



HAL
open science

Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons

Umberto Veronesi, Roberto Orecchia, Alberto Luini, Viviana Galimberti, Stefano Zurrída, Mattia Intra, Paolo Veronesi, Paolo Arnone, Maria Cristina Leonardi, Mario Ciocca, et al.

► **To cite this version:**

Umberto Veronesi, Roberto Orecchia, Alberto Luini, Viviana Galimberti, Stefano Zurrída, et al.. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. *Breast Cancer Research and Treatment*, 2010, 124 (1), pp.141-151. 10.1007/s10549-010-1115-5 . hal-00565899

HAL Id: hal-00565899

<https://hal.science/hal-00565899v1>

Submitted on 15 Feb 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Intraoperative Radiotherapy During Breast Conserving Surgery – A Study on 1,822 Cases Treated with Electrons (ELIOT)

Umberto Veronesi¹, Roberto Orecchia^{2,3}, Alberto Luini^{4,3}, Viviana Galimberti⁴, Stefano Zurrada^{4,3}, Mattia Intra⁴, Paolo Veronesi^{4,3}, Paolo Arnone⁴, Maria Cristina Leonardi², Mario Ciocca⁵, Roberta Lazzari², Pietro Caldarella⁴, Nicole Rotmensz⁶, Claudia Sangalli³, Daniele Sances⁷, Patrick Maisonneuve⁶

¹ Scientific Director, European Institute of Oncology, Milan - Italy

² Division of Radiotherapy, European Institute of Oncology, Milan – Italy

³ University of Milan School of Medicine, Milan – Italy

⁴ Division of Senology, European Institute of Oncology, Milan – Italy

⁵ Division of Nuclear Medicine, European Institute of Oncology, Milan – Italy

⁶ Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan – Italy

⁷ Division of Anaesthesiology, European Institute of Oncology, Milan – Italy

*correspondence should be addressed to: Prof. Umberto Veronesi, Scientific Director, European Institute of Oncology, via Ripamonti 435, 20141 Milan (Italy). Tel +390257489221. Fax +390257489210.

E-mail: umberto.veronesi@ieo.it and maria.villardita@ieo.it

Key words: Breast cancer, Intraoperative Radiotherapy, Conserving Surgery

SUMMARY

Purpose. Intraoperative radiotherapy with electrons (ELIOT) after conservative surgery for breast carcinoma was introduced at the IEO in 1999 as a research programme. The results on 1,822 patients treated from January 2000 to December 2008 are reported.

Patients and methods. Women with unicentric primary breast carcinoma, of less than 2.5 cm in the largest diameter assessed by imaging. All patients were treated with breast-conserving surgery (quadrantectomy). ELIOT was delivered by two mobile linear accelerators immediately after breast resection with a single dose of 21 Gy.

Results. Local side effects of ELIOT were mainly liponecrosis (4.2%) and fibrosis (1.8%). After a mean follow-up of 36.1 months, 42 women (2.3%) developed a local recurrence, 24 (1.3%) a new primary ipsilateral carcinomas and 26 (1.4%) distant metastases as first event. Forty-six women died (2.5%), 28 for breast carcinoma and 18 for other causes. Five and ten-year survival were respectively 97.4 and 89.7 percent.

Conclusions – ELIOT appears a promising feature in early breast cancer treated with breast conserving surgery, reducing the exposure of normal tissues to radiations and shortening the radiation course from 6 weeks to one single session.

INTRODUCTION

The standard approach to breast cancer patients after wide resection or quadrantectomy has, for 30 years, been a 6-week postoperative course of radiotherapy. The Milan trial of the 1980s evaluating the efficacy of radiotherapy after breast-conserving surgery confirmed that this treatment plays an important role in the local control of breast carcinoma [1-3]. However two different new trends were developed in the last 10 years. The first regards “the length” of the treatment. In this new development the total time of postoperative radiotherapy (RT) may be considerably reduced to one-half and perhaps to one-third. This objective implies a new fractionation policy, with far less fractions being administered and consequently an increase of radiotherapy dosage for each application [4-6].

The second trend regards the amount of breast tissue to be irradiated. In fact, the results of our trial and other studies highlighted that the highest incidence of local relapse (85% of cases) occurred in the area of the breast where the primary carcinoma was excised (true recurrences); the remaining 15% of relapses occurred in other quadrants with a likelihood similar to the contralateral breast and therefore must be considered as new primary ipsilateral carcinomas. This important observation is the rationale for partial breast irradiation (PBI), that is, reduction of radiation fields from the whole organ to the involved portion of the breast [7-9].

Another important theme under discussion is intraoperative radiotherapy (IORT), which has been utilised in the last few decades to irradiate, with an external single dose, different types of tumours, mainly in the abdominal cavity

during surgery [10-12]. The limitation of its use, due to the necessity of transferring the patient from the surgical theatre to the radiotherapy department during surgery, was recently overcome by the availability of mobile linear accelerators, which can enter the surgical theatre.

In 1999 we developed the idea of combining the two procedures (PBI and IORT) to irradiate the breast in a single session during conserving surgery. Intraoperative radiotherapy with electrons (ELIOT) delivers a single dose of radiation equivalent to the total dosage with external fractionated radiotherapy directly to the tumour bed after wide resection or quadrantectomy, using a mobile linear accelerator located in the operating theatre: with this technique it is possible to treat only the involved quadrant of the breast, thereby shortening the radiotherapy course from 6 weeks to a single 3-minute session during surgery.

PATIENTS AND METHODS

From January 2000 to December 2008, 2,792 breast cancer patients received ELIOT after breast-conserving surgery as the sole radiation treatment modality. Six hundred and fifty one of them were part of a randomised clinical trial and 319 of them suffered from a previous cancer event and therefore are not considered in the present report. The remaining 1,822 patients (mean age 58, range 33-83) had unicentric primary carcinoma, less than 2.5 cm in the largest diameter assessed preoperatively by imaging. Still, the largest diameter of the resected tumour was greater than 2.5 cm in 89 women (5%) and greater than 5 cm in 2 women (Table 1).

We treated 2 patients with 16 Gy ELIOT, 6 patients with 17 Gy, 7 patients with 18 Gy and 7 with 19 Gy as part of the initial dose-finding study. The remaining 1,800 patients received 21 Gy prescribed at the 90% isodose as the sole radiation treatment. All patients were fully informed of the experimental nature of the treatment and signed an informed consent document. A description of our ELIOT cases in the time interval described is given in Table 1.

SURGERY

Most patients (1,714) received quadrantectomy with sentinel node biopsy; 1,375 (80.2%) of these patients had a negative sentinel node and no axillary dissection was performed. The 339 patients (19.8%) with sentinel node metastasis received complete axillary dissection; 54 had a positive SN but no dissection was performed, being part of a randomised trial. Among patients who did not have sentinel node biopsy, 102 patients received quadrantectomy with complete axillary dissection due to the clinical diagnosis of axillary metastases: 82 of them had positive axillary nodes at final histology, while six patients received simple quadrantectomy. Overall, 441 patients (24.2%) had complete axillary dissection.

As regards the surgical technique, the ELIOT procedure does not interfere with the oncologic criteria of 'classic' breast conserving surgery (BCS) in which 1.5-2.0 cm grossly free margins of resection are required. After the tumour removal, the wide mobilisation of the mammary gland from the fascia of the pectoralis major and, superficially, from the skin, represents a critical step, permitting the optimal exposure of the 'target' to the radiation beam.

To minimise the radiation delivered to the chest wall and to guarantee the delivery of the full radiation dose to the gland, a dedicated disk of lead and aluminium, available in various diameters (4, 5, 6 and 8 cm), is used as a protective device. The disk is inserted (lead side down, aluminium side up) in the space between the gland and the pectoralis muscle. To allow the best protection of the thoracic wall, the disk must be greater in size than the breast target size.

The sterile polymethyl methacrylate (Perspex; Hitesys SpA, Aprilia, Italy) collimator of the linear accelerator (LINAC) is introduced through the skin incision and placed directly in contact with the breast target.

RADIOTHERAPY

The ELIOT technique has been described in previous papers [13-16]. Briefly, two mobile linear accelerators (Figure 1) a Novac7 (Hitesys Srl, Latina, Italy) and a Liac (Info&Tech, Roma, Italy), installed in two different operating rooms were used to deliver electrons. These linear accelerators, which can be easily manoeuvred by means of motors acting on the wheels and on the robotic arm, deliver electrons at the following different nominal energies: 3-5-7-9 MeV (Novac7) and 4-6-8-10 MeV (Liac). The collimation of the beam is achieved by a hard-docking system, consisting of perspex applicators, 5 mm thick. The flat-ended and bevelled (15° up to 45°) round applicators have a diameter ranging from 4 to 12 cm. The nominal source to surface distance (SSD) is 80-100 cm for Novac7 and 60 cm for Liac. Radiation protection is obtained by a primary

beam stopper, consisting of a trolley-mounted 1.5 cm thick lead shield and some mobile 1.5 cm thick lead shields (100 cm long, 150 cm high).

In keeping with the Quality Assurance program for such dedicated linear accelerators we have implemented an in vivo dosimetry procedure, aimed at controlling the dose delivered to the patient [17].

The portion of the breast (CTV, Clinical Target Volume) that needs to be irradiated is generally an area of 4 to 6 cm in diameter. This field size allows to keep a safe margin around the tumour bed of at least 1-1.5 cm. Other sizes of applicator can be selected based on the breast size, tumour bed site and technical capacity to mobilise the gland. The appropriate electron energy is selected based on the gland thickness measured after the temporary reconstruction of the breast. The dose of 21 Gy is prescribed at the level of 90% of the isodose.

PATHOLOGY

Pathological assessment included evaluation of the primary tumour size, histological type and of lymph nodes status including a sentinel node biopsy, when applicable. Tumour grade was evaluated according to Elston and Ellis [18] and peritumoral vascular invasion (PVI) was assessed according to Rosen [19]. Estrogen (ER) and Progesterone Receptor (PgR) status, Ki-67 labelling index (assessed with the MIB 1 monoclonal antibody), and Her2/neu over-expression (routinely performed since 1999) were evaluated immunohistochemically as previously reported [20]. Tumours were classified according to their molecular characteristics and grouped into: Luminal A [(ER>0

or PgR>0) and Ki-67<14% and Her2/neu not overexpressed], Luminal B [(ER>0 or PgR>0) and (Ki-67≥14% or Her2/neu overexpressed)], Cerb+++ [ER=0 and PgR=0 and Her2/neu overexpressed], and Basal [ER=0 and PgR=0 and Her2/neu not overexpressed].

ADJUVANT TREATMENTS

Adjuvant treatments were administered in accordance with the rules and protocols in force during the period of patient accrual at the European Institute of Oncology.

One thousand three hundred and eighty one (1381) patients received only endocrine treatment; 176 patients were treated with chemotherapy alone, 198 had both treatments and 67 had no adjuvant medical therapy. Fifty-eight women operated since 2005 for Her2/neu overexpressing tumors received Trastuzumab (Herceptin).

In our institute, the treatment rule does not contemplate regional node irradiation in case of lymphnodal involvement if the axillary dissection was complete, including all three axillary nodes levels.

FOLLOW-UP

Side effects were evaluated according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. Every patient was evaluated at 1, 3, 6, and 12 months after surgery, and thereafter every 6 months, to ascertain any early, intermediate and late complications. At follow-up, the area treated by ELIOT was identified by x-ray radiograms, on the basis of the radio-opaque markers

left during surgery. When possible, the vital status of women not presenting at the institute for more than one year was obtained either by telephone contact or through local Italian death registers. The follow-up ranged from 1 to 122 months (mean 36.1 months until last visit and 39.8 months until last vital status notification). Sixty patients were lost to follow-up after surgery.

STATISTICAL METHODS

Events rates were calculated dividing the number of first events observed during follow-up with the number of person-years of observation accumulated from the date of surgery to the date of last visit. Mortality rates were calculated dividing the number of deaths with the number of person-years of observation accumulated from the date of surgery to the date of death or last notification of patients' vital status. Curves of the cumulative incidence of events and overall survival curves were plotted according to the Kaplan-Meier method and differences according to strata assessed by the log-rank test (considered significant for $P < 0.05$). Univariate and multivariate Cox proportional hazards regression models were used to assess the independent effect of selected patients or tumours characteristics on the incidence of local recurrence. All P values were 2-sided. SAS version 8.02 (Cary, NC) was used to perform the analyses.

RESULTS

LOCAL SIDE EFFECTS (table 2)

Immediate postoperative events

One hundred and one (5.5%) patients developed acute haematoma, and 24 (1.3%) had post-operative infections in the treated portion of the breast.

Fibrosis

Two patients who received 21 Gy developed severe fibrosis, one of which was associated with post-surgical haematoma. An additional 32 (1.8%) patients suffered from mild fibrosis; the development of the fibrosis was progressive during the first months after surgery, reaching a maximum at 12 months, remained stable for another 6-12 months and within 36 months from surgery slowly regressed. At the time of publication 5 patients still have clinical evidence of mild fibrosis in the treated area. Fourteen patients experienced moderate skin retraction.

Liponecrosis

A limited number of patients experienced a mild postoperative complication which we defined as 'Liponecrosis'. A localised collection of brown fluid with skin erythema, with no sign of infection, was the clinical manifestation of this complication. We observed 78 (4.2%) cases of liponecrosis 2 to 4 weeks after surgery. This complication resolved with simple clinical care. This complication appears to be more frequent in patients with a high proportion of fat tissue in the breast.

Local oncological events

The unfavourable events are described in Table 3. Local relapses were carefully divided into two different categories: "true recurrences" were

considered the reappearances of the carcinoma in the same quadrant as the primary carcinoma and “new ipsilateral carcinomas” the reappearances in other quadrants. We observed 42 cases of true recurrences (2.3%). The median time of appearance for local recurrences was 29.2 months (range 10.0-92.5) from the operation. More than 70% were detected by radiological examination (mammography, ultrasound and RM).

These 42 patients either underwent second breast conserving operation (16 cases) or a total mastectomy (21 cases). Three patients were not otherwise specified, and 1 underwent only punch biopsy.

Thirty-four patients are well without evidence of disease. Three patients developed multiple metastases two years after the second operation and died due to progressive disease. Twenty-four women (1.3%) developed a second primary carcinoma (ipsilateral breast cancer) in other quadrants. 12 cases had a second breast resection and 11 underwent total mastectomy. One patient had only biopsy and chemotherapy for inflammatory cancer. Four patients died due to progressive disease. One patient died from other causes.

We performed univariate and multivariate analysis of predictors of local events (true recurrences and new primary ipsilateral carcinomas) (Figure 2, Tables 4-5). In univariate, the risk of recurrences is higher in younger women and it increases with the dimension of the primary, the number of positive nodes, the presence of peritumoural vascular invasion, an elevated proliferative index (ki-67), in tumours lacking estrogen or progesterone receptors or overexpressing Her2/neu. As regards the molecular classification it appears that patients in the Luminal A category have a very low risk both of local recurrences, (0.15/100-

year) and new ipsilateral carcinoma (0.20/100-year), while the cases with Luminal B carcinoma showed a higher incidence of local recurrences (0.96/100-year) as well as of new primaries (0.55/100-year) (Table 5). In multivariate analysis, age <50 years, tumour size >2cm, and unfavourable molecular subtypes remain independent predictors of local relapse (Table 4).

Distant events and deaths

Twenty-six patients (1.4%) developed distant metastases as first event: none of them had signs of local relapse. The overall survival of all series appears very high: 46 patients died, 28 of whom for progression of breast cancer and 18 for other causes. Figure 3 shows the overall survival and breast cancer specific survival. Ten-year overall and breast cancer specific survival were respectively 89.7% (95% CI, 85.6-93.7) and 94.6% (95% CI, 91.8-97.3).

DISCUSSION

Breast-conserving surgery followed by radiotherapy is the standard treatment option for most women with breast carcinoma [21-24]. Also, sentinel node biopsy has been confirmed as a safe and reliable technique to predict axillary status in most patients who are candidates for conservative surgery; this technique makes it possible to conserve the axillary lymph nodes in most breast cancer patients [25]. These two techniques combined constitute a minimally mutilating approach to breast cancer that achieves an acceptable local control and no difference in survival compared with mastectomy and axillary dissection.

Some interesting studies have been published, which aimed at testing the impact of partial breast irradiation on breast cancer treatment; different radiotherapy techniques were used for these studies with controversial results. An early trial at the Christie Hospital showed that whole breast irradiation was superior compared to partial breast irradiation in local control after breast conserving surgery (10% local recurrences compared to 19.5% respectively) [26]. On the contrary, Reitsamer [27], in a non-randomised study, showed that the boost given with intraoperative electron radiotherapy is superior to the external breast electron boost irradiation. Partial breast irradiation can be delivered also with interstitial brachytherapy and more recently by external sources with three-dimensional radiotherapy (3D-RT) and intensity modulated radiotherapy (IMRT) [28-29].

A report of a study group convened by the National Cancer Institute in 2002 [30] concluded that partial breast irradiation is a new development in breast cancer radiotherapy which deserves to be encouraged. A following consensus statement from the American Society for Radiation Oncology (ASTRO) [31] and assenting reports [32-33] indicated that accelerated partial-breast irradiation is a new technology that may ultimately demonstrate long-term effectiveness and safety comparable to that of whole breast irradiation for selected patients with early breast cancer. Intraoperative radiotherapy was first applied nearly one century ago [34] and was developed with interesting results in the subsequent decades, mainly to treat abdominal carcinomas or sarcomas, locally advanced or inoperable [35]. The main limitation of the procedure was the logistical problem of transferring the sleeping patient from the surgical theatre to the

radiotherapy department, a complicated manoeuvre not readily acceptable to surgeons. The recent appearance of mobile linear accelerators, as a result of new advances in technological research has overcome these difficulties.

A new method for intraoperative radiotherapy is known as 'Intrabeam', which is used in the TARGIT trial. Intrabeam is a miniature electron beam-driven X-ray source that provides a point source of low-energy x-rays (50KV maximum) at the tip of a 3.2 mm diameter tube [36]. A phase III randomised trial comparing single dose intraoperative radiotherapy targeted to the tumour bed to conventional external radiotherapy in early breast carcinoma is presently in progress [37].

Ten years ago we decided to combine the two procedures (PBI and IORT), considering that the single session procedure instead of the conventional six-week course of whole breast irradiation, would substantially ease the difficulties of those women who have to contend with long RT waiting lists or who live far away from a radiotherapy centre. We began clinical research on IORT in 1999. As we decided to use electrons we defined our procedure ELIOT (ELECTRON IntraOperative Therapy). The first task was to estimate the single dose of electrons biologically equivalent to standard fractionated radiotherapy for breast cancer. To do this, we used the linear-quadratic surviving fraction model, otherwise known as multi-target surviving fraction model, which indicated that a single dose in the range 20-22 Gy is equivalent to 58-60 Gy delivered in 2 Gy daily fractions, five days a week over six weeks [38].

Initially we began with intraoperative doses lower than this level and then increased them. We studied dose-levels of 10, 15, 17, 19 and 21 Gy.

The toxicity of ELIOT is low; there were just 2 cases of severe fibrosis that resolved spontaneously within three years from their initial observation. A further 32 cases (1.8%) of mild fibrosis did not cause serious cosmetic impairment. The 78 cases of liponecrosis represent an issue that further follow-up should clarify; this non-severe complication seems unrelated to postoperative infection and involved mainly patients with breast tissue largely represented by fat. Not one patient had any sign of lung fibrosis in the follow-up.

Among the many advantages of ELIOT we underline the following:

1) The skin remains intact and plastic surgery may be easily conducted if necessary [39].

2) A major advantage is the complete change of life for patients living in remote places, far away from radiotherapy centres, who often decide on a mastectomy, even for a tiny carcinoma, due to the problem of undergoing daily post surgical radiotherapy for 6 weeks at these distant centres. In some cases, travel distance to a radiation-treatment facility may influence the receipt of postoperative breast irradiation [40]. As an alternative, accelerated, hypofractionated 3-week schedule of whole-breast irradiation seems to be as effective as standard radiation treatment for invasive breast cancer with clear surgical margins and negative axillary nodes

3) An additional advantage of ELIOT is that there is no delay in administering RT in cases that need adjuvant anthracyclines. There is some evidence that the delay of radiotherapy increases the risk of local recurrences [41-44], although updated data from a prospective randomised trial show no advantage to giving

RT before adjuvant chemotherapy [45]. The authors of this later study recognized however that the study does not have enough statistical power to rule out a clinically important survival benefit for either sequence.

4) Finally, the complete radioprotection will abolish any side effects in the lung, and in the contralateral mammary gland that could occur if conventional whole breast radiotherapy were administered.

One area of concern in the use of ELIOT is the management of positive surgical margins as positivity is discovered at the final histology, a few days after surgery and intraoperative radiotherapy. The adoption of an extensive breast resection (quadrantectomy) as a standard procedure in breast conserving surgery keeps the incidence of positive surgical margins to very low rates. Moreover, data from different studies show that margin positivity does not influence the rate of local recurrences if effective radiotherapy is delivered [46-47]. We had six cases with positive margins (two with in situ neoplasia) and 48 cases with cancer “close to the margins” that were not re-resected. All 54 cases showed no signs of recurrences (1.2 to 28.1) months after treatment.

As expected, the rate of local recurrence in our series of women treated with full dose intraoperative radiotherapy is higher than that reported in comparable series of women treated with breast conserving surgery and conventional radiotherapy [22-23]. The analysis of the data of the local recurrences and of the new ipsilateral carcinoma shows that small cancers (less than one centimetre),and luminal A cancer subtypes have a very low rate of local reappearances (respectively 0.54/100-year and 0.35/100-year) and of death (respectively 0.20/100-year and 0.24/100-year).

Although the mean follow-up of our series of patient is relatively short, the mortality is so far very low, with ten-year survival estimate higher than that observed in comparable historical series of women with small breast carcinoma treated with breast-conserving surgery [3,23-24].

In conclusion, although a longer follow-up will be needed, ELIOT appears a promising feature in breast conservation: the reduction of the radiation field makes the exposure of normal tissues dramatically lower (Fig. 1), and the shortening of the radiation course from 5/6 weeks to one session is extremely positive in terms of patient quality of life and costs.

Acknowledgments

We thank the American-Italian Cancer Foundation, New York, Jacqueline Seroussi Foundation, Tel Aviv for financial support, William Russell-Edu for help with the English revision, and Maria Grazia Villardita for her constant help in the preparation of the manuscript.

REFERENCES

1. Veronesi U, Saccozzi R, Del Vecchio M, et al (1981). Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *New Engl J Med* 305:6-11
2. Veronesi U, Luini A, Del Vecchio M, et al (1993) Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Eng J Med* 328:1587-159
3. Veronesi U, Marubini E, Mariani L, et al (2001) Radiotherapy after breastconserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol* 12:997–1003
4. Whelan TJ, Pignol JP, Levine MN, et al (2010) Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 362(6):513-520
5. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, et al (2008) The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 9(4):331-341
6. Kirova YM, Campana F, Savignoni A, et al (2009) Institut Curie Breast Cancer Study Group. Breast-conserving treatment in the elderly: long-term results of adjuvant hypofractionated and normofractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 75(1):76-81
7. Bernier J, Viale G, Orecchia R, et al (2006) Partial irradiation of the breast: Old challenges, new solutions. *Breast* 15:466-475

8. Orecchia R, Fossati P (2007) Partial breast irradiation: ready for routine? *Breast, Suppl 2*:S89-297
9. Vicini FA, Beitsch PD, Quiet CA, et al (2005) First analysis of patient demographics, technical reproducibility, cosmesis, and early toxicity: results of the American Society of Breast Surgeons MammoSite breast brachytherapy trial. *Cancer* 104(6):1138-1148
10. Orecchia R, Jereczek-Fossa BA, Ciocca M, et al (2007) Intraoperative radiotherapy for locally advanced prostate cancer: treatment technique and ultrasound-based analysis of dose distribution. *Anticancer Res* 27:3471-3476
11. Tepper JE, Cohen AM, Wood WC, et al (1986) Intraoperative electron beam radiotherapy in the treatment of unresectable rectal cancer. *Arch Surg* 121:421-423
12. Wood WC, Shipley WU, Gunderson LL, et al (1982) Intraoperative irradiation for unresectable pancreatic carcinoma. *Cancer* 49:1272-1275
13. Veronesi U, Orecchia R, Luini A, et al (2001) A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 37:2178-2183
14. Veronesi U, Gatti G, Luini A, et al (2003) Full-dose intraoperative radiotherapy with electrons during breast conserving surgery. *Arch Surg* 138:1253-1256

15. Veronesi U, Orecchia R, Luini A, et al (2005) Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery. Experience with 590 cases. *Ann Surg* 242:101-106
16. Veronesi U, Gatti G, Luini A et al (2003) Intraoperative radiotherapy for breast cancer: technical notes. *Breast J* 9:106-112
17. Ciocca M, Orecchia R, Garibaldi C, et al (2003) In vivo dosimetry using radiochromic films during intraoperative electron beam radiation therapy in early-stage breast cancer. *Radiother Oncol* 69:285-289
18. Elston CW, Ellis IO (1991) Pathological prognostic factors in breast cancer: the value of histological grade in breast cancer. *Histopathology* 19: 403–410
19. Rosen PP, Oberman HA. (1993) Tumors of the mammary gland. In: *Atlas of tumor pathology, 3rd ser., fasc. 7*. Washington, DC: Armed Forces Institute of Pathology, 1993:135-156
20. Viale G, Regan MM, Mastropasqua MG, et al (2008) Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. *J Natl Cancer Inst* 100:207–212
21. Veronesi U, Cascinelli N, Mariani L, et al (2002) Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 16:1227–1232
22. Fisher B, Anderson S, Bryant J, et al (2002) Twenty-five-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and

- lumpectomy plus irradiation for the treatment of invasive breast cancer.
N Engl J Med 8:1233-1241
23. Nguyen PL, Taghian AG, Katz MS, et al (2008). Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 26:2373-2378
 24. Kim KJ, Huh SJ, Yang JH, et al (2005) Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. Jpn J Clin Oncol 35:126-133
 25. Veronesi U, Paganelli G, Viale G, et al (2006) Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of randomised controlled study. Lancet Oncol 7(12):983-990
 26. Ribeiro GG, Magee B, Swindell R, et al (1993) The Christie Hospital breast conservation trial: an update at 8 years from inception. Clin Oncol 5:278-283
 27. Reitsamer R, Peintinger F, Kopp M, et al (2004) Local recurrence rates in breast cancer patients treated with intraoperative electron-boost radiotherapy versus postoperative external-beam electron-boost irradiation. A sequential intervention study. Strahlenther Onkol 180:38-44
 28. Giraud P, Simon L, Saliou M et al (2005) Respiratory gated radiotherapy: the 4D radiotherapy. Bull Cancer 92:83-89

29. Vicini FA, Sharpe M, Kestin L, et al (2002) Optimizing breast cancer treatment efficacy with intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 54:1336-1344
30. Wallner P, Arthur D, Bartelink H, et al (2004) Workshop Participants. Commentary. Workshop on Partial Breast Irradiation: State of the art and the science, Bethesda, MD, December 8-10, 2002. *J Natl Cancer Inst* 96:175-184
31. Smith BD, Arthur DW, Buchholz TA, et al (2009) Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 74:987-1001
32. Antonucci JV, Wallace M, Goldstein NS, et al (2009). Differences in patterns of failure in patients treated with accelerated partial breast irradiation versus whole-breast irradiation: a matched-pair analysis with 10-year follow-up. *Int J Radiat Oncol Biol Phys* 74: 447-52
33. Polgar C, Major T, Fodor J, et al (2010). Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. *Radiother Oncol* 94:274-9
34. Finsterer H (1915) Zur therapie inoperable magen - und Darmkarzinome mit freilegend und nachfolgender Rontgenbestrahlung. *Strahlentherapie* 6:205-213
35. Abe M Takahashi M (1981) Intraoperative radiotherapy: the Japanese experience. *Int J Radiat Oncol Biol Phys* 7:863-868

36. Vaidya JS, Baum M, Tobias JS, et al (2001) Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 12:1075-1080
37. Holmes DR, Baum M, Joseph D (2007) The TARGIT trial: targeted intraoperative radiation therapy versus conventional postoperative whole-breast radiotherapy after breast-conserving surgery for the management of early-stage invasive breast cancer (a trial update). *Am J Surg* 194:507-510
38. Sindelar WF, Johnstone PA, Hoekstra H, et al (1999) Normal tissue tolerance to IORT: The NCI experimental studies, in Gunderson LL, Willett CG, Harrison LB (eds): *Intraoperative Irradiation: Techniques and Results*. Totowa, NJ, Humana Press, pp 131-146
39. Rietjens M, De Lorenzi F, Veronesi P, et al (2006) Breast conservative treatment in association with implant augmentation and intraoperative radiotherapy. *J Plast Reconstr Aesthet Surg* 59(5):532-555
40. Athas WF, Adams-Cameron M, Hunt WC, et al (2000) Travel distance to radiation therapy and receipt of radiotherapy following breast conserving therapy. *J Natl Cancer Inst* 92:269-271
41. Fietkau R (2000) Effects of the time interval between surgery and radiotherapy on the treatment results. *Strahlenther Onkol* 176:452-457
42. Recht A, Come SE, Henderson IC, et al (1996) The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. *N Engl J Med* 334:1356-1361

43. Hershman DL, Wang X, McBride R, et al (2006) Delay in initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival. *Int J Radiat Oncol Biol Phys* 65:1353-1360
44. Mikeljevic JS, Haward R, Johnston C, et al (2004) Trends in postoperative radiotherapy delay and the effect on survival in breast cancer patients treated with conservation surgery. *Br J Cancer* 90:1343-1348
45. Bellon JR, Come SE, Gelman RS et al (2005) Sequencing of Chemotherapy and Radiation Therapy in Early-Stage Breast Cancer: Updated Results of a Prospective Randomized Trial. *J Clin Oncol* 23:1934-1940
46. Mariani L, Salvadori B, Marubini E, et al (1998) Ten year results of a randomised trial comparing two conservative treatment strategies for small size breast cancer. *Eur J Cancer* 34:1156-1162
47. Chism DB, Freedman GM, Li T, et al (2006) Re-excision of margins before breast radiation-diagnostic or therapeutic? *Int J Radiat Oncol Biol Phys* 65:1416-1421

TABLE 1. Characteristics of 1,822 ELIOT Patients

Characteristic	N	%	Characteristic	N	%
Age (years)			Grading		
Median (range)	58 (33-83)		G1	467	25.6
<50	368	20.2	G2	853	46.8
50-59	665	36.5	G3	459	25.2
60+	789	43.3	Not evaluable	43	2.4
Surgical treatment			Peritumoral vascular invasion		
Quadrantectomy	1381	75.8	Absent	1528	83.9
Quadrantectomy + AD	441	24.2	Present	294	16.1
Margins			Ki-67		
Negative	1768	97.0	<14%	664	36.4
Close	48	2.6	≥14%	1152	63.2
Positive	6	0.4	Not evaluable	6	0.3
Histology			Estrogen receptor (ER)		
Ductal carcinoma	1426	78.3	Negative	194	10.6
Lobular carcinoma	202	11.1	Positive	1625	89.2
Others	194	10.6	Not evaluable	3	0.2
Tumour size (cm)			Progesterone receptor (PgR)		
Median range	1.3 (0.01-5.5)		Negative	398	21.8
<0.5 cm	108	5.9	Positive	1420	77.9
0.5 – 1.0 cm	503	27.6	Not evaluable	4	0.2
1.0 – 2.0 cm	938	51.5	Her2Neu		
2.0 – 5.0 cm	261	14.3	Not overexpressed	1639	90.0
>5.0 cm	3	0.2	Overexpressed	173	9.5
Not evaluable	9	0.5	Missing	10	0.5
Positive nodes			Molecular subtype		
0	1301	71.4	Luminal A	648	35.6
1-2	371	20.4	Luminal B	977	53.6
3+	146	8.0	cerbB+++	53	2.9
Not evaluated	4	0.2	Basal	137	7.5
			Unknown	7	0.4

Table 2. Side effects among 1,822 patients

Side effects	N	%
Mild fibrosis	32	1.8
Severe fibrosis	2	0.1
Lyponecrosis	78	4.2
Hematoma	101	5.5
Oedema	24	1.3
Pain	13	0.7
Wound infection	24	1.3
Sieroma	235	12.9
No side effect	1434	78.7
1 side effect	292	16.0
2 side effects	76	4.2
3 side effects	16	0.9
4 side effects	3	0.2
5 side effects	1	<0.1

Table 3. First unfavourable event and deaths

First event	N	%	Annual rate (%)
True local recurrence	42	2.3	0.77
Ipsilateral breast cancer	24	1.3	0.44
Regional metastasis	18	1.0	0.33
Contralateral carcinoma	19	1.0	0.35
Distant metastasis	26	1.4	0.47
Other carcinoma	33	1.8	0.60
Death as first event	11	0.6	0.20
Any first event*	171	9.4	3.12

* One patient developed simultaneously distant metastasis and contralateral breast cancer and another patients axillary metastasis and contralateral breast cancer.

Deaths	N	%	Annual death rate (%)
Deaths due to breast cancer	28	1.5	0.46
Deaths due to other causes	12	0.7	0.20
Unspecified cause of death	6	0.3	0.10
Any cause of death	46	2.5	0.76

Table 4. Univariate and multivariate predictors of local relapse (True local recurrences and second ipsilateral cancer)

Characteristics	Patients (n=1822)	Local relapses (n=66)	Univariate analysis		Multivariate analysis			
			HR (95% CI)	pvalue	HR (95% CI)	pvalue		
Age								
< 50	368	26	2.21 (1.25-3.90)	0.006	2.10 (1.18-3.74)	0.01		
50-59	665	22	1.00		1.00			
> 60	789	18	0.80 (0.43-1.49)	0.48	0.79 (0.42-1.49)	0.47		
Histology								
Ductal carcinoma	1426	50	1.00		1.00			
Lobular carcinoma	202	9	1.36 (0.67-2.77)	0.39	1.89 (0.90-3.95)	0.09		
Others	194	7	0.86 (0.39-1.89)	0.70	0.98 (0.44-2.18)	0.96		
Tumour size*								
< 1 cm	611	10	1.00		1.00			
1.1-2cm	938	36	2.12 (1.08-4.17)	0.03	1.46 (0.73-2.92)	0.29		
> 2 cm	264	19	4.26 (2.02-8.97)	0.0001	2.29 (1.02-5.15)	0.04		
Positive nodes								
0	1301	36	1.00		1.00			
1-2	371	16	1.44 (0.80-2.59)	0.23	1.02 (0.54-1.93)	0.95		
3+	146	13	3.05 (1.62-5.76)	0.0006	1.32 (0.64-2.72)	0.45		
Grading								
G1	467	4	1.00		Excluded from multivariate model due to colinearity with molecular subtype			
G2	853	26	3.55 (1.24-10.2)	0.02				
G3	459	33	8.71 (3.08-24.6)	<.0001				
Peritumoral vascular invasion								
Absent	1528	45	1.00		1.00			
Present	294	21	2.45 (1.46-4.11)	0.0007	1.63 (0.90-2.96)	0.10		
Ki-67								
<14%	664	7	1.00		Ki-67, ER receptor, PgR receptor and Her2/Neu overexpression are part of the molecular subtype			
≥14%	1152	58	4.81 (2.20-10.5)	<.0001				
Estrogen receptor								
Negative	194	15	1.00					
Positive	1625	51	0.42 (0.23-0.74)	0.003				
Progesterone receptor								
Negative	398	24	1.00					
Positive	1420	42	0.59 (0.36-0.97)	0.04				
Her2/Neu								
Not overexpressed	1639	51	1.00					
Overexpressed	173	15	3.19 (1.79-5.67)	<.0001				
Molecular subtype								
Luminal A	648	7	1.00		1.00			
Luminal B	977	44	4.23 (1.90-9.39)	0.0004	3.46 (1.52-7.90)	0.003		
CerB+++	53	6	10.6 (3.56-31.6)	<.0001	5.68 (1.72-18.8)	0.004		
Basal	137	9	5.95 (2.22-16.0)	0.0004	5.26 (1.84-15.0)	0.002		

Hazards Ratio (HR) and 95% confidence intervals (CI) obtained from univariate and multivariable Cox proportional hazards regression model.

* Tumour size is missing for 9 patients, number of positive nodes for 4 patients, molecular subtype for 7 patients

Table 5. True local recurrences and second ipsilateral cancer according to selected patient and tumour characteristics.

	All patients	True Local Recurrences			Second ipsilateral cancer			Deaths		
	N	N	%	Annual rate (%)	N	%	Annual rate (%)	N	%	Annual rate (%)
Total	1822	42	2.31%	0.77%	24	1.32%	0.44%	46	2.52%	0.76%
Age										
< 50	368	16	4.35%	1.40%	10	2.72%	0.88%	7	1.90%	0.54%
51-59	665	13	1.95%	0.62%	9	1.35%	0.43%	16	2.41%	0.70%
> 60	789	13	1.65%	0.58%	5	0.63%	0.22%	23	2.92%	0.94%
Tumour size*										
< 1 cm	611	7	1.15%	0.38%	3	0.49%	0.16%	4	0.65%	0.20%
1.1-2cm	938	23	2.45%	0.81%	13	1.39%	0.46%	26	2.77%	0.83%
> 2 cm	264	12	4.55%	1.56%	7	2.65%	0.91%	16	6.06%	1.81%
Positive nodes*										
0	1301	27	2.08%	0.70%	9	0.69%	0.23%	22	1.69%	0.52%
1-2	371	8	2.16%	0.69%	8	2.16%	0.69%	9	2.43%	0.70%
3+	146	7	4.79%	1.57%	6	4.11%	1.35%	15	10.27%	2.97%
Grading										
G1	467	2	0.43%	0.14%	2	0.43%	0.14%	4	0.86%	0.26%
G2	853	14	1.64%	0.54%	12	1.41%	0.46%	16	1.88%	0.57%
G3	459	26	5.66%	1.91%	7	1.53%	0.52%	25	5.45%	1.61%
Peritumoural vascular invasion										
Absent	1528	30	1.96%	0.65%	15	0.98%	0.33%	32	2.09%	0.64%
Present	294	12	4.08%	1.37%	9	3.06%	1.03%	14	4.76%	1.40%
Molecular subtype*										
Luminal A	648	3	0.46%	0.15%	4	0.62%	0.20%	5	0.77%	0.24%
Luminal B	977	28	2.87%	0.96%	16	1.64%	0.55%	27	2.76%	0.84%
Cerb+++	53	6	11.32%	3.88%	0	-	-	2	3.77%	1.06%
Basal	137	5	3.65%	1.19%	4	2.92%	0.95%	12	8.76%	2.59%

* Tumour size is missing for 9 patients, number of positive nodes for 4 patients, molecular classification for 7 patients

Figures legend

Fig. 1 - The linear accelerator used for ELIOT and thoracic wall protection

Fig. 2 - Cumulative incidence of local recurrences (true local recurrences and second ipsilateral cancer) in women with breast cancer treated with ELIOT

Fig. 3 - Overall survival and breast cancer survival of women with breast cancer treated with ELIOT

Figure 1



Figure 2

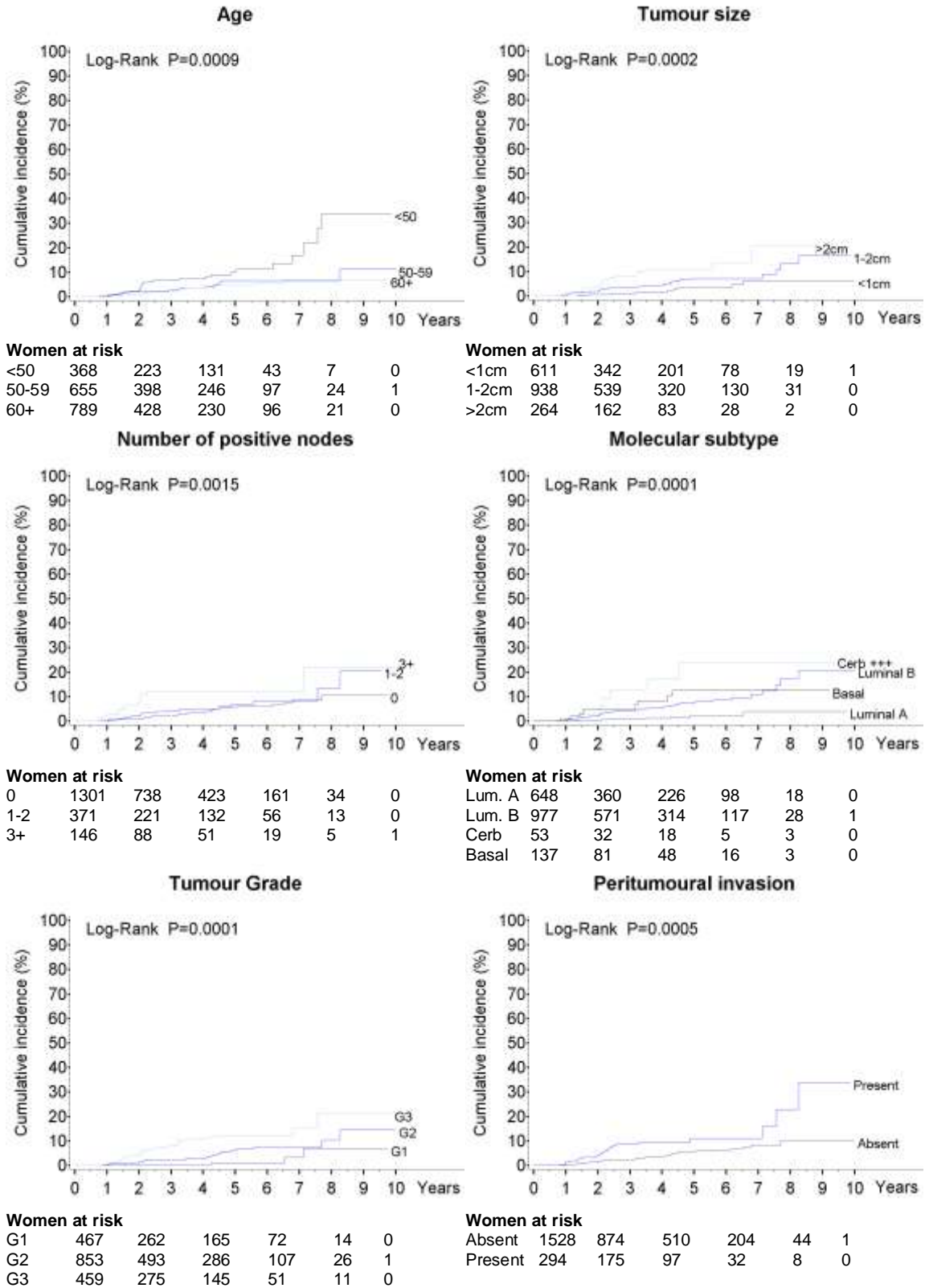


Figure 3

