Breast Cancer and Intra-operative Radiotherapy with Electrons at the European Institute of Oncology

a report by

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The current standard treatment for early breast cancer includes conservative surgery followed by radiotherapy to the whole breast.[1] Long-term follow-up of patients included in the Milan Three Trial (Quart versus Tart) showed that most local relapses occur in the area of the scar tissue,[2] suggesting that total irradiation of the breast may not always be necessary.

We started our experience in intra-operative radiotherapy for breast cancer in June 1999 with a dose-finding study to test the feasibility of this new approach during breast-conserving surgery.[3] Electron intra-operative therapy (ELIOT) exploits new technologies that make it possible to deliver radiation to a more circumscribed area of the breast. The technique also markedly reduces the time required for a radiotherapy course, improving the quality of life of the patients. From June 1999 to October 2000, we experimented with different dose levels and verified the tolerance of 21Gy prescribed at 90% isodose as a full dose of intra-operative radiotherapy for small-size breast tumours (maximum tumour diameter 2.5cm).[4,5]

The different dose levels are reported in *Table 1*. Dose levels of 10 and 15Gy were followed by a reduced course of external fractionated radiotherapy. We obtained excellent results in terms of acute and intermediate tolerance of treatment and we adopted the dose of 21Gy prescribed at 90% isodose as the full dose approach for the randomised trial.[6,7]

In the pilot study (escalation dose) on 101 patients, after a mean follow-up of 42 months, 16 patients (16%) developed breast fibrosis (mild in 15 and severe in one), which resolved within 24 months, three patients suffered post-operative haematoma and four developed a lyponecrosis in the treated area. The phase III randomised trial started on 20 November 2000 and enrolled patients older than 48 years affected by unifocal breast carcinoma with a diameter ≤2.5cm. Patients received breast-conserving surgery were randomised during the operation for ELIOT 21Gy or external fractionated conventional radiotherapy (50Gy whole breast and 10Gy boost to tumour bed).[1] Up to August 2006, we included 1,064 patients in the trial: 535 patients received conventional radiotherapy (60Gy) and 529 received ELIOT (21Gy). We are still recruiting patients and the follow-up of treated patients is ongoing.[8]

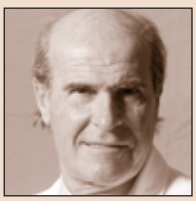
From a surgical point of view, most patients received wide excision with sentinel node biopsy, while a more limited number of patients received wide excision with axillary dissection.[9,10] We also treated 1,129 other patients with ELIOT outside the randomised trial by specific request of the patients themselves. From February 2000 to August 2006, we treated 59 cases and the follow-up of these patients is also ongoing. Globally, our experience with 21Gy ELIOT involves 1,759 patients with infiltrating breast carcinomas.[11]

We are testing ELIOT on selected cases of ductal carcinoma *in situ* (DCIS) with the premise that DCIS treatment with breast-conserving surgery benefits from post-operative radiotherapy, but whole breast irradiation may appear excessive in very limited size DCIS. Finally, from March 2002 to June 2006 we adopted ELIOT (16Gy) for irradiating the nipple areola complex during nipple-sparing subcutaneous mastectomy for multicentric *in situ* ductal carcinomas or multicentric infiltrating cancer with negative retro-areolar frozen sections. This is a new technique we developed to relieve the feeling of mutilation during mastectomy, by reducing the risk of local relapse thanks to ELIOT. The preliminary results are encouraging on 666 patients (225 cases of *in situ* carcinomas) with an excellent cosmetic result.[12]

Surgical Procedures

Electron Intra-operative Therapy 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. Immediately after the removal of the breast quadrant, the remaining parenchyma should be separated from the pectoralis fascia to place an aluminium–lead shielding disc posterior to the parenchyma to protect the thoracic wall, the heart and the lung (see *Figure 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



Umberto Veronesi is Scientific Director of the European Institute of Oncology in Milan, Italy. Professor Veronesi was the first to demonstrate that conservative breast surgery plus radiotherapy, which leaves the breast intact, can replace mutilating mastectomy and yet obtain the same cure rates. More recently, he has developed new researches with the sentinel node biopsy procedure to avoid axillary dissection when the lymph nodes are not involved. Professor Veronesi was awarded eight *honoris causa* in medicine and has published over 700 papers and many textbooks. He gained his medical degree in 1951 from Milan University, qualifying as Professor of Pathological Anatomy in 1957 and Professor of Surgery in 1961 at Milan University.

Stefano Zurrida is Executive Advisor to the Scientific Director of the European Institute of Oncology (EIO) in Milan, Italy, and Co-Director of the EIO's Division of Senology. He was recently appointed Associate Professor of General Surgery at the University of Milan, and has been a contract lecturer at the Specialisation School of Oncological Surgery, University of Varese. Professor Zurrida is a member of numerous national and international scientific societies, including the American Society of Clinical Oncology and the Society of Surgical Oncology. He gained his degree in medicine and surgery from the University of Cagliari in 1986.

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Figure 1: Placement of Shielding Disc Behind the Breast Parenchyma after Tumour Excision

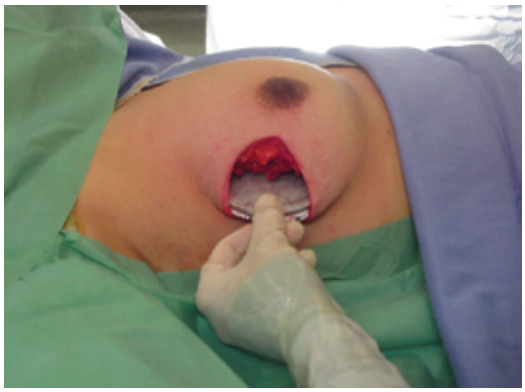


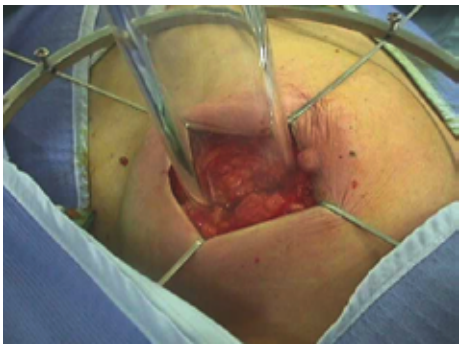
Table 1: The Different Dose Levels

Dose Level (Gy)	Aim	Number of Patients
10	Anticipated boost	10
15	Anticipated boost	7 (1 bilateral)
17	Whole treatment	8 (1 bilateral)
19	Whole treatment	6
21	Whole treatment	70 (46 patients at 90% isodose)

a safety margin of 1.5–3cm. A metallic ring with non-traumatic hooks is used to hold open the skin and the applicator is positioned (see *Figure 2*). A wet sterile gauze 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 two minutes, and the entire procedure lasts about 15–20 minutes. After irradiation, all the materials are removed and cosmetic reconstruction of the breast is performed.[9]

To perform ELIOT, we currently using two dedicated, mobile linear accelerators – a Novac7 and a Liac – installed in two different operating rooms and delivering electron beams at high dose rate. The two linear accelerators, which can be easily manoeuvred by means of motors acting on the wheels and the articulated arm, deliver electrons at the following different nominal energies: 3, 5, 7 and 9MeV (Novac7) and 4, 6, 8 and 10MeV (Liac). Beam collimation is achieved by a hard-docking system, consisting of round perspex applicators that are 5mm thick. Flat-ended and bevelled (22.5° and 45°) applicators of 4, 5, 6, 8 and 10cm diameter are employed. The nominal source-to-surface distance (SSD) is 100cm for the 10cm applicator and 80cm for all others. For radiation protection, a primary beam stopper (a trolley-mounted 15cm-thick lead shield) and mobile 1.5cm-thick lead shields (100cm long, 150cm high) are used.

Figure 2: The Linac used for Electron Intra-operative Therapy (ELIOT) and ELIOT Applicator in Position



Based on our experience, we believe that ELIOT will be rapidly utilised for the treatment of breast carcinoma, with a positive impact on the quality of life of patients and on the treatment organisation. Data from our randomised trial will be critical to establish the effectiveness of ELIOT in preventing local relapse of disease in the breast. ■

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