 or lower) from the single-fraction treatment. An important area that needs to be explored is the influence of combined treatment with EBRT and/or chemotherapy on the tolerances of IOERT.

In conclusion, IOERT has the radiobiological advantage of eliminating or reducing repopulation by eliminating the interval between surgery and radiotherapy and between radiotherapy fractions during which tumor cells might proliferate. Moreover, tissues treated during surgery still have rich vascularization and aerobic metabolism, which (because of the oxygen effect) makes them more sensitive to radiation than they might be after surgery, when they may become hypoxic because of postoperative changes.

### IOERT as a Boost

The most common fractionation scheme used for the conservative treatment of early-stage breast cancer after surgery is to give 45 to 50 Gy to the entire breast, followed by a boost of 10 to 16 Gy given to the tumor bed. The role of the boost in reducing the incidence of local recurrences for patients with microscopically uninvolved margins has been shown by the EORTC “boost versus no boost” randomized trial. This showed a significant improvement in local control in patients receiving a tumor-bed boost of 16 Gy in addition to 50 Gy given to the entire breast, compared with treatment of the breast only.<sup>5</sup> This benefit was greatest for women younger than 50 years. Similar results were found in another randomized trial of more than 1,000 patients performed in Lyon, France, who were randomized to receive or not receive a boost dose of 10 Gy, with a median follow-up of 5 years.<sup>6</sup>

There are several techniques for delivering the boost.<sup>7</sup> The main constraint is accurately defining the boundaries of the tumor bed after surgery. This can be difficult, particularly when the breast has been reconstructed, when marking clips

have not been placed, or when there is no radiologic evidence of its location (scarring or a seroma cavity). These inaccuracies could increase the rate of local recurrence or require an increase in the volume of the irradiated tissue, which might increase the risk of late tissue reactions or poor cosmetic outcome.

Thus, IOERT offers important advantages compared with conventional EBRT. The direct exposure of the operating bed eliminates the possible inaccuracy of tumor-bed localization, allowing treatment of a more limited volume of breast tissue. Other critical structures adjacent to the tumor bed (heart and lung) can be spared by shielding, and the skin is moved outside the field of irradiation, minimizing late sequelae. Moreover, using an electron beam ensures a homogeneous dose distribution in the target volume.

Only a few patients have been treated with IOERT as a boost in the past.<sup>8,9</sup> More recently, local and distant recurrence rates were compared for patients with invasive cancer treated in Salzburg, Austria. One hundred eighty-eight patients (group 1) received a conventional external-beam electron boost (12 Gy in 6 fractions), and 190 patients (group 2) received a boost using IOERT (9 Gy in a single fraction).<sup>10</sup> All patients received postoperative EBRT radiation therapy to the whole breast (51-56.1 Gy in 1.7 Gy fraction). The median follow-up periods were different in the 2 groups (55.3 and 25.8 months, respectively). The local recurrence rates were 4.3% in group 1 and 0% in group 2.

Thus, IOERT appears to be an effective alternative to the conventional EBRT boost. By giving the boost in a single intraoperative session, which only modestly increases operative time (15-20 minutes) when a dedicated IOERT unit is available, the total time of external treatment is reduced by 1 to 2 weeks, with consequent economic savings and improvement in the general well-being of the patient.

### IOERT as the Sole Radiotherapy Treatment

The rationale for using segmental radiation therapy in place of whole-breast irradiation is the observations from long-term studies that (with few exceptions) 80% or more of local relapses after conservative surgery and radiation therapy occur at the original tumor site.<sup>11-14</sup> For example, in the Milan III trial, which compared quadrantectomy alone versus the same conservative surgery plus EBRT given to the entire breast, 85% of local failure were in or close to the index quadrant.<sup>15</sup> The incidence of local relapse was reduced substantially by radiotherapy for patients younger than age 55, but the rates were equal in both arms for patients older than age 65.

Thus, in theory, IOERT could reduce the radiotherapy course from 5 to 7 weeks to a single dose given in the operating room immediately following tumor resection. This would overcome some of the constraints that may prevent patients from having breast-conserving therapy, such as accessibility to a radiotherapy center and the effects of a prolonged treatment course on patients' social and economic lives.<sup>16</sup> Moreover, IOERT could minimize some of the potential side effects associated with conventional EBRT because

the skin and subcutaneous tissues are not irradiated and the irradiated volumes of lung and heart are significantly reduced. Another important advantage is avoidance of interactions with systemic therapy that may delay the initiation or of conventional EBRT.

IOERT thus lends itself, together with other techniques described in this issue, to implementing the treatment philosophy of partial-breast irradiation of treating only the excision site and the adjacent tissues.<sup>17</sup> However, studies are not available yet that clearly show which patients can be appropriately treated with partial-breast irradiation and which should receive whole-breast irradiation. Therefore, this technique should not be used as a standard treatment. We believe its use currently should be limited to a subgroup of patients at low risk of local recurrences who have the following characteristics: age older than 45 years, tumor diameter less than 3 cm, infiltrating ductal histology, no mammographic evidence of multifocality, negative resection margins, negative or no more than 3 positive axillary nodes, and no extensive intraductal component.

### IOERT in Conjunction With Nipple-Sparing Mastectomy

The present consensus on surgical treatment of breast cancer is to limit the disfigurement of the patient as much as possible by performing lumpectomy or quadrantectomy if possible. However, a mastectomy is still required in patients with large or multifocal infiltrating tumors, in some cases of local recurrence after conservative treatment, and in diffuse in situ carcinomas. Skin-sparing mastectomy facilitates immediate breast reconstruction, but the removal of the nipple-areola complex (NAC) dramatically increases the feeling of mutilation.<sup>18</sup> To reduce this psychological impact, the NAC could be spared and IOERT used to treat the remaining glandular tissue behind the areola. The aim of this approach would be to maintain the blood supply and the sensitivity of the NAC, while reducing the risk of recurrence in the central area of the breast. A study of this approach has begun (see later).

## The Milan Experience Using ELIOT

### Overview

The technique of intraoperative radiotherapy used at our institute has been termed ELIOT. More than 6 months of extensive testing and training of the involved personnel was needed before the first patients were successfully treated on July 19, 1999. This clinical experience was planned and developed in 4 phases:

- A dose-escalation study: to define the maximum tolerated single-fraction dose and establish an equivalence to conventionally-fractionated EBRT. This phase closed in April 2000, with 58 patients treated.
- A phase II study: conducted from May to November 2000 at the maximum tolerated dose level (21 Gy) to

assess acute and intermediate-term toxicity in an additional group of patients (51 cases).

- A prospective randomized phase III study: started in December 2000 and currently ongoing, this compares standard EBRT (50 Gy to the entire breast and a 10 Gy boost to the tumor bed) with a single dose of ELIOT (21 Gy prescribed to the 90% isodose line) in a group of patients older than 48 years with invasive cancers 2.5 cm or smaller. All women underwent quadrantectomy, followed by sentinel node biopsy (with completion axillary dissection only if the sentinel node was positive). The aim of the study is to evaluate the effectiveness of this new approach in terms of local control, disease-free, distant disease-free, and overall survival rates; cosmetic outcome; and cost. As of June 2004, 610 of a planned total accrual of 824 patients have been enrolled, of whom 307 were assigned to the ELIOT arm.
- Nipple-sparing mastectomy (NSM): opened in March 2002, this ongoing study is testing a new technique to preserve the NAC during skin-sparing mastectomy. A 16 Gy dose is given to this area with IOERT. As of June 2004, 184 patients have been enrolled.

In summary, 600 patients participating in these trials have been treated with ELIOT, and another 250 patients have been treated with ELIOT (21 Gy) after breast conserving surgery at their own request outside of these formal protocols after giving written informed consent.

### Radiation Technique

"Dedicated accelerators" are electron-beam accelerators that can be used in the operating room without modifications of the room itself. They have been designed to require only limited shielding (15 cm in width) to be placed around the operating table. Such dedicated accelerators are mobile and can therefore be transported from 1 operating room to another. They are also articulated so they can be positioned properly in relation to the operating table and then make precisely controlled incremental small motions to facilitate alignment and the docking with the applicator.

The EIO has 2 such dedicated accelerators, which have enormously facilitated the implementation of a broad program of intraoperative radiation, allowing the treatment of a large number of patients in a relatively short period of time. The radiation therapy department bought the first accelerator, known as NOVAC 7 (Hitesys, Latina, Italy), in 1998, and the second, called LIAC (Info & Tec, Udine, Italy), in 2003. These accelerators produce only electron beams, with energies from 3 to 12 MeV. The typical dose rate is 15 to 20 Gy per minute, much higher than that of conventional accelerators. The hardware is completed by a set of several Perspex applicators, varying in shape, diameter (4 to 10 cm), and position relative to the tumor bed (perpendicular or oblique, with angles ranging from 15° to 45°), and by shielding devices used to diminish the exposure of normal tissues.

The ELIOT program requires a specialized staff and strict attention to scheduling of the operating rooms. All procedures and the personnel involved have been explicitly de-

**Figure 1** Placement of shielding disks behind the breast parenchyma after tumor excision. (Color version of figure is available online).



scribed, as has the required training, with special emphasis on dosimetry.<sup>19</sup>

This technique requires special dosimetric determinations, which are different than those needed for conventional EBRT. First, the dimensions and depth of the treated volume are directly determined in the operating room, where the team selects the appropriate diameter of the applicator, the energy of the electron beam, and the proper reference isodose to prescribe the dose. Second, the use of specific applicators contributes to the determination of the quality, output, homogeneity, and other physical and geometrical characteristics of the electron beams. These dosimetric data are needed to allow the calculation of the monitor units needed to deliver the prescribed dose to the target volume. Our experience contributed substantially to the creation of the “Guidelines for Quality Assurance in Intra-Operative Radiation Therapy,” published by the Istituto Superiore di Sanità in Rome, which have been translated into English and are available on the Istituto Superiore di Sanità Web site.<sup>20</sup>

## Surgical Procedures

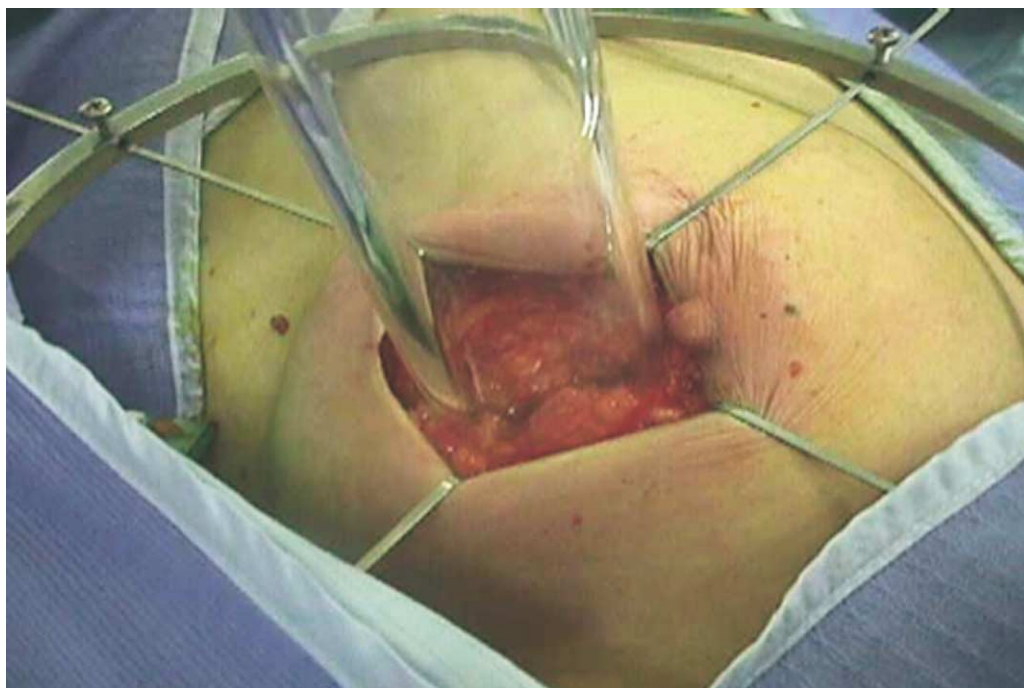
### ELIOT After Quadrantectomy

Patients undergo quadrantectomy, according to the Veronesi's technique, with sentinel node biopsy (SNB). (Only patients with positive SNB undergo axillary dissection.) ELIOT requires a special sequence of procedures to facilitate the radiation treatment.<sup>21,22</sup> Immediately after the removal of the breast quadrant, the remaining parenchyma should be separated from the pectoralis fascia to place an aluminum-lead shielding disk posterior to the parenchyma to protect the thoracic wall, the heart, and the lung (Fig. 1). The anatomy of the breast is temporally restored by suturing the gland, taking care to correctly expose the clinical target volume. The

treated volume should include the entire surgical scar plus a safety margin of 1.5 to 3 cm. A metallic ring with nontraumatic hooks is used to hold open the skin. The applicator is placed (Fig. 2). A wet sterile gaze is positioned between the applicator and the surrounding tissues to absorb the low-energy electrons scattered around the applicator edge. The applicator is connected to the head of the treatment machine (hard docking), the monitor units needed to deliver the prescribed dose using an electron beam of appropriate energy are calculated, and the patient treated. Beam-on time is less than 2 minutes, and the entire procedure lasts about 15 to 20 minutes. After irradiation, all the materials are removed, and cosmetic reconstruction of the breast is performed.

### ELIOT and NSM

The skin incision is made over the tumor site. An elliptical skin paddle is removed whose size is determined in relation to the distance between the tumor and the dermis, not including the areola, with the incision stopping about 0.5 to 1 cm from the lateral borders of the areola. A preliminary subcutaneous dissection is performed with a smooth Hegar dilator or with long scissors to avoid any injury to the subdermal vascular network. A 0.5-cm thick parenchymal layer is left attached to the dermis to preserve the blood supply and the sensitivity of the NAC. This glandular “patch” should extend 1 or 2 cm beyond the lateral borders of the areola. The gland is undermined and separated from the pectoral fascia in the same way as in the classical mastectomy. Thus, the only remaining glandular tissue after surgery after the specimen has been removed and sent to the pathologist is that behind the NAC. ELIOT is performed only after intraoperative pathological examination of tissue taken from this thin layer left behind the areola to verify that it is free of cancer. The clinical target volume includes the remaining



**Figure 2** ELIOT applicator in position. (Color version of figure is available online).

glandular tissue behind the NAC and thus corresponds to the diameter of the NAC diameter and its periphery. Two protective devices (aluminum-lead disks) are placed between the NAC and the pectoralis muscle to minimize irradiation of the thoracic wall (Fig. 3). The sterile collimator of the mobile linear accelerator is placed in contact with the NAC, and a dose of 16 Gy is delivered. Breast reconstruction is performed immediately after irradiation with the use of a prosthesis or a myocutaneous flap.<sup>23</sup>

## Results

### Dose-Escalation Study

Between July 1999 and May 2000, 58 patients (of whom 2 women had bilateral breast carcinoma, for a total of 60 treated breasts) with T1 or T2 breast cancers no larger than 2.5 cm without evidence of distant disease underwent breast-conserving surgery, SNB (with completion axillary dissection

**Figure 3** Patient undergoing nipple-sparing mastectomy with ELIOT, with shielding disks placed behind the nipple-areolar complex before delivering treatment. (Color version of figure is available online).



**Table 1** Dose Escalation Study (July 1999-May 2000): Distribution of Doses

ELIOT Dose (Gy)	EBRT Dose (Gy)/ No. of Fractions	No. of Patients
10	44/22	8
15	40/20	7
17	—	8
19	—	6
21	—	31
<b>Total</b>	—	<b>60</b>

if positive), and ELIOT, with or without EBRT. The mean age was 57 years. The most common histology was invasive ductal carcinoma (45 cases or 78%). ELIOT was administered at doses of 10, 15, 17, 19, and 21 Gy, if no EBRT was to be given; when EBRT was to be used, doses of 10 and 15 Gy dose were used (Table 1). All doses were prescribed at the 90% isodose line. The average, minimum, and maximum doses are reported in Table 2 for patients receiving the full dose of 21 Gy. Patients were followed at 2- to 3-month intervals after therapy, with a minimum follow-up time of 4 years.

No major side effects were observed. No treatment-related deaths occurred. Three patients treated with ELIOT alone developed ipsilateral local recurrences (1 patient received 17 Gy and 2 patients 19 Gy); only one of them was a true recurrence ("in field"), which was detected at 36 months after treatment, whereas the other 2 were located in other quadrants of the breast. Two patients developed contralateral cancer (one of them treated with a 10-Gy dose of ELIOT and then 44 Gy EBRT, the other treated with a dose of 17 Gy with ELIOT alone), and 2 patients developed distant metastases (one with brain and the other with bone and liver metastases).

Thus, the single dose of 21 Gy (corresponding to an average dose of 22.53 Gy) was found to be tolerable and appeared equivalent to a full course of conventional EBRT. This dose was selected for the phase II trial of ELIOT at our institute.

### Phase II Study

In this section, we analyze together results from 558 patients treated from May 2000 to December 2003 who were enrolled either in the phase II study or the ELIOT arm of the randomized phase III study and patients receiving ELIOT outside this ongoing trial, all of whom received 21 Gy (Table 3). Some preliminary results have been previously published.<sup>24-26</sup> Patients were older than 48 years, with an average age of about

**Table 2** Average ( $D_{ave}$ ), Minimum ( $D_{min}$ ), and Maximum Dose ( $D_{max}$ ) Given to the Surface and Tumor Bed With ELIOT Dose of 21 Gy Prescribed to the 90% Isodose

Parameters	Dose (Gy) (SD)
$D_{ave}$ at surface	19.87 (0.51)
$D_{min}/D_{max}$ at surface	18.66/20.53
$D_{ave}$ at tumor bed	22.53 (2.26)
$D_{min}/D_{max}$ at tumor bed	7.84*/23.33

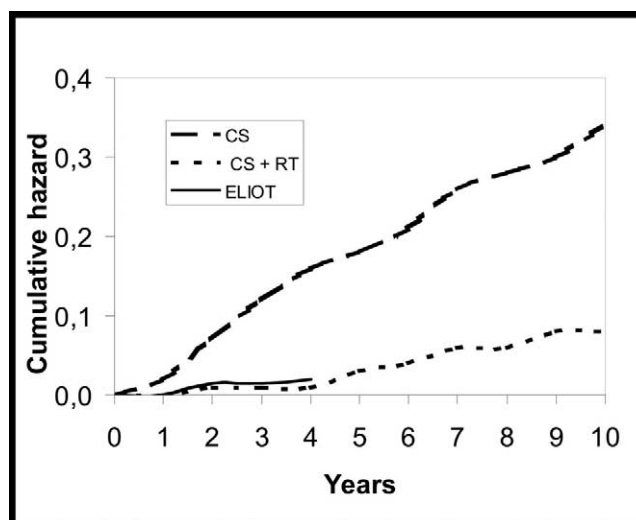
\*Two cases with target depth >3 cm.

**Table 3** Number of Patients Treated With ELIOT (21 Gy) After Quadrantectomy

Year	No. of Patients
2000	48
2001	112
2002	127
2003	241
<b>Total</b>	<b>558</b>

61 years. All patients had unifocal breast carcinoma, with a maximum size of 2.5 cm, with 65% smaller than 1.5 cm. Of these tumors, 77% were located in the upper quadrants, and 78% were ductal carcinoma, whereas only 11% pure lobular or mixed. Each patient was evaluated at 1, 3, 6, and 12 months after treatment and then every 6 months thereafter. As of June 2004, the cumulative risk of in-breast recurrence was very low (Fig. 4). Three patients presented with local relapse at 28, 29, and 39 months after ELIOT. All 3 patients have been surgically treated and are alive 9 to 23 months after the second surgery. Another 3 patients developed ipsilateral carcinoma in another quadrant of the breast, clearly located outside the radiation field. Five patients developed contralateral breast carcinoma, and 3 developed other primary tumors. Thirteen patients developed distant metastases without local relapse.

The toxicity of ELIOT was very low. Fibrosis occurred in fewer than 3% of patients. These were almost always mild, progressing during the first months after surgery, reaching a peak at 12 months, then remaining stable for another 6 to 12 months, and finally slowly regressing within 36 months after ELIOT. Only 1 patient developed severe fibrosis, which lasted for about 6 months and then disappeared. Fat necrosis



**Figure 4** Local recurrence rate in patients treated with ELIOT (2-Gy single dose), compared with results of the Milan III trial. There was no statistical difference at 4-year follow-up between ELIOT and the radiotherapy arm of this trial (in which patients received 50 Gy to the entire breast plus a 10-Gy boost). CS, conservative surgery; CS+RT, conservative surgery plus external fractionated radiotherapy; ELIOT, electron intraoperative therapy.

was observed in 2.5% of patients between 1 to 4 weeks after surgery. This resolved spontaneously; only 1 patient required curettage of the necrotic area. This complication seems to be more frequent in older patients, who have a higher proportion of fat tissue in the breast, but further follow-up will be needed to clarify factors correlating with this problem.

## NSM With ELIOT

From March 2002 to June 2004, 184 NSMs have been performed with ELIOT (8 patients had bilateral NSM). The median age of the patients was 46 years. The single dose currently used at the NAC site is 16 Gy. Eight patients developed complete necrosis of the NAC necrosis (4%), and there were 15 partial necroses (8%). It was necessary to remove the NAC in 11 cases (6%). The follow-up period is still too short to make definitive conclusions regarding the ultimate risk of complications or recurrence.

## Conclusions

Based on our experiences, ELIOT has a number of advantages in the conservative management of initial-stage breast cancer compared with conventional EBRT. These are radiobiological (giving a single large dose to the operative bed without allowing time for repopulation or the development of postoperative hypoxia), technical (more accurate localization of the tumor bed, which can be homogeneously treated while shielding uninvolved normal tissues), clinical (avoiding the need to delay the start of radiotherapy until chemotherapy is completed or vice versa), and psychosocial and economic (shortening or eliminating the prolonged course of conventional EBRT with its associated loss of work and time away from home and stress and a decrease in the cost of delivering radiotherapy). Thus, ELIOT, as well as other treatment modalities of partial breast irradiation,<sup>27-30</sup> may be an excellent alternative to traditional postoperative radiotherapy. Caution is still needed in the selection of patients until the results of new studies allow the specific characteristics of appropriate candidates to be defined. Moreover, further intensive, long-term follow-up is needed to better evaluate local control and possible side effects.

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