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

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

Umberto Veronesi[1], Roberto Orecchia[2,3], Alberto Luini[4,3], Viviana Galimberti[4], Stefano Zurrida[4,3], Mattia Intra[4], Paolo Veronesi[4,3], Paolo Arnone[4], Maria Cristina Leonardi[2], Mario Ciocca[5], Roberta Lazzari[2], Pietro Caldarella[4], Nicole Rotmensz[6], Claudia Sangalli[3], Daniele Sances[7], Patrick Maisonneuve[6]

[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

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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 had 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.

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TABLE 1. Characteristics of 1,822 ELIOT Patients

Characteristic	N	%
Age (years)		
Median (range)	58 (33-83)	
<50	368	20.2
50-59	665	36.5
60+	789	43.3
Surgical treatment		
Quadrantectomy	1381	75.8
Quadrantectomy + AD	441	24.2
Margins		
Negative	1768	97.0
Close	48	2.6
Positive	6	0.4
Histology		
Ductal carcinoma	1426	78.3
Lobular carcinoma	202	11.1
Others	194	10.6
Tumour size (cm)		
Median range	1.3 (0.01-5.5)	
<0.5 cm	108	5.9
0.5 – 1.0 cm	503	27.6
1.0 – 2.0 cm	938	51.5
2.0 – 5.0 cm	261	14.3
>5.0 cm	3	0.2
Not evaluable	9	0.5
Positive nodes		
0	1301	71.4
1-2	371	20.4
3+	146	8.0
Not evaluated	4	0.2

Characteristic	N	%
Grading		
G1	467	25.6
G2	853	46.8
G3	459	25.2
Not evaluable	43	2.4
Peritumoral vascular invasion		
Absent	1528	83.9
Present	294	16.1
Ki-67		
<14%	664	36.4
≥14%	1152	63.2
Not evaluable	6	0.3
Estrogen receptor (ER)		
Negative	194	10.6
Positive	1625	89.2
Not evaluable	3	0.2
Progesterone receptor (PgR)		
Negative	398	21.8
Positive	1420	77.9
Not evaluable	4	0.2
Her2Neu		
Not overexpressed	1639	90.0
Overexpressed	173	9.5
Missing	10	0.5
Molecular subtype		
Luminal A	648	35.6
Luminal B	977	53.6
cerbB+++	53	2.9
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 HR (95% CI)	pvalue	Multivariate analysis 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

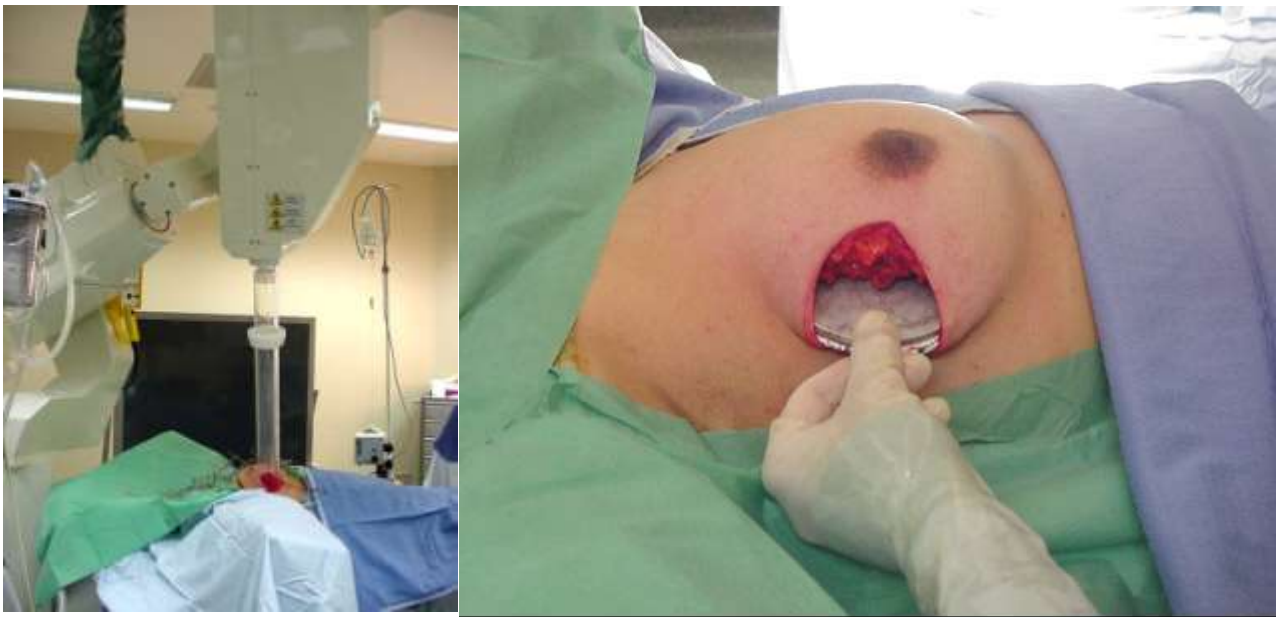
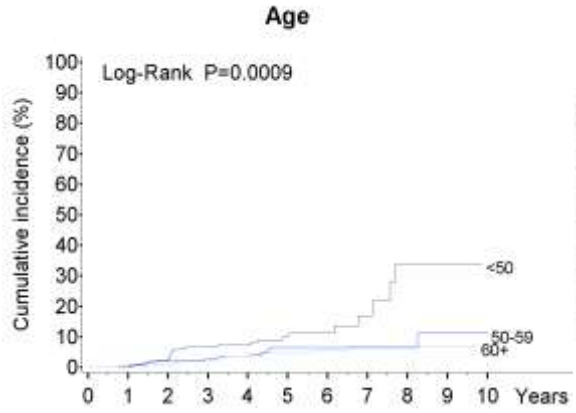
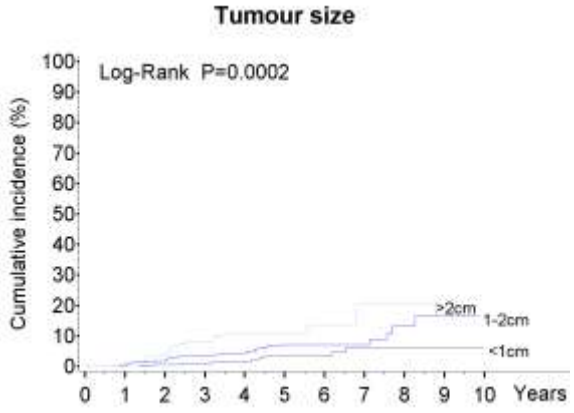


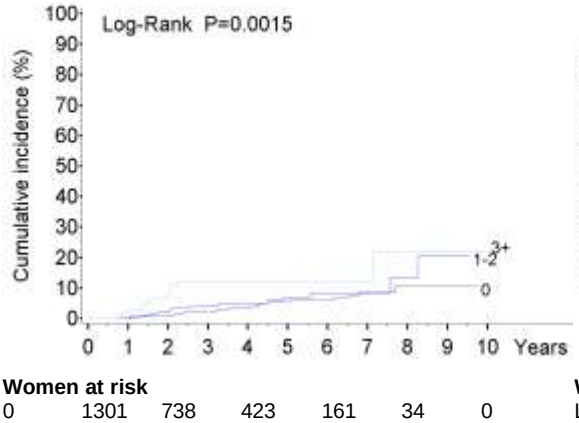
Figure 2



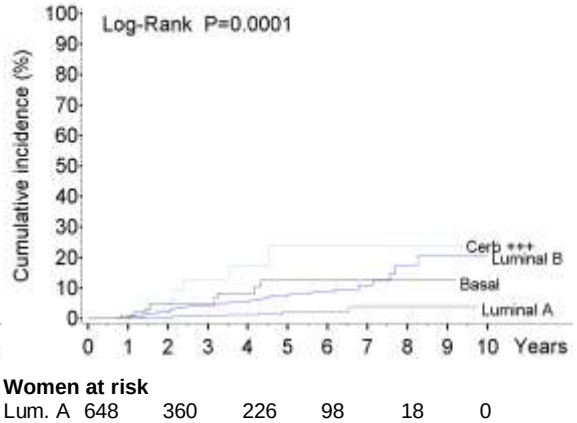
Women at risk						
<50	368	223	131	43	7	0
50-59	655	398	246	97	24	1
60+	789	428	230	96	21	0



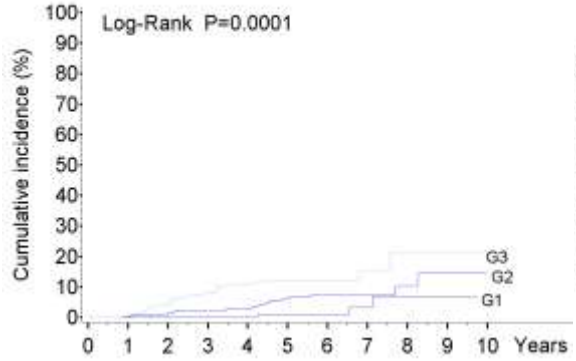
Women at risk						
<1cm	611	342	201	78	19	1
1-2cm	938	539	320	130	31	0
>2cm	264	162	83	28	2	0



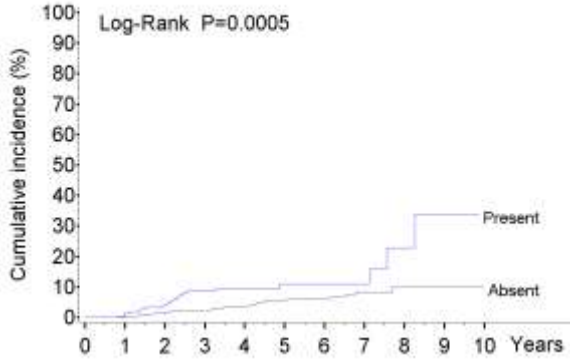
Women at risk						
0	1301	738	423	161	34	0
1-2	371	221	132	56	13	0
3+	146	88	51	19	5	1



Women at risk						
Lum. A	648	360	226	98	18	0
Lum. B	977	571	314	117	28	1
Cerb	53	32	18	5	3	0
Basal	137	81	48	16	3	0

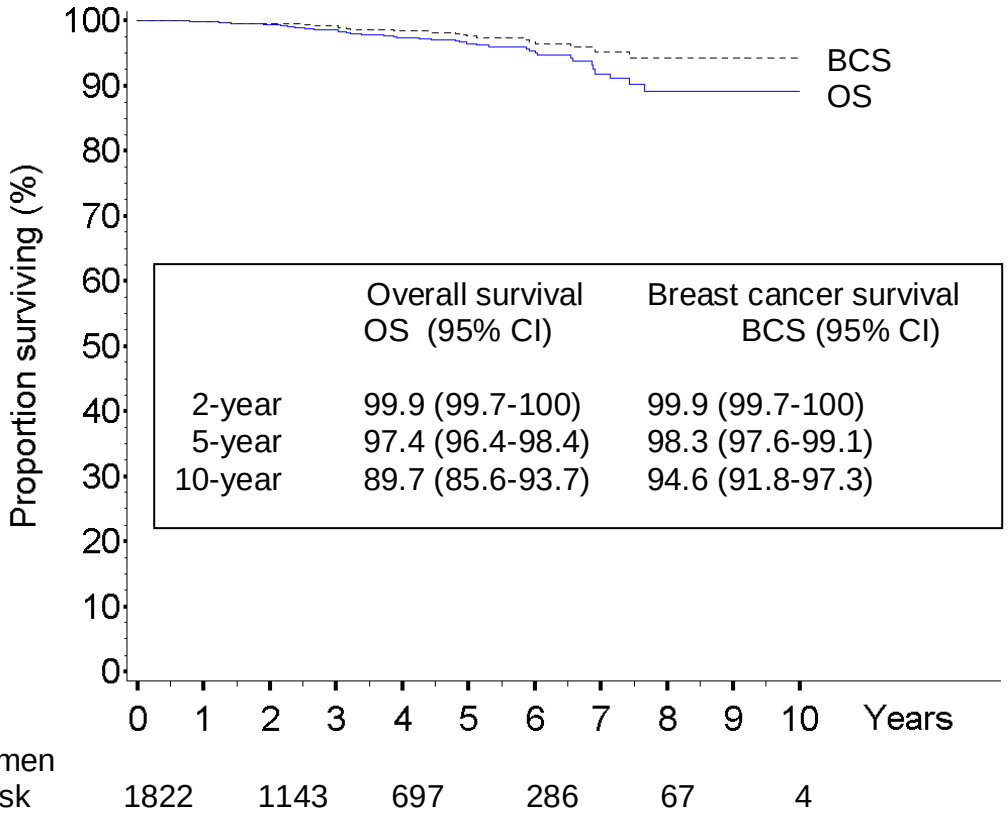


Women at risk						
G1	467	262	165	72	14	0
G2	853	493	286	107	26	1
G3	459	275	145	51	11	0



Women at risk						
Absent	1528	874	510	204	44	1
Present	294	175	97	32	8	0

Figure 3


100
90
80
70
60
50
40
30
20
10
0
Proportion surviving (%)
BCS
OS
Overall survival
OS (95% CI)
Breast cancer survival
BCS (95% CI)
2-year
99.9 (99.7-100)
99.9 (99.7-100)
5-year
97.4 (96.4-98.4)
98.3 (97.6-99.1)
10-year
89.7 (85.6-93.7)
94.6 (91.8-97.3)
0 1 2 3 4 5 6 7 8 9 10 Years
Women at risk
1822 1143 697 286 67 4