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# Ipsilateral Breast Recurrence After Breast Conserving Surgery in Patients with Small ( $\leq 2$ cm) Breast Cancer Treated with Modern Adjuvant Therapies

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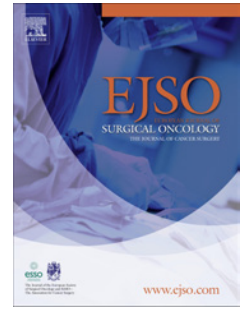
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# Accepted Manuscript

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**Ipsilateral Breast Recurrence After Breast Conserving Surgery in Patients with  
Small ( $\leq 2$  cm) Breast Cancer Treated with Modern Adjuvant Therapies**

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**Key words: Breast cancer, Breast conserving surgery, Local recurrence, Radiotherapy**

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**ABSTRACT**

**Background:** Modern multimodality treatment greatly influences the rate and the predictive factors for ipsilateral cancer recurrence (IBR) after breast conserving surgery.

**Material and Methods:** The study is based on 1,297 patients with pT1 breast cancer and treated with breast conserving surgery in February 2001 to August 2005. The median duration of follow-up was 57 months.

**Results:** IBR occurred in 27 (2.1%) patients. It was located in the quadrant of prior breast resection in 17 (63%) cases. The median time to an IBR was 41 months (range, 6-78) regardless of whether the recurrence was located in the same or in another quadrant. Omission of radiotherapy was associated with a higher IBR incidence, HR 10,344 (95% CI 1,904-56,184); p= 0.007). The IBRs occurred particularly often, in 27% of the 11 patients who refused radiotherapy. Patients diagnosed with ER+ cancer had a lower risk of IBR when compared with those with ER-/HER2+ cancer, HR 0,215 (95% CI 0,049-0,935); p= 0.040).

**Conclusions:** The risk of IBR was low during the first 5 years after breast resection among patients with pT1 breast cancer and treated with modern surgical and adjuvant therapies. The majority IBRs still occur at or close to the prior resection site underlining the importance of local therapies. Omission of radiotherapy was the most significant risk factor for IBR.

## Introduction

The cumulative incidence of breast cancer recurrences after breast conserving surgery and adjuvant radiotherapy (RT) varies between 9% and 14% within the first 20 years after surgery.<sup>1,2</sup> The majority of ipsilateral breast recurrences (IBRs) occur close to or at the site of prior resection.<sup>3-5</sup> Most IBRs that arise at the site of prior resection are likely true local recurrences, and are generally diagnosed earlier than recurrent cancers detected in other breast quadrants.<sup>4,5</sup> Late recurrences, and those located in other breast quadrants, are usually associated with more favourable prognosis than early recurrences and those found at the site of the prior resection.<sup>4,5</sup> In fact, many IBRs detected outside of the quadrant of prior tumour excision may not be true recurrent tumours, but rather second primary breast cancers that arise in the remaining ipsilateral breast tissue.

The risk factors for IBR after breast conserving surgery have been studied extensively.<sup>6-10</sup> The most frequently identified factors include young age, presence of an extensive intraductal component (EIC), and a positive resection margin.<sup>6-10</sup> RT reduces the risk of locoregional breast cancer recurrence approximately 70% and improves survival compared to surgery alone.<sup>11</sup> A booster radiation dose to the tumour site reduces further the IBR rate after breast conserving surgery, especially among premenopausal women.<sup>12,13</sup> Since good local control likely contributes to favourable survival, it is important to minimize the risk of IBR.

The rate of IBR after breast conserving surgery has recently been reported to decline particularly among patients <50 years at diagnosis.<sup>14</sup> This may be due to more effective adjuvant treatments, more frequent use of booster radiation, or improved quality of surgery.<sup>14,15</sup> Our aim was to evaluate, if the patterns of and risk factors for early IBR after conservative breast surgery have changed along with the declining risk of IBR.

## Patients and Methods

### Patients

A total of 1,865 consecutive patients, with histologically verified pT1 ( $\leq 2.0$  cm in diameter) invasive breast cancer, were operated at the Breast Surgery Unit of the Helsinki University Central Hospital (HUCH), Helsinki, Finland, in February 2001 to August 2005. Most ( $n = 1,313$ , 70.4%) out of the 1,865 patients were treated with breast conserving surgery. Sixteen (1.2%) out of these 1,313 patients were lost to follow-up. The remaining 1,297 patients form the basis of the current study.

All study participants underwent mammography and breast ultrasonography prior to breast surgery; breast MRI was not routinely used. The patient and tumour characteristics are provided in Table 1, and the treatments given are summarized in Table 2. The median age at diagnosis was 58 years (range, 25-91). The study protocol was approved by an Ethics Committee of the HUCH.

### Surgery

Breast surgery was done or supervised by an experienced breast surgeon. A wide local tumour excision was performed aiming at 1 to 2 cm free lateral margins, and including the pectoral fascia and usually a slice of the overlying skin in the resected tissue. A second operation (usually mastectomy) was performed whenever the resection margins were involved or close ( $< 3$  mm). However, free margins of 10 mm were usually required whenever cancer was multifocal with multiple satellite foci or had EIC. Patients who underwent a second breast resection due to close or positive margins were included in the study, whereas those who were ultimately treated with mastectomy were not.

Axillary nodal staging was performed using sentinel node biopsy in 1,196 (92.2%) cases and axillary clearance in 98 (7.6%); 3 (0.2%) patients had no axillary surgery.

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The breast tissue specimens were oriented by the surgeon and shipped unfixed to the pathology laboratory. Breast and lymph node specimens were handled according to published guidelines.<sup>16</sup> The primary tumour diameter, presence of an EIC or multifocality, cancer histological type, histological grade, steroid hormone receptor status, *HER2* amplification status, and the proliferation index MIB-1 were assessed by specialized breast pathologists. The steroid hormone receptor status and MIB-1 were assessed using immunohistochemistry. *HER2* expression was evaluated using immunohistochemistry, and whenever immunohistochemistry was considered positive (2+ or 3+ on a scale from 0 to 3+), the *HER2* status was confirmed with chromogen *in situ* hybridisation. The histological classification and grading were based on the World Health Organisation (WHO) classification of tumors.<sup>17</sup>

### **Radiation therapy**

Postoperative radiotherapy was given to the ipsilateral breast after breast conserving surgery using a linear accelerator to a cumulative dose of 50 Gy in 25 fractions. Premenopausal women received a booster dose of 10 to 16 Gy given in 5 to 8 fractions to the tumour bed. Other indications for a booster dose consisted of close resection margins and presence of lymphovascular invasion. The whole breast was treated from 2 tangential fields. Axillary, supra- and infraclavicular, and often also parasternal nodes were included in the target volume in patients with >1 macrometastatic axillary nodes. Patients with parasternal sentinel node metastases received radiotherapy to the ipsilateral parasternal nodes (Table 2).

### **Systemic adjuvant therapy**

Systemic adjuvant treatment was administered based on the patient and disease characteristics at the discretion of the treating physician. In general, women with node-positive disease and those considered to have moderate-to-high risk node-negative disease received adjuvant systemic therapy. Premenopausal women with oestrogen receptor (ER)- or progesterone receptor (PgR)-positive cancer received tamoxifen and postmenopausal women either tamoxifen or an aromatase inhibitor for 5 years. Patients  $\leq 65$  years of



age with moderate-to-high risk HER2-positive cancer received adjuvant trastuzumab and chemotherapy<sup>18</sup> (Table 2). None of the patients received neo-adjuvant systemic therapy.

### **Follow-up**

The median follow-up time was 57 months (range, 7-87 months) calculated from the date of surgery. Planned follow-up visits took place at 1, 3, and 5 years after breast surgery. In addition, the study participants had an access to a hospital out-patient unit whenever there was concern of cancer recurrence. Physical examination, blood cell counts and blood chemistry, and a bilateral mammogram with or without breast ultrasound examination were performed at the planned visits and whenever considered indicated. When a recurrence was suspected, an isotope bone scan and computed tomography were usually carried out as the initial staging examinations. After the first 5 years, follow-up was continued at a local health centre or at a private health care company based on patient preference.

Data on cancer recurrence and survival were collected from the hospital records and registries, and the files of the Finnish Cancer Registry. The Finnish Cancer Registry has coverage close to 100%.<sup>19</sup>

### **Statistical analysis**

The time to IBR was computed from the date of breast surgery to the date of IBR. Life tables were constructed according to the Kaplan-Meier method, and the IBR incidence between the groups was compared with the Cox univariate and multivariate proportional hazards models. P- values < 0.05 were considered as statistically significant.

### Cancer recurrence and survival events

An IBR occurred in 27 patients during follow-up. It was located at the previous resection site in 17 out of the 27 patients and outside the quadrant of the prior resection in the remaining 10 cases. The median time from surgery to an IBR was 41 months (range, 6-78 months) regardless of whether the recurrence was located in the same or in another breast quadrant. The 5-year cumulative IBR incidence was 2.1% (Figure 1). Contralateral breast cancer was detected in 14 patients, none of whom was also diagnosed with an IBR. The median time from surgery to the date of the diagnosis of contralateral breast cancer was 34 months (range, 10-61 months).

Cancer recurrences in the regional lymph nodes were also few. Only 5 patients had an ipsilateral axillary recurrence (isolated axillary recurrence, n = 1; breast and axillary recurrence, n = 2; axillary recurrence and concomitant distant recurrence, n= 2). Three patients had a nodal recurrence in the contralateral axilla, in one case an IBR preceded contralateral axillary recurrence. One patient had a supraclavicular nodal recurrence and one a parasternal recurrence. Table 3.

Distant metastases were detected in 2 patients with an IBR and in 55 of those who did not have an IBR. In 3 patients contralateral breast cancer was diagnosed prior to or concomitantly with distant metastases. Thirty-two patients died from breast cancer during the follow-up, 15 patients from another cause than cancer, and in 9 cases the cause of death was unknown (Table 3).

### IBR and age

According to the univariate analysis, patients between 54 and 70 years at diagnosis had the lowest 5- year IBR incidence (1,0%) with a HR of 0,244 (95%CI 0,082-0,727) , when compared with patients older than 70 years, p= 0.011. Table 1. Especially the IBRs incidence outside of the quadrant of the previous

resection was lower (0,4%) in these patients, HR 0,145 (95% CI 0,027-0,793) ; p=0,026. The patients younger than 40 years had the highest 5-year IBR incidence (25,0%) outside of the quadrant of the previous resection, but the difference was not statistically significant when compared with the oldest patients, p=0.882. In general, age had no influence on the IBRs at the previous resection site.

### **IBR and RT**

IBRs were more frequent in patients who did not receive breast RT. The 5- year IBR incidence was 13,7% in these patients. The HR for IBR was 11,235 (95% CI 2,475-50,994); p=0.002 in these patients, when compared with those who received RT and a booster dose. Table 1. However, breast RT was not significantly associated with a lower incidence of cancer recurrence at the site of the previous resection, p= 0.491. The 5- year IBR incidence outside of the quadrant of the previous resection was 11,3% patients without RT, 0,7% in patients with RT given without a booster dose, and 0,5 % patients who received a booster dose . The HR was 24,974 (95% CI 2,506-248,836); p <0.0001, between patients without RT and those with RT and an additional booster.

RT was omitted in 30 patients due to fragility or co-morbidities at the discretion of the treating physician, or for an unknown reason (n = 1). Two (6%) of these 31 patients had an IBR. Three (27%) out of the 11 patients who refused the recommended RT had an IBR; none of these 3 patients completed the recommended systemic therapy.

### **IBR and systemic adjuvant treatment**

Administration of systemic adjuvant treatment was not significantly associated with the IBR incidence (Table 1), but there was a tendency for higher recurrence incidence at site of the previous resection among patients who did not receive systemic adjuvant therapy compared to those who received it ( 1,8% vs. 0,7 % , respectively, HR 2,465 (95% CI 0,938-6,482) ; p =0.067). Cancer recurrence incidence elsewhere in the breast did not differ significantly between these 2 groups (0,4 % vs. 1,1%, respectively; p =0.371).

### **IBR and histological and biological tumour features**

Tumour histological type or grade, presence of EIC or tumour multifocality, cancer ER status, the HER2 status or the proliferation index MIB-1 were not associated with the IBR rate when evaluated separately. (Table 1). Sixteen (1.2%) out of the 1,297 tumours were not classified into biological subtypes since the HER2 expression was not verified using chromogen *in situ* hybridisation. When the remaining 1,281 tumours were classified into biological subgroups, 23 (1.8%) patients had ER-/HER2+ cancer, 80 (6.2%) triple negative cancer (ER-, PgR-, HER2-) and 1,178 (92.0%) ER+ cancer (either HER2+ or HER2-, corresponding to the luminal types A or B). Compared to the other subtypes, the 5-year IBR incidence tended to be higher among patients with ER-/HER2+ subtype (p =0.074, Table 1). IBRs incidence at the previous resection site was lower (1,0%) among patients who had ER+ tumours compared to the 9,7% in those with the ER- HER2+ subtype, HR 0,155 (95% CI 0,035-0,686); p =0.014). No significant association was found between these biological subtypes and IBRs outside of the quadrant of the prior resection site (p =0.756). Ten out of the 23 patients with ER-/HER2+ disease received adjuvant trastuzumab, of whom 1 had an IBR.

### **Multivariate analysis**

The three most significant risk factors for IBR in a univariable analysis were omission of RT, age at diagnosis, and the biological subtype of tumour (Table 1). When these factors were entered into a Cox multivariate model as covariables, omission of RT (p= 0.007) and the biological subtype (p= 0.040) turned out as the independent risk factors for IBR. Table 4

The ER-HER2+ subtype and systemic therapy were the most significant risk factors for recurrences at the site of the previous resection. These two factors were included in the multivariate model. The biological subtype was a significant risk factor (p=0.011 between the ER+ and the ER- HER2+ subtypes). Systemic therapy was marginally significant (p=0.058)

The significant risk factors for IBR elsewhere in the breast in the univariate analysis were the age and omission of RT. However, the small number of observed events (10) did not allow multivariate modeling.

## Discussion

The low local recurrence rate found in the present study is in a good agreement with an annual rate of ipsilateral recurrence of approximately 0.5% reported in recent studies.<sup>3,20</sup> Some local recurrences surface late, but approximately 70% to 80% are diagnosed within the first 5 years after surgery.<sup>5,11</sup> Approximately two thirds of IBRs occurred at the prior resection site (in the same quadrant), which is in line with the findings of other studies, where 59% to 85% of the IBRs were located at the site of the previous resection.<sup>3-5,15,20</sup> In the present study the median time to an IBR was similar regardless the site of the recurrence, whereas some other studies found that recurrences at the previous resection site occur earlier.<sup>1,5,20</sup> Since many of the IBRs found outside the quadrant of the primary tumour, these, in particular, may be second breast cancers developed *de novo* in the ipsilateral breast. The median time interval observed between the date of the diagnosis of the first cancer and the date of diagnosis of breast recurrence may increase with the duration of follow-up in such cases.

Some of the recurrences may also arise from missed multicentric cancer. In the current series the risk of IBRs outside the previous resection site was very low in patients between 55 and 70 years at the time of the diagnosis. In premenopausal women, multisentric cancer may be missed more often because of dense breast tissue, especially when preoperative MRI is not carried out, as was the case in the present series.

Nevertheless, we found recurrences outside of the quadrant of the previous resection to arise approximately as frequently as contralateral breast cancers.

As expected, breast RT reduced IBRs, but somewhat unexpectedly the effect appeared to be limited to recurrences located outside of the quadrant of the prior resection. The reasons for the presumably undetected effect of RT on the rate of recurrences occurring at the prior resection site may include the relatively wide resection margins used by us, and the small numbers of breast recurrence events available for these analyses. RT may be omitted in elderly (>70) women with small ER-positive cancer who are treated with adjuvant tamoxifen with little effect on survival within the first years of follow-up.<sup>21-23</sup> We observed IBRs relatively often in patients over 70 years treated without RT, in 5.9% during the entire follow-up, despite that 82% of these women received adjuvant endocrine therapy. The IBRs were particularly frequent among the few patients who refused radiotherapy. Of note, all the three IBR patients who had refused RT had also refused or discontinued systemic adjuvant treatments.

A frequent use of a booster dose to the tumour bed may have contributed to the low rate of IBRs in the present series.<sup>12,13</sup> Similarly, systemic adjuvant treatments also likely reduced the numbers of IBRs. Systemic adjuvant treatment did not have a significant effect on the overall IBR rate in the present series, but it was administered selectively to patients who were considered to have a high risk for systemic disease recurrence, and most probably it reduced also IBRs in these patients.

Most tumour-related histological and biological factors did not have an impact on the IBR when investigated as single factors, as observed also by others.<sup>13,24,25</sup> Gene expression profiling-derived biological breast cancer subtypes may be more useful with this respect.<sup>24-26</sup> We found cancer recurrence at the prior resection site to be associated with HER2-positive subtype (ER-/HER2+), which is in line with some prior observations.<sup>24</sup> Patients diagnosed with basal-like or triple negative cancer have also been found to have a high IBR rate<sup>24</sup>, which was not verified in the present study possibly due to infrequency of such cancers in the pT1 subset and the rarity of recurrences in the present series. Moreover, not all the triple

negative cancers are high-risk basal-like tumours. We found no association between the rate of IBR outside of the quadrant of prior surgery and the ER-/HER2+ subtype, which lends support to the hypothesis that many of the recurrences found in other quadrants are new cancers with a different biological behaviour.

The current study has some limitations. The median follow-up time of 57 months was likely too short for all IBRs to surface. This limitation may concern ER+ cancer in particular. The number of locoregional recurrences was small despite the relatively large size of the cohort, which may have prevented detection of some clinically important associations.

## **Conclusions**

Patients with breast cancer 2 cm or smaller in diameter have a low risk of IBR during the first 5 years after breast conservation surgery when treated with post-operative radiation therapy and modern adjuvant therapies. The majority of the recurrences still occur at the prior tumour resection site. Omission of breast radiotherapy was the most significant risk factor for IBR.

## **Conflict of interest**

With this statement all authors mentioned in this study disclose that there are no financial or personal relationships with other people or organizations that could inappropriately influence this work.

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**Table 1. Patient and tumour characteristics and risk factors for ipsilateral breast recurrence**

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(IBR)				
Variable	N	IBRs	p	HR 95% CI)
		at 5 years		Univariate analysis
Age at diagnosis (yrs)				
<40	35	3,0%	0.721	1,332 (0,277-6,415)
40-54	445	2,9%	0.398	0,668 (0,263-1,702)
55-70	623	1,0%	0.011	0,244 (0,082-0,727)
>70	194	3,4%	0.045	1
Tumour palpability				
Palpable	799	2.2%	0.998	0,999 (0,457-2,184)
Not palpable	497	1,9%		1
N.A.	1			
Tumour presentation				
Occult	716	1,8%	0.519	0,780 (0,366-1,659)
Symptomatic	571	2,4%		1
N.A.	10			
Histological T-stage				
pT1a	54	11,1%	0.871	0,847 (0,133-6,329)
pT1b	398	3,4%	0.610	0,798 (0,335-1,899)
pT1c	845	2,0%	0.873	1
Lymph node status				
pN0 or N0 (i-)	866	2,1%	0.710	1,227 (0,417-3,608)
pN0(i+)	54	3,8%	0.282	2,540 (0,465-13,881)
pN1mi	139	1,7%	0.732	0,744 (0,136-4,063)

pN1 or N2	235	1,5%	0.633	1
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N.A.	3			
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#### Extensive intraductal component

Absent	1167	2,2%	0.283	2,999 (0,406-22,033)
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Present	130	0,8%		1
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#### Multifocal disease

Absent	1192	2,0%	0.380	0,584 (0,175-1,943)
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Present	104	3,0%		1
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N.A.	1			
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#### Histological grade

Gr. 1	501	2,1%	0.848	1,135 (0,312-4,124)
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Gr. 2	600	2,1%	0.649	1,339 (0,381- 4,702)
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Gr. 3	184	1,9%	0.868	1
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N.A.	12			
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#### Histological type

Ductal	811	1,4%	0.774	0,859 (0,306- 2,415)
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Other	233	3,6%	0.180	2,114 (0,708-6,312)
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Lobular	253	2,3%	0.106	1
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#### Tumour ER content

Negative	115	2,2%	0.683	1,295 (0,390-4,301)
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Positive	1178	2,0%		1
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N.A.	4			
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#### Tumour PgR content

Negative	341	2,1%	0.431	1,380 (0,620-3,072)
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Positive	951	2,1%		1
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N.A.	5			
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#### MIB-1 proliferation index

Very low or low	823	2,2%	0.284	2,216 (0,517-9,486)
Medium	252	2,4%	0.435	1,921 (0,373-9,909)
High	206	1,1 %	0.557	1
N.A.	16			
<i>HER2 amplification</i>				
negative	1051	1,9%	0.698	0,751 (0,176-3,205)
positive	68	3,5%		1
N.A.	178			
<i>Biological subtype</i>				
Triple negative	80	3,4%	0.174	0,169 (0,015-1,867)
ER+ HER2 +/-	1178	2,0%	0.147	0,268 (0,063-1,137)
ER- HER2+	23	9,7%	0.074	1
N.A.	16			
<i>Systemic adjuvant therapy</i>				
No	449	2,2%	0.325	1,474 (0,681-3,188)
Yes	846	1,8%		1
N.A.	2			
<i>Radiotherapy</i>				
No	42	13,7%	0.002	11,235 (2,475-50,994)
Yes, no booster	899	1,7%	0.309	1,884 (0,556-6,386)
Yes, with booster	353	0,9%	0.002	1
N.A.	3			

Abbreviations: N.A. = not available, ER = oestrogen receptor, PgR = progesterone receptor, HER2 = human epidermal growth factor receptor-2, MIB-1 = an antibody against Ki-67.

**Table 2. Treatment given**

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Treatment	N
Breast surgery	
Breast conserving surgery	1297
Axillary surgery	
None	3
SNB	807
SNB + AC	398
AC due to unsuccessful SNB	53
AC without SNB	48
Radiotherapy	
None	42
Breast only, no booster dose	899
Breast only, booster dose	353
Breast + regional lymph nodes	222
N.A.	3
Systemic treatment	
None	449
Endocrine therapy	495
Chemotherapy	71
Endocrine and chemotherapy	276
Trastuzumab + other systemic therapy	15
N.A.	2

Abbreviations: SNB = sentinel node biopsy, AC = axillary clearance, N.A. = not available.

**Table 3. Events observed**

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Event	N
<hr/>	
Site of cancer recurrence	
Ipsilateral breast	27
Contralateral breast	14
Ipsilateral axilla	6
Contralateral axilla	3
Subclavicular nodes	1
Parasternal nodes	1
Distant metastases	57
Death, breast cancer	32
Death, other	15
Death, unknown cause	9

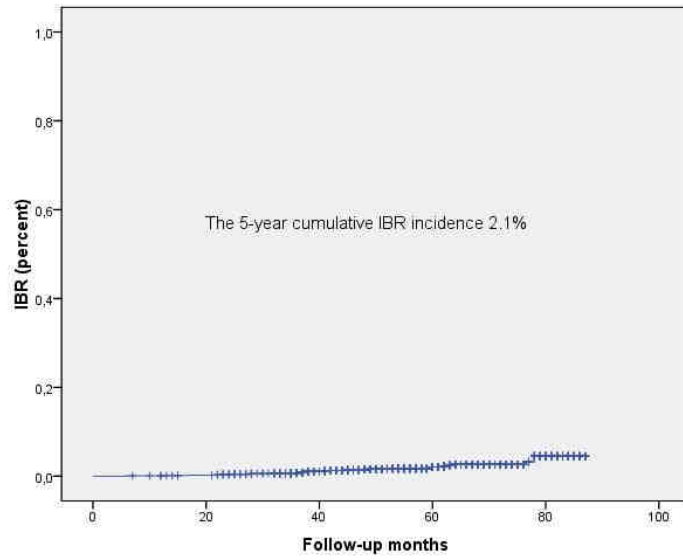
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**Table 4. The risk factors for ipsilateral breast recurrence (IBR) in the Cox proportional hazards**

Variable	IBRs	p	HR (95% CI)
at 5 years			
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Age at diagnosis (yrs)			
<40	3,0%	0.377	2,143 (0,395-11,631)
40-54	2,9%	0.992	1,056 (0,352-3,172)
55-70	1,0%	0.137	0,390 (0,113-1,347)
>70	3,4%	0.111	1
Biological subtype			
Triple negative	3,4%	0.118	0,145 (0,013-1,633)
ER+ HER2 +/-	2,0%	0.040	0,215 (0,049-0,935)
ER- HER2+	9,7%	0.108	1
Radiotherapy			
No	13,7%	0.007	10,344 (1,904-
56,184)			
Yes, no booster	1,7%	0.245	2,077 (0,606-7,120)
Yes, with booster	0,9%	0.019	1

Abbreviations: ER = oestrogen receptor, HER2 = human epidermal growth factor receptor-2,





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