Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

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Summary

Background Intraoperative radiotherapy with electrons allows the substitution of conventional postoperative whole breast irradiation with one session of radiotherapy with the same equivalent dose during surgery. However, its ability to control for recurrence of local disease required confirmation in a randomised controlled trial.

Methods This study was done at the European Institute of Oncology (Milan, Italy). Women aged 48–75 years with early breast cancer, a maximum tumour diameter of up to 2·5 cm, and suitable for breast-conserving surgery were randomly assigned in a 1:1 ratio (using a random permuted block design, stratified for clinical tumour size [<1·0 cm *vs* 1·0–1·4 cm *vs* ≥1·5 cm]) to receive either whole-breast external radiotherapy or intraoperative radiotherapy with electrons. Study coordinators, clinicians, and patients were aware of the assignment. Patients in the intraoperative radiotherapy group received one dose of 21 Gy to the tumour bed during surgery. Those in the external radiotherapy group received 50 Gy in 25 fractions of 2 Gy, followed by a boost of 10 Gy in five fractions. This was an equivalence trial; the prespecified equivalence margin was local recurrence of 7·5% in the intraoperative radiotherapy group. The primary endpoint was occurrence of ipsilateral breast tumour recurrences (IBTR); overall survival was a secondary outcome. The main analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01849133.

Findings 1305 patients were randomised (654 to external radiotherapy and 651 to intraoperative radiotherapy) between Nov 20, 2000, and Dec 27, 2007. After a medium follow-up of 5·8 years (IQR 4·1–7·7), 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had had an IBTR (p<0·0001). The 5-year event rate for IBRT was 4·4% (95% CI 2·7–6·1) in the intraoperative radiotherapy group and 0·4% (0·0–1·0) in the external radiotherapy group (hazard ratio 9·3 [95% CI 3·3–26·3]). During the same period, 34 women allocated to intraoperative radiotherapy and 31 to external radiotherapy died (p=0·59). 5-year overall survival was 96·8% (95% CI 95·3–98·3) in the intraoperative radiotherapy group and 96·9% (95·5–98·3) in the external radiotherapy group. In patients with data available (n=464 for intraoperative radiotherapy; n=412 for external radiotherapy) we noted significantly fewer skin side-effects in women in the intraoperative radiotherapy group than in those in the external radiotherapy group (p=0·0002).

Interpretation Although the rate of IBTR in the intraoperative radiotherapy group was within the prespecified equivalence margin, the rate was significantly greater than with external radiotherapy, and overall survival did not differ between groups. Improved selection of patients could reduce the rate of IBTR with intraoperative radiotherapy with electrons.

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Introduction

Until the 1970s, surgical management of breast cancer was based on the Halsted mastectomy, with minor modifications. From the 1970s, studies[1–3] showed that breast-conserving surgery plus radiotherapy resulted in much the same outcomes as the Halsted mastectomy for tumours up to 5 cm in size; however, when radiotherapy was omitted, women had an increased likelihood of local recurrence.[4,5] Thus, breast-conserving surgery followed by whole breast irradiation became the mainstay of surgical treatment for small breast carcinoma. In the past 10 years, new regimens have been developed: studies[6] have shown that the duration of whole breast irradiation can be abbreviated from 6 weeks to 3 weeks and partial breast irradiation has reduced the irradiation field to the quadrant in which the carcinoma arose.[7]

Despite these advances, most women are still required to attend postoperative radiotherapy for about 30 days consecutively. Many women living a substantial distance from a radiotherapy centre have serious difficulties attending every day, especially those living in small villages, mountainous regions, or islands. Intraoperative

radiotherapy, in which postoperative whole breast irradiation is substituted for one session of radiotherapy with the same equivalent dose during surgery, solves this problem.[8] In this context, the European Institute of Oncology developed electron intraoperative radiotherapy (ELIOT), which involves administering electrons in one session during surgery with a total dose of 21 Gy. Importantly, in most cases when a local recurrence occurs after conservative treatment a mastectomy is indicated. Nowadays, total mastectomy is generally skin-sparing and often nipple-sparing, with a prosthesis implant; the integrity of the skin is important for the success of the operation. Previously irradiated skin can undergo necrosis, whereas skin damage is largely avoided with intraoperative radiotherapy with electrons. However, the expected advantages in quality of life must be balanced with any possible increase in recurrence.

The European Institute of Oncology began treating patients with intraoperative radiotherapy with electrons in 1999, and the outcomes of patients treated outside of clinical trials have been reported.[9] We present the results of a randomised equivalence study comparing local recurrence and overall survival after electron intraoperative radiotherapy with postoperative external radiotherapy.

Methods

Study design and patients

This single-centre study was done at the European Institute of Oncology (Milan, Italy), a comprehensive cancer centre and referral centre for the treatment of patients with breast cancer. Eligible patients were women aged 48–75 years with early breast cancer with a maximum tumour diameter up to 2·5 cm and suitable for breast-conserving therapy. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from patients before assignment to treatment.

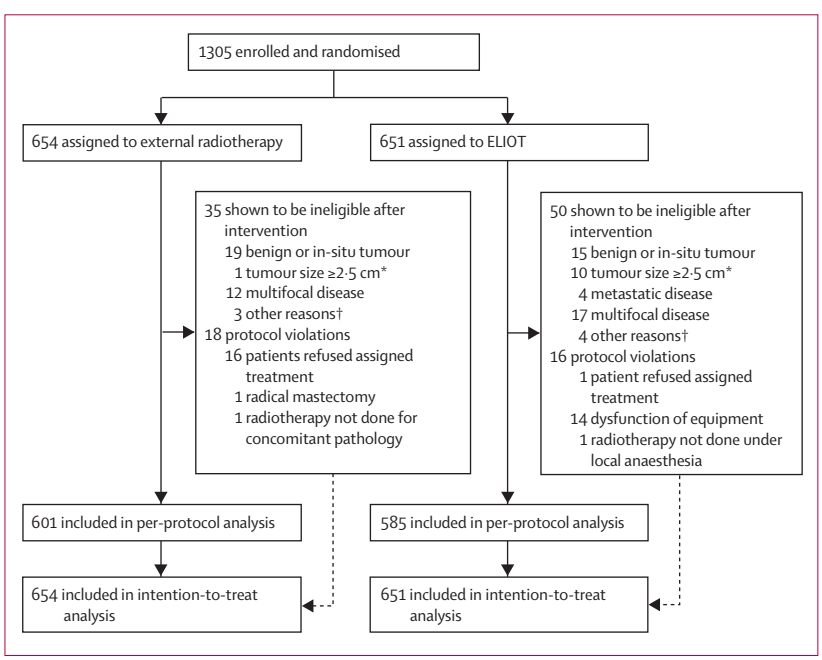

Figure 1: **Trial profile**
ELIOT=intraoperative radiotherapy with electrons. *At pathological examination. †Four patients were shown to have a previous malignancy (two in the external radiotherapy group and two in the intraoperative radiotherapy group), two patients in the intraoperative radiotherapy group had an excisional biopsy done elsewhere, and one patient in the external radiotherapy group was over age 75 at intervention.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive external radiotherapy or intraoperative radiotherapy with electrons. Immediately before the intervention, the surgeon contacted the data centre by telephone to receive the allocation group. At the data centre, allocation was done by telephone with a computer-generated list using a randomly permuted block design, stratified by tumour size (<1·0 cm *vs* 1·0–1·4 cm *vs* ≥1·5 cm). Study coordinators, clinicians who verified eligibility criteria after pathological assessment of the surgical specimen, clinicians who followed up patients, investigators who did the statistical analyses, and the patients themselves were aware of the assignment.

Procedures

We assessed histological tumour type according to the WHO classification.[10] We assessed tumour grade according to the combined histological grade (Elston-Ellis modification of Scarff-Bloom Richardson grading system).[11] Oestrogen and progesterone receptors were assessed by immunohistochemistry.[12] At least 2000 tumour cells were counted and the number of positive cells was recorded as a percentage: the presence of more than 1% of immunoreactive cells was defined as hormone-receptor positivity. We established *HER2* status by immunohistochemistry using the HercepTest kit (Dako, Glostrup, Denmark). Cases showing intense circumferential membrane staining in more than 10% of tumour cells were deemed positive. Tumours with weak to moderate membrane staining in more than 10% of cells were tested for gene amplification by fluorescence in-situ hybridisation (Vysis PathVysion; Abbott, Chicago, IL, USA). A HER2-to-CEP17 ratio of two or greater was deemed evidence of gene amplification. We assessed Ki-67 proliferative index using the MIB-1 monoclonal antibody (1:200 dilution; Dako). We classified tumours into four molecular subtypes (luminal A, luminal B, *HER2*, and triple negative) using surrogate immunohistochemical markers.[13]

The electron intraoperative radiotherapy technique, as previously described,[14] was done by means of two dedicated linear accelerators: NOVAC 7 (Hythesis, latina, Italy) and Liac (Info and Tech, Rome, Italy). We intended that all patients in the experimental group would receive one full dose of 21 Gy, to the 90% isodose, to the tumour bed after tumour removal. A Perspex applicator tube with a 4 cm, 5 cm, 6 cm, or 8 cm diameter collimated the electron beam with 6–9 MeV energies. The clinical target volume was decided

according to the site and size of the tumour. The energy of the electron beams was selected according to the thickness of the gland measured by a graduated needle. Protection of the thoracic wall was achieved using aluminium and lead discs. Intraoperative radiotherapy with electrons was compared with postoperative whole breast irradiation (external radiotherapy group): 50 Gy given in 25 fractions using tangential beams, followed by a boost dose of 10 Gy in five fractions delivered using a direct external electron beam. The treatment plans were normalised at the International Commission on Radiation Units and Measurements reference point. We did dose-volume histogram analysis for all surrounding structures (contralateral breast, heart, and ipsilateral lung). We also measured the central lung distance and, for left-sided breasts the maximum heart distance. The organ-at-risk constraints were that 5% of the heart and 20% of the lung were kept to less than 50% of the prescribed dose and no point of the contralateral breast could receive more than 15% of the prescribed dose.

All patients with a positive sentinel biopsy specimen received axillary dissection. For patients with three or fewer positive nodes no additional irradiation was undertaken. In patients with four or more positive axillary nodes, additional irradiation was given as a conventional fractionation of 2 Gy to a total dose of 50 Gy, concomitantly to breast irradiation in the external radiotherapy group and postponed for 8–12 weeks in the intraoperative radiotherapy group. The linear quadratic model is most commonly used to compare, in terms biologically equivalent dose, conventional external radiotherapy with a single intraoperative fraction of 21 Gy.[15] With reference to these calculations, assuming that the α-to-β ratio of tumour cells and early normal tissue reactions is equal to ten, one dose of 21 Gy should result in the same local control and acute reactions as the standard conventionally fractionated dose of 65·10 Gy. Conversely, assuming that α-to-β ratio of breast tumour cells is equal to four, 21 Gy full dose should be equivalent to 131·2 Gy in 2 Gy fractions.[15] When α-to-β ratios are so low, as for late normal tissue reactions, there might be an increased risk of fibrosis from the single-fraction treatment.[16]

Adjuvant treatments were administered according to European Institute of Oncology policy during the period of accrual of patients. Patients were followed up with a clinical examination every 3 months, an ultrasound mammary scan every 6 months, and a mammogram every year; examinations of the lung, liver, and bone were modulated according to a personalised assessment of risk.

Local recurrences are often defined and regarded as ipsilateral breast tumour recurrences (IBTR). However, in this study, it was important to distinguish true local recurrences in the index quadrant from second (or new)

	External radiotherapy	Intraoperative radiotherapy with electrons
Age*		
48–49 years	43 (7%)	44 (7%)
50–59 years	267 (41%)	286 (44%)
60–69 years	269 (41%)	259 (40%)
≥70 years	75 (11%)	62 (10%)
Histology†		
Ductal	514 (79%)	524 (81%)
Lobular	57 (9%)	53 (8%)
Ductal and lobular	21 (3%)	17 (3%)
Other	55 (9%)	53 (8%)
Pathological size‡		
≤1 cm	194 (30%)	199 (31%)
1–1·5 cm	235 (36%)	243 (38%)
1·5–2 cm	115 (18%)	120 (19%)
>2 cm	103 (16%)	83 (13%)
Number of positive nodes†		
None	471 (73%)	478 (74%)
1–3	138 (21%)	138 (21%)
≥4	38 (6%)	31 (5%)
Tumour grade§		
G1	160 (25%)	196 (31%)
G2	328 (52%)	305 (48%)
G3	145 (23%)	129 (20%)
Oestrogen receptor¶		
Negative	56 (9%)	63 (10%)
Positive	589 (91%)	583 (90%)
Progesterone receptor‖		
Negative	132 (20%)	158 (24%)
Positive	512 (80%)	487 (76%)
Proliferative index (Ki-67)**		
<14%	242 (38%)	263 (41%)
14–20%	138 (21%)	138 (21%)
>20%	265 (41%)	244 (38%)
Molecular subtype¶		
Luminal A	237 (37%)	256 (40%)
Luminal B	352 (55%)	327 (51%)
HER2 positive (non-luminal)	24 (4%)	20 (3%)
Triple negative	32 (5%)	43 (7%)
Adjuvant treatment*		
Control	26 (4%)	25 (4%)
Endocrine therapy alone	485 (74%)	489 (75%)
Chemotherapy alone	47 (7%)	53 (8%)
Endocrine and chemotherapy	96 (15%)	84 (13%)

Data are n (%). Some percentages do not total 100% because of rounding. 654 patients were assigned to external radiotherapy, and 651 to intraoperative radiotherapy with electrons. *n=654 for external radiotherapy, n=651 for intraoperative radiotherapy with electrons. †n=647 for both groups. ‡n=647 for external radiotherapy, n=645 for intraoperative radiotherapy with electrons. §n=633 for external radiotherapy, n=630 for intraoperative radiotherapy with electrons. ¶n=645 for external radiotherapy, n=646 for intraoperative radiotherapy with electrons. ‖n=644 for external radiotherapy; n=645 for intraoperative radiotherapy with electrons. **n=645 for both groups.

***Table 1*: Characteristics of patients according to allocated group (intention-to-treat population)**

ipsilateral carcinomas in other quadrants, of which we expected an increased number in the intraoperative radiotherapy group compared with the external radiotherapy group in which whole breast irradiation protected all of the breast. We defined local recurrence as the reappearance of the carcinoma at the site of the surgical intervention. We defined second ipsilateral breast tumours as any new carcinoma appearing in other quadrants of the same breast. IBTR was defined as the sum of local recurrence plus second ipsilateral tumours. A regional nodal failure included any recurrence in the ipsilateral axillary, supraclavicular, or internal mammary nodal regions. Distant metastases were defined as any recurrence to distant organs. Overall survival was defined as the time from diagnosis to last follow-up or time of death. Side-effects were scored using the Late Effect of Normal Tissue-Subjective Objective Management Analytic criteria.[17]

The primary endpoint was the occurrence of IBTR (ie, true local relapse plus new ipsilateral breast tumour). The secondary endpoint was overall survival. We had planned to assess quality of life as a secondary endpoint; however, data for quality of life were poorly collected and inadequate for analysis.

Statistical analysis

This study is an equivalence trial, aiming to show that local recurrence at 5 years in the intraoperative radiotherapy group is within an equivalence margin and not significantly greater than in the external radiotherapy group. Assuming a 5-year local recurrence of 3% (on the basis of our previous experience) in the external radiotherapy group and equivalence of the two groups if 5-year local recurrence in the intraoperative radiotherapy group did not exceed 7·5% (which was the level accepted in most institutions when the study was designed), a sample of 412 patients per group provides 90% power to show equivalence, using a one-tailed test.

The main analysis was by intention to treat, including all randomised patients. We also did a per-protocol analysis, restricted to patients who received the allocated treatment and satisfied eligibility criteria after final pathological assessment of the surgical specimen.

5-year events rates and their 95% CIs were obtained from actual survival curves, and cumulative incidence and survival plots were drawn using the Kaplan-Meier method. We used the log-rank test to assess the survival difference between the two treatment groups. The log-rank test was also used to assess differences in survival of patients treated with intraoperative radiotherapy according to clinicopathological characteristics of the breast cancer. We obtained hazard ratios (HRs) for IBTR and deaths for intraoperative radiotherapy versus external radiotherapy from univariate Cox proportional hazards regression models. We used multivariable Cox proportional hazards regression to identify independent factors associated with IBTR among patients who received intraoperative radiotherapy. All analyses were done with SAS (version 8.2). All p values were two-sided.

This trial is registered with ClinicalTrials.gov, number NCT01849133.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1305 patients were randomised (654 to external radiotherapy and 651 to intraoperative radiotherapy) between Nov 20, 2000, and Dec 27, 2007 (figure 1). The outcomes were assessed 5 years from the end of the accrual (median follow-up for all patients 5·8 years [IQR 4·1–7·7]; for external radiotherapy 5·9 years [4·2–7·8]; for intraoperative radiotherapy with electrons 5·5 years [4·0–7·4]). The main analysis was by intention to treat. We also did a per-protocol analysis, excluding women allocated to the external radiotherapy group who received intraoperative radiotherapy, those who did not received intraoperative radiotherapy because of dysfunction of the intraoperative radiotherapy machine, and those who were shown to be ineligible after surgery (figure 1). 1186 patients were included in the per-protocol analysis (601 in the external radiotherapy group and 585 in the intraoperative radiotherapy group).

Table 1 shows the characteristics of the patients according to treatment group. 1254 (96·1%) patients received adjuvant treatment; 974 (74·6%) patients received endocrine treatment only, and 100 (7·7%) chemotherapy alone. 180 (13·8%) patients had both treatments.

	External radiotherapy (n=654)		Intraoperative radiotherapy with electrons (n=651)		Log-rank p value
	Number	5-year event rate (95% CI)	Number	5-year event rate (95% CI)	
Ipsilateral breast tumour recurrence	4	0·4% (0·0–1·0)	35	4·4% (2·7–6·1)	<0·0001
Local relapse	4	0·4% (0·0–1·0)	21	2·5% (1·2–3·8)	0·0003
New ipsilateral breast tumour	0	0	14	1·9% (0·8–3·1)	0·0001
Axillary or other regional lymph node metastasis	2	0·3% (0·0–0·8)	9	1·0% (0·2–1·9)	0·03
Locoregional tumour recurrence	6	0·8% (0·0–1·5)	44	5·4% (3·5–7·2)	<0·0001
Contralateral breast tumour	13	1·7% (0·6–2·7)	8	1·1% (0·2–2·1)	0·34
Distant metastasis*	35	4·8% (3·1–6·5)	33	5·1% (3·3–6·9)	0·94
Other primary cancer	22	3·2% (1·8–4·7)	20	2·5% (1·2–3·8)	0·88
Death as first event	7	0·9% (0·1–1·7)	8	1·0% (0·1–2·0)	0·69
Total deaths	31	3·1% (1·7–4·5)	34	3·2% (1·7–4·7)	0·59
Breast cancer	20	2·0% (0·9–3·2)	23	2·1% (0·9–3·3)	0·56
Other cause	11	1·1% (0·2–2·0)	11	1·1% (0·2–2·0)	0·93

Person-years until last visit 3920 for external radiotherapy, 3716 for intraoperative radiotherapy with electrons. Person years until last contact 4107 for external radiotherapy, 3997 for intraoperative radiotherapy with electrons. *As first or secondary event (including four diagnosed at the time of surgery, all in the intraoperative radiotherapy group).

Table 2: **Events identified during follow-up according to allocated group (intention-to-treat population)**

There were 35 occurrences of IBTR in the intraoperative radiotherapy group, yielding a 5-year event rate of 4·4% (95% CI 2·7–6·1), within the prespecified equivalence margin of 7·5%. However, the occurrence of IBTR was significantly greater in the intraoperative radiotherapy group than in the external radiotherapy group (four cases, 0·4% [0·0–1·0]; p=0·0001; table 2, figure 2). The HR for the development of IBTR was 9·3 (95% CI 3·3–26·3) for women allocated to receive intraoperative radiotherapy compared with those allocated to receive external radiotherapy. The 5-year occurrence of true local relapse (occurring in the index quadrant) was also significantly greater in the intraoperative radiotherapy group (21 cases, 2·5% [95% CI 1·2–3·8]) than in the external radiotherapy group (four cases, 0·4% [0·0–1·0]; p=0·0003). New ipsilateral breast carcinomas occurred in 14 patients in the intraoperative radiotherapy group (1·9% [95% CI 0·8–3·1]) but in none of the patients in the external radiotherapy group (p=0·0001).

Nine women (5 year event rate 1·0% [95% CI 0·2–1·9]) in the intraoperative radiotherapy group and two women (0·3% [0·0–0·8]) in the external radiotherapy group had developed axillary or other regional lymph node metastasis (p=0·03). Development of contralateral breast cancer was recorded in eight patients (1·1% [95% CI 0·2–2·1]) in the intraoperative radiotherapy group and in 13 patients (1·7% [0·6–2·7]) in the external radiotherapy group (p=0·34). Development of distant metastasis was much the same in the two groups (5·1% in the intraoperative radiotherapy group *vs* 4·8% in the external radiotherapy group; p=0·94; table 2). Development of primary cancer in other sites was recorded in 20 women (2·5% [95% CI 1·2–3·8]) in the intraoperative radiotherapy group and 22 women (3·2% [1·8–4·7]) in the external radiotherapy group (p=0·88; table 2).

Overall survival at 5 years did not differ between the intraoperative radiotherapy group (34 deaths) and external radiotherapy group (31 deaths; p=0·59; figure 2). The numbers of deaths attributable to breast cancer (23 in the intraoperative radiotherapy group *vs* 20 in the external radiotherapy group) and attributable to other causes (11 in the intraoperative radiotherapy group *vs* 11 in the external radiotherapy group) were also much the same in the two groups. 5-year overall survival was 96·8% (95% CI 95·3–98·3) for the intraoperative radiotherapy group and 96·9% (95·5–98·3) for the external radiotherapy group. The per-protocol analysis resulted in similar findings for all outcomes (appendix).

All four women who developed IBTR during follow-up after receiving external radiotherapy had an oestrogen receptor positive tumour, including two with high Ki-67 expression (>20%); two had lymphnodal involvement at surgery. We identified no other notable features.

For patients in the intraoperative radiotherapy group, we analysed characteristics associated with local relapse, to allow identification of patients who might benefit from subsequent whole breast irradiation. 5-year IBTR exceeded 10% in patients with large (>2 cm) tumours, with four or more positive lymph nodes, with poorly differentiated (grade 3) tumours, with oestrogen-receptor

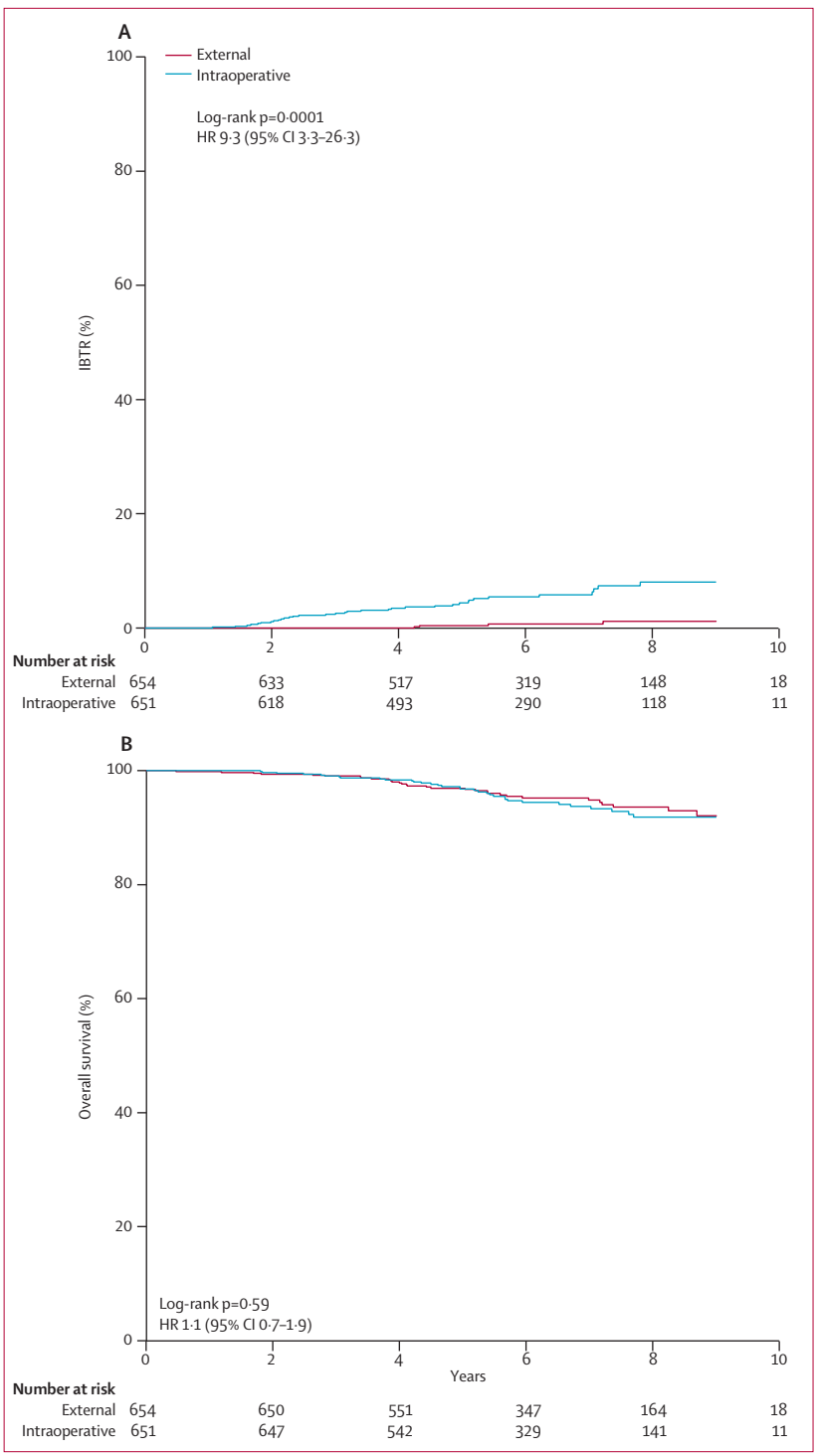

Figure 2: **Cumulative incidence of (A) ipsilateral breast tumour recurrence and (B) overall survival (intention-to-treat population)**
HR=hazard ratio.

See **Online** for appendix

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Total	35/651	4·4% (2·7–6·1)	..
Age			
48–49 years	0/44	0	..
50–59 years	21/286	5·6% (2·7–8·5)	..
60–69 years	10/259	3·1% (0·8–5·4)	..
≥70 years	4/62	7·2% (0·4–14·1)	0·11
Histology			
Ductal	28/524	4·5% (2·6–6·5)	..
Lobular	3/53	4·6% (0·0–10·8)	..
Ductal and lobular	2/17	6·3% (0·0–18·1)	..
Other	2/53	2·1% (0·0– 6·1)	0·69
Pathological size			
≤1 cm	5/199	1·9% (0·0–4·0)	..
1–1·5 cm	13/243	4·2% (1·5–6·9)	..
1·5-2·0 cm	7/120	4·7% (0·7–8·8)	..
>2·0 cm	10/83	10·9% (3·7–18·1)	0·006
Number of positive nodes			
None	21/478	3·5% (1·7–5·3)	..
1–3	10/138	5·3% (1·5–9·2)	..
≥4	4/31	15·0% (1·4–28·7)	0·06
Overall p value	..	..	
Tumour grade			
G1	5/196	1·1% (0·0–2·7)	..
G2	15/305	3·8% (1·5–6·1)	..
G3	15/129	11·9% (5·7–18·2)	0·0003
Oestrogen receptor			
Absent	8/63	14·9% (5·2–24·5)	..
Present	21/583	3·3% (1·8– 4·9)	0·004
Overall p value	..	..	
Progesterone receptor			
Absent	12/158	7·4% (2·9–11·8)	..
Present	23/487	3·5% (1·7– 5·2)	0·17
Proliferative index (Ki-67)			
<14%	8/263	1·8% (0·0–3·5)	..
14–20%	5/138	1·5% (0·0–3·6)	..
>20%	22/244	9·1% (5·1–13·1)	0·002
Molecular subtype			
Luminal A	7/256	1·4% (0·0–3·0)	..
Luminal B	20/327	4·9% (2·4–7·4)	..
HER2-positive (non-luminal)	1/20	5·9% (0·0–17·1)	..
Triple negative	7/43	18·9% (6·1–31·7)	0·001
Characteristics suggesting subsequent whole breast irradiation			
No	14/452	1·5% (0·3–2·7)	..
Yes†	21/199	11·3% (6·4–16·1)	<0·0001

IBTR=ipsilateral breast tumour recurrence. *Overall p value. †Tumour larger than 2·0 cm, or four or more positive nodes, grade 3, or triple negative.

Table 3: **Factors associated with IBTR among patients randomised to receive intraoperative radiotherapy with electrons**

	External radiotherapy	intraoperative radiotherapy with electrons	p value†
Any skin toxicity			
No	427	401	..
Yes, acute	32	5	..
Yes, chronic	5	6	0·0002
Erythema			
No	7	24	..
Grade 1–2	35	5	..
Grade 3	2	0	..
Grade 4	3	0	..
Grade 5	0	0	<0·0001
Dryness			
No	128	147	..
Grade 1–2	20	10	..
Grade 3–5	0	0	0·04
Hyper-pigmentation			
No	138	146	..
Grade 1–2	36	11	..
Grade 3-5	0	0	0·0004
Pruritus (scale 0–10)			
0	174	153	..
1–2	6	5	..
≥3	11	0	0·006
Overall p value	..	..	
Necrosis (radiological)			
Absent	136	129	..
Present	10	22	0·04

*Information available only for a subset of patients. †Overall p value.

Table 4: **Skin side-effects (per-protocol analysis)***

negative tumours, and with triple-negative breast tumours (table 3). In multivariable analysis, tumour size greater than 2 cm (HR 2·24, 95% CI 1·03–4·87), the presence of four or more positive lymph nodes (2·61, 0·91–7·50), a poorly differentiated tumour (2·18, 1·00–4·79), and triple-negative subtype (2·40, 0·94–6·10) roughly doubled the risk of IBTR. Overall, 5-year occurrence of IBTR was 11·3% for the 199 women (30·6%) who had at least one of these unfavourable characteristics, but only 1·5% for the remaining 452 women (69·4%; p<0·0001). The findings were much the same in the per-protocol analysis (appendix).

Information about side-effects of radiotherapy was not available for all patients. For patients with data available (464 patients in the intraoperative radiotherapy group, 412 patients in the external radiotherapy group), overall, skin side-effects showed a significant difference in favour of the intraoperative radiotherapy group (p=0·0002). In particular, very few skin side-effects occurred in the intraoperative radiotherapy group compared with the external radiotherapy group (table 4): erythema (p<0·0001), dryness (p=0·04), hyper-pigmentation (p=0·0004), pruritus (p=0·002). We identified no differences for mammary fibrosis, mammary retraction, pain, or burning (data not shown). We identified a higher occurrence of fat

necrosis in the intraoperative radiotherapy group than in the external radiotherapy group (p=0·04; table 4).

A subgroup of 178 volunteers (95 from the intraoperative radiotherapy group and 83 from the external radiotherapy group) agreed to undergo a follow-up spiral CT. Pulmonary fibrosis was diagnosed in 42 (23·6%) of the patients examined: four (9·5%) had received intraoperative radiotherapy and 38 (90·5%) external radiotherapy (p<0·0001). 26 of these events were grade 1 (one in the intraoperative radiotherapy group), 15 grade 2 (three in the intraoperative radiotherapy group), and one was grade 3 (in the external radiotherapy group).

Discussion

In women with early small breast carcinoma, intraoperative radiotherapy with electrons resulted in significantly higher local recurrence than did conventional postoperative external radiotherapy after 5 years of follow-up. Both true local recurrences (in the index quadrant) and new ipsilateral breast tumours were significantly more common in the intraoperative radiotherapy group than in the external radiotherapy group. Overall survival did not differ between the groups, with about the same numbers of deaths from breast cancer and other causes. There were fewer side-effects involving the skin with intraoperative radiotherapy compared with external radiotherapy.

As far as we are aware, this is the first single-centre randomised trial comparing the outcome of patients with breast cancer who received intraoperative radiotherapy with electrons compared with conventional external radiotherapy (panel). Over the past 30 years, several pilot studies have detailed the rationale and the techniques of partial breast irradiation, including intraoperative approaches, but before establishing a new standard of care, randomised trials with large populations of patients and adequate follow-up are recommended.[25]

In this series of 1305 unselected patients, we identified an excess of IBTR in the intraoperative radiotherapy group compared with the external radiotherapy group, both as true recurrences, in the quadrant initially affected by the disease (2·5% *vs* 0·4% at 5 years), and as new tumours in the other quadrants of the same breast (1·9% *vs* 0% at 5 years). The 5-year occurrence of IBTR in the intraoperative radiotherapy group (4·4%) was, however, lower than we predicted (up to 7·5%) and is less than reported in the scientific literature in patients undergoing whole breast irradiation. In randomised trials analysed by the Early Breast Cancer Trialists' Collaborative Group, the proportion of patients with isolated local recurrence at 5 years with whole breast irradiation was 6·7% for those with negative nodes and 11% for those with positive nodes.[26] In a study[27] done in Hungary, occurrence of relapse in patients who received partial breast irradiation was 4·7% at 5 years, much the same as that recorded in the intraoperative radiotherapy group in the present study. In the TARGIT study[21–23] in selected patients with early breast cancer, one dose of x-ray intraoperative irradiation resulted in much the same proportions of patients having local recurrence as with conventional radiotherapy at 4 years (1·20% *vs* 0·95%), but by 5 years, local recurrence was significantly greater in the TARGIT group (3·3% *vs* 1·3%; p=0·042).[22]

The significant difference in local recurrence in the present trial is probably mainly attributable to the very low rate of recurrence in the external radiotherapy group (0·4% at 5 years), which is indicative of the high quality of comprehensive management of early breast cancer reached in our high-volume referral cancer centre. In previous studies,[26,28–30] recurrence at 5 years has been higher than 3%. Local recurrence in the intraoperative radiotherapy group in the present study is lower than

Panel: Research in context

Systematic review

Four randomised trials of intraoperative or external partial breast irradiation have been reported up to now, two of them—the Yorkshire Breast Cancer Group trial,[18] undertaken from 1986 to 1990, and the Christie Hospital trial,[19] from 1982 to 1987—failed to prove the effectiveness of this approach for local control. Conversely, the Budapest trial[20] (1998–2004) based its success on a strict selection of patients. After a median follow up of 10·2 years, this trial did not show any differences between partial and whole breast irradiation in terms of local control and survival endpoints. TARGIT-A[21–23] (2000–2008) is a phase 3 trial, designed in the same period as the ELIOT trial, which reported preliminary results in 2010. This intraoperative technique uses low-energy x-rays of 50 kV; the prescribed dose is 20 Gy in one fraction to the applicator surface, which corresponds to 5–7 Gy at 1 cm from the applicator. After a median follow-up of 24·6 months, the Kaplan-Meier estimate of local recurrence at 4 years did not differ between TARGIT and control (whole breast irradiation). However, in an updated report,[22] the 5-year risk of local recurrence was significantly greater in the TARGIT group (3·3% *vs* 1·3%; p=0·042). As far as we are aware, the only meta-analysis of partial breast irradiation was reported in 2010;[24] it showed that when compared with whole breast irradiation, there was an increased risk for both local and regional recurrence with partial breast irradiation, without any survival difference for the available follow-up.

Interpretation

As far as we are aware, this is the first randomised study using intraoperative electrons for partial breast irradiation. Our data confirm the need for longer follow-up and outline the importance of proper selection of patients. Failure of local control was partly attributable to ipsilateral events in sites other than the index quadrant, which have a long mean time to relapse, and partly to recurrences around the original tumour. So, the difficulty is not only to define patients at low risk of harbouring microscopic disease beyond the tumour site, but also to define the proper coverage of the tumour bed. The eligibility criteria for patients were simple and limited, based on age, tumour size, and clinically negative nodal involvement. They were adequate at the time at which the study was designed, but nowadays it is recognised that clinical and pathological factors will help to identify ideal candidates for partial breast irradiation. The very low incidence of local failure in the external radiotherapy group of our trial confirms the great improvement in all treatments for breast cancer, from surgery to systemic therapies to radiation therapy, over the years. However, advances such as intraoperative radiotherapy might help to further improve the quality of life for patients, and the findings of our trial will enable clinicians to better use to biomolecular factors along with traditional clinical and histopathological factors to identify the patients who ideal candidates for partial breast irradiation.

that achieved after mastectomy in the Milan I trial.[2] We have also identified a decrease of incidence of relapses with external beam radiotherapy.[31] In the present study, we also noted an excess of recurrences in the axilla in the intraoperative radiotherapy group, although the number of events was too low to allow any statistical analysis. The results of the American College of Surgeons Oncology Group's Z0011 trial[32] suggest that this finding might be related to the coverage of axillary level 1, as also occurs when tangential fields are used for whole breast irradiation.

Intraoperative radiotherapy with electrons was associated with about the same number of distant metastases and deaths as external radiotherapy, showing that distant disease control and overall survival are much the same in two treatment groups, at least in the short term. The continued active follow-up of patients in our trial will allow us to reassess the safety of intraoperative radiotherapy with electrons on the development of distant metastases and death in the long term.

Some patients did not receive the treatment allocated at randomisation and some were shown not to be eligible after surgery. We therefore did a secondary per-protocol analysis, the findings of which were much the same as with the intention-to-treat approach (appendix).

We also reported fewer side-effects among women who received intraoperative radiotherapy with electrons; however, this analysis was based on a limited subset of women because such information was not systematically recorded. It is therefore potentially subject to bias.

What will be the future developments in intraoperative breast irradiation? Provided that overall survival is identical, the problem is the identification of the patients at greater risk of local recurrence, who are therefore more suitable to external whole breast irradiation or intraoperative radiotherapy plus whole breast irradiation. We assessed the associations between characteristics of patients in the intraoperative radiotherapy group and local recurrence to identify those characteristics that seem unfavourable for intraoperative radiotherapy alone. The characteristics of tumour size greater than 2 cm, tumour of grade 3, four of more positive nodes, and triple-negative tumours were significantly associated with local recurrence (table 3; appendix). These criteria require further validation.

The logical conclusion is that intraoperative radiotherapy with electrons should be restricted to suitable patients, once characteristics defining suitability have been defined. However, because many variables will only be available after histological examination of the specimen, suitability will be difficult to establish preoperatively. One option would be to use preoperative criteria such as tumour size, breast volume, age of the patient, and pathological and biological studies of preoperative biopsy specimens to help with identifying suitable patients. Another possibility would be to treat all patients with full-dose intraoperative radiotherapy with electrons during surgery and, after final categorisation, to give additional external whole breast irradiation to patients at high risk of local recurrence; in this circumstance, intraoperative radiotherapy with electrons would be deemed an anticipated boost. This aspect should be a topic for further studies.

Intraoperative radiotherapy should be part of discussions to decide a personalised treatment regimen because it offers the advantage to patients of not having to attend a radiotherapy centre every day for many weeks, and has about the same overall survival as external radiotherapy; however, these advantages must be weighed against the possibility of an increased risk of local recurrence.

Contributors

The study was conceived by UV and RO. NR and CS were responsible for randomisation and data collection. PM analysed the data. GV supervised pathological evaluation of surgical specimens. UV, AL, PV, VG, SZ, OG, MI, PC, BB were responsible for surgery. RO, MCL, RL, FC were responsible for radiotherapy. UV, OR, and PM wrote the first draft of the manuscript. All authors provided feedback and made revisions to the manuscript. UV, RO, and PM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

We declare that we have no conflicts of interest.

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