INTERNATIONAL CORNER

THE INTRAOPERATIVE RADIOTHERAPY WITH ELECTRONS (ELIOT) AT THE EUROPEAN INSTITUTE OF ONCOLOGY IN MILAN: RESULTS AND PERSPECTIVES

Paolo Veronesi[1,2], Pietro Caldarella[1], Giovanna Gatti[1], Mario Ciocca[3], Roberto Orecchia[4,2], Alberto Luini[1,2]

[1]Division of Breast Surgery, European Institute of Oncology, Milan, Italy - [2]University of Milan, School of Medicine
[3]Unit of Medical Physics, European Institute of Oncology, Milan, Italy - [4]Division of Radiotherapy, European Institute of Oncology, Milan, Italy

Indirizzo per corrispondenza: Prof. Paolo Veronesi
Division of Breast Surgery, European Institute of Oncology, Milan, Italy
via Ripamonti 435, 20141 Milano (MI) Italia
tel: +39 0257 489656; fax: +39 0257489780; e-mail: paolo.veronesi@ieo.it

ABSTRACT

Intraoperative Radiotherapy with Electrons (ELIOT) is a technique of partial breast irradiation based on the delivery of multi-energy electrons by linear accelerators kept and easily moved in the operating theatre. In this paper we briefly present the experience of the European Institute of Oncology in Milan with ELIOT in breast cancer.
Key words: *intraoperative radiotherapy; breast cancer*

RIASSUNTO

La radioterapia intraoperatoria con elettroni (ELIOT) rappresenta l'evoluzione più moderna del concetto di terapia conservativa del carcinoma mammario. Le esperienze sono ormai numerose in tutto il Mondo; all'Istituto Europeo di Oncologia di Milano questo tipo di radioterapia viene intensamente studiato grazie alla presenza in sala operatoria di due acceleratori lineari multienergia. In questo articolo si presenza l'esperienza preliminare IEO con la ELIOT nel carcinoma mammario.
Parole chiave: *radioterapia intraoperatoria; carcinoma mammario*

ACKNOWLEDGEMENTS

We wish to acknowledge the American Italian Cancer Foundation and AIRC (Associazione Italiana per la Ricerca sul Cancro).

INTRODUCTION

The purpose of breast irradiation after conservative breast surgery is to prevent local recurrence. The volume of breast irradiated is based on the theoretical volume of breast at risk for local recurrence: in general, the entire breast is considered at risk, and therefore the entire breast is included in the treatment volume. But where do local recurrences actually occur in the breast? Whether an in-breast recurrence is a true local recurrence or an "elsewhere" recurrence is sometimes difficult to determine. However, in general, the majority of in-breast local recurrences occur in the region of the prior lumpectomy site whether patient undergoes postoperative breast irradiation or not. Because the rate of development of breast tumors outside the area of the initial primary tumor — the so-called ipsilateral second primary breast cancer tumors — is similar to the rate of development of contralateral breast cancer irrespective of whether a patient has received whole-breast irradiation, it is unlikely that irradiation of the whole breast after breast-conserving surgery prevents such occurrences.

Partial breast irradiation can be delivered intraoperatively with either a linear accelerator emitting electrons (at the EIO this technique is known as ELIOT: electron bream intraoperative radiotherapy) or other devices. ELIOT is delivered in a single, intensive dose in the operating theatre immediately following surgical resection of the tumour.

Compared to postoperative external beam radiotherapy, ELIOT is purported to have the advantages of normal tissue sparing through marked dose attenuation, greater capacity of normal tissue retraction away from the radiation field, and more homogeneous dose distribution as well as virtually no delay between surgery and the irradiation of any residual cancer cells. Moreover, women who must travel from rural areas to metropolitan centers for weeks of postoperative radiotherapy may also be more inclined to choose breast-conserving surgery, if the only radiotherapy involved can be delivered during the operation itself or the postoperative course shortened.

THE EIO EXPERIENCE

Our experience with ELIOT reached the 6th year of activity with promising results.

We started our experience June 1999 with a dose-finding study to test the feasibility of intraoperative radiotherapy during breast-conserving surgery. From June 1999 to October 2000 we experimented different dose-levels and we verified the tolerance of 21 Gy prescribed at the 90% isodose as a full dose of intraoperative radiotherapy for small size breast tumors (maximum tumor diameter 2.5 cm) (1-4).

The different dose-levels can be summarized as in Table I. The dose-levels of 10 and 15 Gy were followed by a reduced course of external fractionated radiotherapy, and were mentioned as "anticipated boost".

Table I. The different dose-levels. The dose-levels of 10 and 15 Gy were followed by a reduced course of external fractionated radiotherapy, and were mentioned as "anticipated boost"

Dose-level (Gy)	Aim	N. 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 pts at 90% isodose

We obtained excellent results in terms of acute and intermediate tolerance of treatment and we adopted the dose of 21 Gy prescribed at the 90% isodose as the full dose approach for the randomized trial. In the preliminary experience, after a mean follow-up of 42 months, 16 patients (16%) developed breast fibrosis, mild in 15, severe in 1, which resolved within 24 months. Two patients suffered of postoperative infection, and 4 developed a lyponecrosis in the treated area.

The phase III randomized trial started November 20th, 2000, and is currently enrolling patients older than 48 years affected by unifocal breast carcinoma with maximum diameter 2.5 cm. Patients receive breast conserving surgery mostly with sentinel node biopsy and are randomized for ELIOT 21 Gy or external fractionated conventional radiotherapy (50 Gy whole breast and 10 Gy boost to tumor bed). Up to 16th November 2006 we included 1,187 patients into the trial: 596 patients received conventional radiotherapy and 591 received ELIOT. We are still recruiting patients, and the follow-up of treated patients is ongoing.

From the surgical point of view, in the randomized trial most patients received wide excision with sentinel node biopsy, while a more limited number of patients received wide excision with axillary dissection.

We have also treated more than 1,000 other patients with ELIOT outside the randomized trial, due to particular situations excluding long courses of whole breast radiotherapy (and the enrollment in the randomized trial), specific request by the patients themselves and the diagnosis of DCIS: in fact, we are testing ELIOT on selected cases of DCIS. The follow-up is ongoing, with the same procedures as for patients enrolled in the randomized trial.

Globally, our experience with 21 Gy ELIOT involves 2475 patients (5-19).

Moreover, ELIOT has been adopted (in a feasibility trial, to be followed by a randomised study) as an intraoperative boost (12 Gy) followed by an accelerated schedule of external radiotherapy (37.5 Gy in 13 sessions): this new technique appears extremely promising because, being radiotherapy concluded in one month, avoids the long delay of radiotherapy after chemotherapy, should this be required. However, to make the new procedure acceptable by the scientific community, the evidence of its favourable results in comparison with the traditional treatment is needed. We have treated 210 women <48 years with breast carcinoma not larger than 2.5 cm.

As a further application of ELIOT, 15 patients, from December 2000 to December 2006, were submitted to ELIOT for breast cancer after a previous diagnosis (with treatments) of lymphoma.

Finally, other 627 cases were submitted to ELIOT (16 Gy) to the nipple-areola complex during nipple-sparing subcutaneous mastectomy for multicentric in situ ductal carcinoma or for multicentric minimal breast carcinomas. This is a new technique we developed to relieve the feeling of mutilation during mastectomy, by reducing the risk of local relapse thanks to the ELIOT: the preliminary results are encouraging.

To perform ELIOT we are currently using two dedicated, mobile linear accelerators: a Novac7 (Hitesys Srl, Latina, Italy), and a Liac (Info&Tech, Roma, Italy), installed in two different operating rooms and delivering electron beams at high dose rate (20-22). 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: 3-5-7-9 (Novac7) and 4-6-8-10 MeV (Liac). Beam collimation is achieved by a hard-docking system, consisting of perspex round applicators, 5 mm thick. 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 (SSD) 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, 150 cm high) are provided.

DISCUSSION AND PRELIMINARY CONCLUSIONS

In terms of costs, time saved and patient quality of life ELIOT has notable advantages over conventional post-operative RT. Firstly it offers the prospect that many patients, particularly those with a negative axillary sentinel node, can receive definitive treatment for their disease in just one day. In Italy, and probably other areas too, many women still receive 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 radiotherapy centre is often geographically distant from the patient's and the costs of travel and accommodation are prohibitive. Another advantage of ELIOT is that the delay in administering RT in cases given adjuvant anthracyclines can be avoided; there is evidence that the delay increases the risk of local recurrence.

One area of concern in the use of ELIOT is the management of positive surgical margins as positivity is discovered at final histology, a few days after surgery and intraoperative radiotherapy. 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.

The adoption of ELIOT in the nipple sparing mastectomy allows the conservation of the nipple and areola in selected cases of extensive breast carcinoma: this modified technique of mastectomy carries better quality of life for patients, due to the preservation of body image

through the spare of nipple and areola complex.
ELIOT in DCIS could spare long radiation treatments to patients affected by a disease with excellent prognosis: some histological types of DCIS need radiotherapy for better local control, and this treatment could be delivered directly during surgery if a preoperative histology (by microbiopsy) is available.
In conclusion, ELIOT is easy to perform in settings characterized by close co-operation between surgeons radiotherapists and medical physicists. The required time for the treatment is currently about 20 minutes. If sentinel node biopsy with intraoperative pathological examination is being performed, this period is amply contained within the 40-50 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 therefore highly encouraging.
Based on our experience, we believe that ELIOT will rapidly take place in the treatment of breast carcinoma, with a positive impact on patients' quality of life and on the treatment organization. Data from our randomized trial will be critical to establish the effectiveness of ELIOT in preventing local relapse of disease in the breast.

REFERENCES

1. *Veronesi U, Orecchia R, Luini A, et al.* **Focalized intraoperative irradiation after conservative surgery for early-stage breast cancer. The Breast 2001; 10:84-9.**
2. *Veronesi U, Orecchia R, Luini A, et al.* **A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. Eur J Cancer 2001; 37:2178-83.**
3. *Gatzmeier E, Orecchia R, Gatti G, et al.* **Intraoperative strahlentherapie (IORT) in der behandlung des mammakarzinoms-eine neue therapeutische alternative im rahmen der brusterhaltenden therapie? Strahlenther Onkol 2001; 177: 330-7.**
4. *Orecchia R, Kyrgias G, Luini A, Gatti G, Ciocca M, Tosi G, Vavassori A, Marsiglia H, Veronesi U. Intraoperative electron-beam radiation therapy (IOERT) after conservative surgery for early stage breast cancer.* **Tumori 2001; 87: S19-S21.**
5. *Orecchia R, Ciocca M, Lazzari R, et al.* **Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. The Breast 2003; 12:483-90.**
6. *Veronesi U, Gatti G, Luini A, et al.* **Full dose intraoperative radiotherapy with electrons during breast-conserving surgery. Arch Surg 2003; 138:1263-6.**
7. *Intra M, Leonardi M, Gatti G, et al.* **Intraoperative radiotherapy during breast conserving surgery in patients previously treated with radiotherapy for Hodgkin's disease. Tumori 2004; 90: 13-6.**
8. *Intra M, Orecchia R, Veronesi U. Intraoperative radiotherapy: the debate continues. Lancet Oncol 2004; 5: 339-40.*
9. *Orecchia R, Ciocca M, Tosi G, et al. Intraoperative electron beam radiotherapy (ELIOT) to the breast: a need for a quality assurance programme.* **Breast 2005; 14(6):541-6.**
10. *Intra M, Leonardi MC, Luini A, et al.* **Full-dose intraoperative radiotherapy with electrons in breast surgery: broadening the indications.** *Arch Surg 2005; 140:936-9.*
11. *Luini A, Orecchia R, Gatti G, et al.* **The pilot trial on intraoperative radiotherapy with electrons (ELIOT): update on the results.** *Breast Cancer Res Treat 2005; 93:55-9.*
12. *Intra M, Luini A, Gatti G, et al.* **Surgical technique of intraoperative radiation therapy with electrons (ELIOT) in breast cancer: a lesson learned by over 1000 procedures. Surgery 2006; 140:467-71.**
13. *Orecchia R, Luini A, Veronesi P, et al.* **Electron intraoperative treatment in patients with early-stage breast cancer: data update.** *Expert Rev Anticancer Ther 2006; 6:605-11.*
14. *Petit JY, Veronesi U, Orecchia R, et al.* **Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): a new type of mastectomy for breast cancer treatment. Breast Cancer Res Treat 2006; 96:47-51.**
15. *Calvo FA, Meirino RM, Orecchia R.* **Intraoperative radiation therapy first part: rationale and techniques. Crit Rev Oncol Hematol 2006; 59(2):106-15.**
16. **Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy part 2. Clinical results. Crit Rev Oncol Hematol. 2006; 59(2):116-27.**
17. *Bernier J, Viale G, Orecchia R, et al.* **Partial irradiation of the breast: Old challenges, new solutions. Breast 2006; 15(4):466-75.**
18. **Ciocca M, Piazzi V, Lazzari R, et al. Real-time in vivo dosimetry using micro-MOSFET detectors during intraoperative electron beam radiation therapy** *in early-stage breast cancer. Radiother Oncol 2006; 78(2):213-6.*
19. *Luini A, Gatti G, Zurrida S, et al.* **The evolution of the conservative approach to breast cancer. Breast 2007; 16(2):120-9.**
20. *Intra M, Gatti G, Luini A, et al.* **Surgical technique of intraoperative radiotherapy in conservative treatment of limited-stage breast cancer. Arch Surg 2002; 137:737-40.**
21. *Veronesi U, Gatti G, Luini A, et al.* **Intraoperative radiotherapy for breast cancer: technical notes. Breast J 2003; 9:106-12.**
22. *Ciocca M, Orecchia R, Garibaldi C, et al.* **In vivo dosimetry using radiochromic films during intraoperative electron beam radiation therapy in early-stage breast cancer. Radiother Oncol 2003; 69:285-9.**