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► To cite this version:

C. Eriksen, J. Frisell, M. Wickman, E. Lidbrink, K. Krawiec, et al.. Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study. *Breast Cancer Research and Treatment*, 2011, 127 (2), pp.439-446. 10.1007/s10549-011-1437-y. hal-00624173

HAL Id: hal-00624173

<https://hal.science/hal-00624173>

Submitted on 16 Sep 2011

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Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study

Eriksen C^{1,2,7}, Frisell J^{1,2,7}, Wickman M^{1,3,7}, Lidbrink E^{4,7}, Krawiec K^{5,7}, Sandelin K^{1,2,7}

Department of Molecular Medicine and Surgery, Karolinska Institutet¹, Department of Breast and Endocrine Surgery², Department of Reconstructive and Plastic Surgery³, Department of Oncology-pathology⁴, Department of Oncology⁵, Oncologic Centre⁶, Karolinska University Hospital, Stockholm⁷

Correspondence:

Catharina Eriksen
Department of Breast and Endocrine Surgery
Karolinska University Hospital
SE-117 76 Stockholm, Sweden
Telephone: +46 8 517 79910
Mail: catharina.eriksen@karolinska.se

Key words: breast cancer, immediate breast reconstruction, recurrence rate, oncological safety, ‘delay adjuvant treatment’, radiotherapy

Abstract

Background: Physicians are still concerned about the oncological safety regarding immediate breast reconstruction (IBR) in breast cancer patients. This study aimed to evaluate possible differences between local, regional and distant recurrences between women having implant-based reconstruction versus women operated with mastectomy alone. Secondary aims were to evaluate time to oncological treatment as well as disease-free and breast cancer specific survival. *Patients and methods:* In a retrospective cohort designed study, 300 reconstructed patients with invasive breast cancer were matched with 300 patients from the population-based Regional Breast Cancer Register of the Stockholm-Gotland health-care region operated with mastectomy alone. They were matched for age, tumor size, nodal stage and year of operation. Also included were patients treated with neoadjuvant chemotherapy and postoperative radiotherapy. The median follow-up for both groups was 11, 5 years (range 2-19). *Results:* There were no significant differences in the local recurrence rate, 8.2 % in the IBR group and 9.0 % in the control group or in the regional recurrence rate, 8.2 % versus 9.7 %. Distant metastases occurred more frequently in the control group (27.1 %) compared to the IBR group (20.3%). There were no significant differences in time to treatment or in complications rate. Breast cancer mortality was 17 % for the IBR group and 23 % in the control group during follow up. *Conclusion:* This long-term follow-up survey with a well matched control group demonstrates that IBR with implants is safe to offer patients with invasive breast cancer without any negative effect on the oncological safety.

Introduction

European guidelines are in agreement that breast reconstruction should be an integral part of breast cancer treatment [1-4]. Previous studies have suggested that after breast reconstruction, women with breast cancer have a better quality of life [5-8]. The timing and type of reconstructions can vary with local traditions but the demand for reconstruction is growing. Traditionally, women with ductal carcinoma in situ and T1-2 tumors are offered immediate breast reconstruction (IBR), while those presumed to receive radiotherapy or those with more advanced breast cancer usually are recommended to have delayed procedures [9-11]. The latter patients are often advised to wait for 1–2 years after adjuvant treatment before starting the reconstruction. This recommendation is often based on an increased risk of local recurrence during the first two years and concern that a reconstruction could hamper detection of a local recurrence. Another issue has been that IBR, especially autologous reconstructions, may influence the oncological treatment in that more extensive surgery with more potential complications such as an increased number of infections could delay adjuvant treatment [12, 13]. Other reasons for postponing immediate breast reconstruction are unsatisfactory cosmetic results in connection with radiotherapy and its administration [14, 15]. IBR with implants has several advantages over late breast reconstructions, such as fewer operations, no breast loss, less morbidity (no donor site), simpler surgical techniques and less expense [16]. Notwithstanding the lack of randomized controlled studies, breast reconstructions are increasing [1-4, 10]. Studies addressing the safety of IBR have shown varying rates of local recurrence [17-26]. As there may be a considerable interval before recurrences occur, confirmation of these results requires a long-term follow-up. There is also a lack of studies in this area, especially in patients receiving neoadjuvant chemotherapy and postoperative radiotherapy [27]. Karolinska University Hospital has 20 years of

experience of implant-based IBR and two previous studies showed low rates of local recurrences [28, 29]. The patients have also been investigated regarding postoperative complications, aesthetic results and quality of life [5, 30].

The principal aim of the study was to analyze the differences in local, regional and distant recurrences between women undergoing IBR and women operated with mastectomy alone. Oncological safety in terms of time to oncological treatment, disease-free survival and breast cancer specific survival in both groups was also evaluated.

Study design

The study is a matched retrospective cohort study.

Ethical approval

The study was approved by the Ethics Committee 2008, number 2008/767-31/4.

Patients and methods

Data collection: During the period 1990–2004, 475 consecutive patients operated with IBR at Karolinska University Hospital were prospectively registered in a hospital database. Only patients with invasive breast cancer and implant-based reconstruction were included, n=300. Patients operated with primary flap reconstruction were excluded and patients with earlier ipsilateral breast cancer were classified as local recurrence and were also excluded from the study. The patient match was performed 1:1 and concerned four categories: age, tumor size (0-20 mm, 21-50 mm, and > 50 mm), nodal status (0, 1-3, ≥4) and year of operation (+/- 3 years), Table I. The matched control group were identified via the population-based Regional Breast Cancer Register of the Stockholm-Gotland health-care region and consisted of 300 women undergoing mastectomy alone. The patients were followed until the end of June 2008. The median follow-up time for the IBR group was 12 years (range 4-18) and for the control group it was 11, 5 years (range 2-20 years). The median follow-up for both groups was 11.5 years (range 2-20). Type of

breast cancer (ductal, lobular and other), hormonal status (ER,PR +/-), time to oncological treatment, type of chemotherapy, radiotherapy and recurrence, time to recurrence, detection mode, disease free survival and breast cancer specific survival were registered and evaluated. Elston grade (I-III) was registered but not evaluated since the analysis was not performed on the majority of the tumors during the study period [31]. Early complications (< 30 days) like infections treated with intravenous antibiotics, re-operations due to bleeding or wound healing problems were registered. *Decision process for IBR:* All newly diagnosed breast cancer patients were discussed preoperatively and postoperatively at the multidisciplinary team conference. Patients with inflammatory breast cancer and tumors adhering to the pectoral muscle were not offered IBR. Similarly, women with a high body mass index and thus considered unsuitable for implant reconstruction and those who were heavy smokers were not recommended immediate reconstruction. Remaining cases where the woman wanted IBR, proceeded to operation. Clinical information, including recurrences and death, was retrieved from medical records (surgery, plastic surgery and oncological journals) and from the National Causes of Death Register. A local recurrence was defined as a relapse of cancer in the skin and the myocutaneous tissue of the chest wall. Regional recurrences were defined as a relapse in the ipsilateral axilla or in the supraclavicular nodes. All other relapses were defined as distant metastases. *Surgical procedure:* Initially the mastectomy incisions aimed to remove as much skin over the tumor as possible when reconstruction was concurrently done. After 1994, more tailor-made skin incisions were performed. Earlier scars and the nipple-areola complex were, however, always excised and the inner layer of the pectoral fascia was left intact in both groups unless there were macroscopic signs of tumor engagement of the muscle. Axillary surgery was performed as level I and II dissections and in 1998 the sentinel lymph node biopsy technique was introduced. *Surgical-*

reconstructive procedure: All patients in the IBR group were operated with permanent or expandable implants. The implants were placed submuscularly and a full muscle cover was always aimed for. All operations were performed by a limited number of breast as well as reconstructive plastic surgeons with extensive experience. One preoperative dose of penicillin V (Cloxacillin) and penicillin G (Benzyl penicillin) or Clindamycin was given exclusively to all patients in the IBR group and they also received low-molecular-weight heparin postoperatively. *Oncological treatment:* Oncological treatment was based on recommendations from the Regional Stockholm-Gotland Breast Cancer Study Group. *Chemotherapy:* The standard adjuvant chemotherapy was CMF (cyclophosphamid, 5-floururacil, and methotrexate) initially; after 1995 the standard regime was anthracycline-based therapy FEC (5-floururacil, epirubicin and cyclophosphamid). A small group received Taxane-based treatment, Table II. The treatment was given every third week in 6 cycles. Neoadjuvant chemotherapy was given to patients with large tumors (> 4 cm) and/or with clinically positive axillary nodes to decrease tumor burden and facilitate loco regional therapy. Based on clinical, pathological and radiological data, no response was defined as progressive or stabile disease, partial response as a decrease of the tumor and/or axillary nodes and complete response was defined as undetectable disease in the breast and the axilla. *Radiotherapy:* Local (chest wall) and locoregional (chest wall, axilla and supraclavicular lymph nodes) radiotherapy of 46 Gy was given in daily 2-Gy fractions with mostly tangential fields and in some cases with electron beams. *Hormonal treatment:* Patients with hormone receptor-positive tumors were offered Tamoxifen or Aromatase inhibitors in the latter part of the study. In the early stage of the study, patients were offered megestolacetate (Megace) as part of a study. Megace and Goserelin (Zoladex) are referred to as “other hormonal treatment” in Table II. *Follow-up:* The patients were reexamined at the Oncological Department every 3 months for the first 2

years and then every 6-12 months for a total of five years. Thereafter, patients with no sign of recurrences were discharged and referred to the general practitioners for further follow-up. Reconstructive revisions and assessments were performed by the reconstructive plastic surgeons.

Statistics

The McNemar test and the Stuart-Maxwell test were used for pairwise comparison of categorical variables. When pairwise comparison was not appropriate, Person's chi-square test for categorical variables and the Mann-Whitney-Wilcoxon test for continuous variables were performed. The Kaplan–Meier method was used to calculate disease-free survival as well as breast cancer specific survival. Hazard ratios and 95 % confidence intervals were estimated with the Cox proportional hazard regression model with stratification on the matched pairs. All statistical analyses were performed in STATA/IC statistical software, version 10.0 [31].

Results

The median age was 48 years in both groups and median tumor size was 19 mm in the IBR group and 20 mm in the control group. Node positive disease in the IBR and the control group was 36% and 36.7%, respectively. Lobular cancers were significantly more prevalent in the IBR group and there were also more hormone receptor-positive tumors in the IBR group, Table I. There were no significant differences between the two groups in the proportion of patients treated with neoadjuvant chemotherapy (13% versus 15,7%), or in those receiving adjuvant chemotherapy and postoperative radiotherapy. Patients in the IBR group received more hormonal treatment. Furthermore, there were no differences between the groups in postoperative early complication rates or in time to oncological treatment, Table II. Among the radiated patients, there were no significant differences in recurrences between the groups (Fig. 1).

The analysis of first events showed that the incidence of total recurrences was 28.4% in the IBR cohort and 32.8 % in the control group. Regarding total number of event there were no significant differences in either local recurrences in the breast (8.2% in the IBR group, 9.0% in the control group) or in the regional recurrence rate (8.2% and 9.7%, respectively) although distant metastases were significantly more frequent in the control group, $p=0.049$. Median time to detection of local recurrence was 1.3 years in the IBR group versus 2.2 years in the control group, Table III. The majority of local recurrences were detected by clinical examination (94%) and there were no significant differences between the two groups in the way regional recurrences and distant metastases were detected, Table III. The IBR group showed better survival than the controls, (Fig. 2 and 3). The differences between breast cancer mortality and all-causes mortality, were statistically significant, $p=0.038$ and 0.026 , Table IV.

Discussion

Since the introduction of IBR, oncological safety has been a debatable issue among physicians and patients and the information given to patients has varied with local traditions regarding knowledge, competence and financial resources. In order to evaluate the possible influence of a reconstructive procedure together with breast cancer surgery, a matched group of women with breast cancer without primary reconstruction was chosen as control. This long-term follow-up study provides evidence that IBR with implants can be considered a safe procedure regarding all oncological aspects. In this matched cohort study, no significant inter-group differences were found in the rates of local recurrence and regional recurrence. Neither were there any differences in the time to oncological treatment or in detection modes. The rate of distant metastases was significantly higher in the control group and the survival figures were better for the reconstructed group. These results are in line with other studies, possibly as a consequence of confounding factors

such as socioeconomic status and selection bias in inclusion criteria as IBR was usually not recommended for overweight patients and smokers [32, 33]. Our results also show that the reconstruction did not influence the start of oncological treatment or given dosages. In both groups the local recurrences were superficial and easy to detect, which is in accordance with other studies [23, 32, 34]. The study is retrospective and while the two groups were well-matched, there were more lobular cancers and a higher rate of hormone receptor-positive tumors among the IBR group. This could indicate an overrepresentation of tumors with a favorable prognosis in the IBR group. On the other hand, lobular carcinoma does not have a better prognostic clinical outcome or survival rate compared to ductal carcinoma [35]. We also performed a statistical correction for hormonal receptor-status which did not alter the results regarding recurrences, but the difference in breast cancer mortality risk was no longer significant. Another limitation is that complications are difficult to evaluate retrospectively and in the control group patients were discharged early and minor complications may have been taken care of by general practitioners. On the other hand the IBR group has been reviewed several times and clinical information was readily accessible from the charts [30]. We choose to report on early complications in order to show any possible effect on time to onset of oncological treatment in both groups.

A review from 2005 concluded that there was a lack of good-quality evidence of how to advise women considering IBR concerning the possible impact on adjuvant treatment and prognosis [13]. Since then, two long-term follow-up studies have been published with a median follow-up time of 5.7 years. In both these studies recurrence rates did not differ significantly between the IBR group and patients undergoing mastectomy alone [32, 34]. These results have since then been corroborated by two review articles, including a meta-analysis of nine non-randomized trials [27, 36]. The strength of our study is the long

follow-up time with a median of 11.5 years. The study was a matched cohort group of patients where both groups had similar rates of adjuvant treatment in terms of chemo- and/or radiotherapy. We also made a separate comparison of recurrences among the patients who had received radiotherapy and found no significant differences regarding local and regional recurrences between the IBR and the control group as this has been a concern [14-15, 37]. Many authors favor autologous tissue reconstructions for primary or delayed procedures. However, these techniques are less well investigated regarding oncological safety and more complications are known to occur [12, 13, 38]. Sentinel lymph node biopsy can be used to predict the need for postoperative radiotherapy and as a guideline in decision-making regarding reconstructive method and timing [39].

According to other studies presenting positive data regarding oncological safety and IBR, our experience is that IBR with implants can be used in combination with irradiation from an oncological point of view, although the aesthetic results tend to be inferior compared to non irradiated reconstructions [40, 41, 42]. Prospective studies are therefore still desirable, especially regarding advantages and disadvantages of breast reconstructions, radiation and which method can be considered oncological safe and aesthetically favorable in the long run.

Conclusion

This long-term follow-up study (median 11.5 years) with a well-matched control group demonstrates that IBR with implants can be offered to and performed on patients with invasive breast cancer without any negative effect on oncological safety.

Acknowledgements

The study was supported by grants from BRO (Swedish Breast Cancer Association) and from Olle Engkvist Foundation. The authors are grateful to Associate Professor Birgit Stark Department of Reconstructive and Plastic Surgery for valuable comments.

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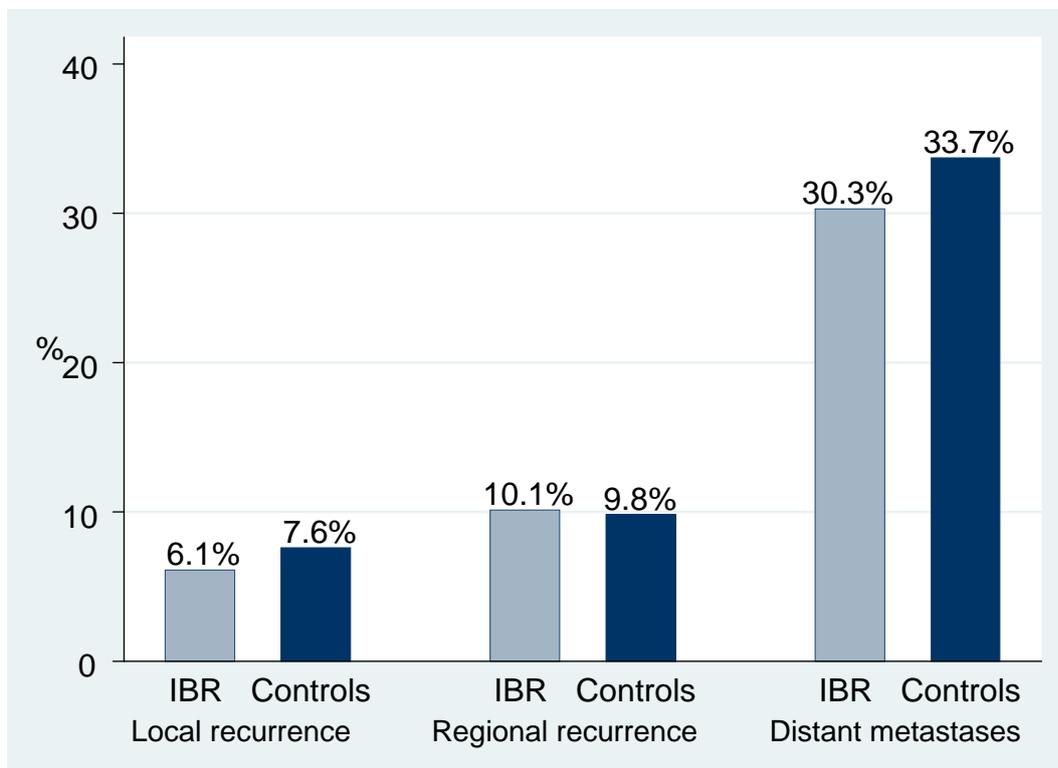


Fig.1 Recurrences in patients treated with radiotherapy. Immediate breast reconstruction (IBR) (n=119) and controls (n=115).

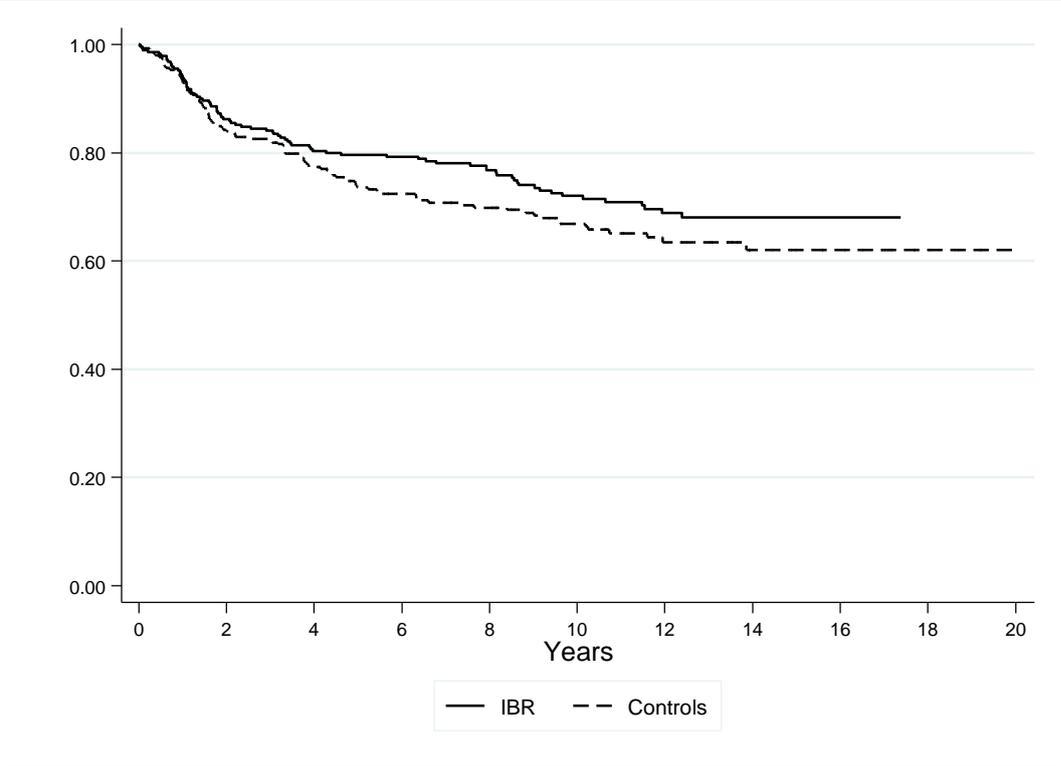


Fig. 2 Kaplan-Meier disease free survival curves. IBR=Immediate breast reconstructions. (IBR followed for 18 years and controls followed for 20 years)

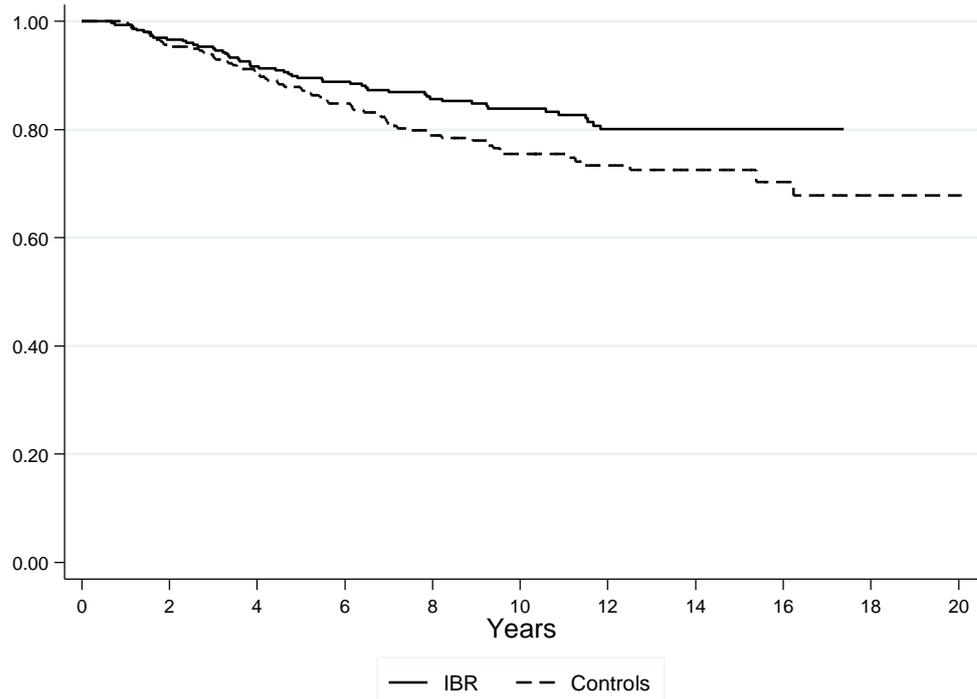


Fig. 3 Kaplan-Meier breast cancer specific survival curves. IBR=Immediate breast reconstructions. (IBR followed for 18 years and controls followed for 20 years)

Table I. Patients' clinical and histopathological characteristics

	IBR n = 300	Controls n = 300	p-value
Age (%)			
21-40	21.7	20.3	
41-60	71.3	72.3	
61-70	7.0	7.3	
Median, years	48	48	
Range, years	23-70	28-69	
Year of operation (%)			
IBR		Controls	
1990-1994	33.7	1988-1994	34.0
1995-2000	51.0	1995-2000	46.0
2001-2004	15.3	2001-2006	20.0
Tumor size (%)			
≤ 20	63.7	61.0	
21-50	33.0	35.0	
> 50	3.3	4.0	
Median (mm)	19	20	
Range (mm)	0-100	0-90	
Lymph nodes (%)			
0	64.0	63.3	
1-3	23.0	22.0	
≥4	13.0	14.7	
Morphology (%)			
	n = 291	n = 283	
Ductal	66.3	79.9	0.003 ¹

Lobular	27.2	16.2	
Other	6.5	3.9	
Hormone receptor status (%)			
	n = 274	n = 287	
ER +	79.9	68.6	0.003 ²
	n = 251	n = 275	
PR +	71.3	61.1	0.008 ²

Immediate breast reconstruction (IBR), estrogen receptor (ER), progesterone receptor (PR). ¹ Stuart-Maxwell test,

²McNemar chi-square test

Table II. Oncological treatment, time to treatment and complications

	IBR n = 300	Controls n = 300	p-value ¹
Neoadjuvant chemotherapy (%)	13.0	15.7	0.346
CMF	1.7	0.0	0.025
FEC	10.7	13.7	0.249
Taxane-based	0.0	1.0	0.083
Other	1.0	1.3	0.706
Response (%)			
	n = 37	n = 44	
No	13.5	15.9	1.000 ²
Partial	78.4	77.3	
Complete	8.1	6.8	
Adjuvant chemotherapy (%)			
	n = 292	n = 290	
Adjuvant chemotherapy	45.2	47.6	0.431
CMF	18.8	15.5	0.325
FEC	21.9	23.8	0.558
Taxane-based	2.7	3.8	0.285
Other	1.4	2.1	0.480
Completed chemotherapy (%)			
	n = 122	n = 119	
Full dose	94.3	92.4	0.569 ²
Time to chemotherapy (weeks)			
	n = 112	n = 105	
Median	5.0	5.1	0.376 ²
Range	2-22	2-33	
Hormonal treatment (%)			
	n = 283	n = 273	
Hormonal treatment	73.9	66.3	0.103
Tamoxifen	68.2	60.4	0.100
Aromatase inhibitors	4.6	5.1	0.842
Other	12.0	12.1	0.456
Completed hormonal treatment (%)			
	n = 198	n = 171	
	88.9	85.4	0.313 ²
Radiotherapy (%)			
	n = 289	n = 284	
Radiotherapy	34.3	32.8	0.825
Local	5.2	1.4	0.046
Loco regional	28.4	29.6	0.808
Localization unknown	0.6	1.8	
Time to radiotherapy (weeks)			
	n = 86	n = 70	
Median	24.1	24.7	0.902 ²
Range	6-48	5-42	
Complications < 30 days (%)	7.3	6.3	0.622

Immediate breast reconstruction (IBR), cyclophosphamid, 5-floururacil, and methotrexate (CMF), 5-floururacil, epirubicin and cyclophosphamid (FEC). ¹ McNemar chi-square test unless otherwise stated, ² Person's chi-square test for categorical variables; Mann-Whitney-Wilcoxon test for continuous variables

Table III. Incidence, detection mode and time to detection of recurrence

	Total number of events			First event		
	IBR	Controls	p-value ¹	IBR	Controls	p-value ¹
Overall recurrence (%)	28.4	32.8	0.239			
Local recurrence (%)	8.2	9.0	0.879	6.9	6.4	0.590
Time to detection (years)						
Median	1.3	2.2	0.763 ²	1.3	1.6	0.673 ²
Range	0.2-11.9	0.5-11.6		0.2-11.9	0.5-11.6	
Regional recurrence (%)	8.2	9.7	0.555	6.5	6.4	1.000
Time to detection (year)						
Median	4.8	1.6	0.008 ²	2.6	1.5	0.014 ²
Range	0.1-12.5	0.3-11.0		0.1-11.5	0.3-5.5	
Distant metastases (%)	20.3	27.1	0.049	14.8	20.1	0.081
Time to detection (year)						
Median	2.7	3.3	0.372 ²	2.3	3.3	0.288 ²
Range	0.0-12.4	0.0-13.9		0.0-12.4	0.0-13.9	
Recurrence detected with (%)						
Image guided radiology	53.8	63.2	0.241 ²			
Clinical examination	46.2	36.8				

Immediate breast reconstruction (IBR). ¹ Memar chi-square unless otherwise stated, ² Person's chi-square test for categorical variables; Mann-Whitney-Wilcoxon test for continuous variables

Table IV. Hazard ratio and confidence interval in total number of events

	IBR	Controls	Hazard rate ratio* (95% CI)	p-value
<i>Total number of events</i>				
Overall recurrence (%)	28.4	32.8	1.2 (0.9-1.7)	0.301
Local recurrence (%)	8.2	9.0	1.0 (0.5-1.8)	1.000
Regional recurrence (%)	8.2	9.7	1.5 (0.8-2.8)	0.173
Distant metastases (%)	20.3	27.1	1.4 (1.0-2.1)	0.070
Death, all causes (%)	22.0	28.0	1.5 (1.0-2.1)	0.038
Death, breast cancer (%)	17.0	23.0	1.6 (1.1-2.4)	0.026

*Controls versus immediate breast reconstruction (IBR)