Does Immediate Breast Reconstruction after Mastectomy and Neoadjuvant Chemotherapy Influence the Outcome of Patients with Non-endocrine Responsive Breast Cancer?

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Abstract. *Background/Aim: In breast cancer (BC) patients, breast surgery followed by immediate breast reconstruction (IBR) might favour recurrences and metastases due to extensive surgical manipulation. We retrospectively investigated whether IBR after mastectomy and neoadjuvant chemotherapy (NT) influenced the outcome in patients with early and locally advanced oestrogen receptor (ER)-negative BC. Patients and Methods: Between 1995 and 2006, 133 BC patients received NT followed by total mastectomy, 59 of whom underwent IBR. Patients receiving IBR (IBR group) were compared to patients who did not receive IBR (no-IBR group) over a prolonged median follow-up time (8.2 years). Results: Patients receiving IBR were on average younger than patients not receiving IBR (p<0.001). The percentage of patients with positive clinical nodal status (cN) was 19% in the IBR group and 7% in no-IBR group (p=0.036), whereas patients without IBR were more frequently diagnosed as clinical T4 (59% vs. 15%, p<0.001). The 5-year cumulative incidence of locoregional recurrences were 14% in the no-IBR group and 21% in the IBR group. The hazard of locoregional events, adjusted for age, clinical T and cN, was significantly greater in the IBR group than in the no-IBR group (hazard ratio (HR)=2.77, p=0.045). The 5-year cumulative incidences of distant metastases were similar in the two groups (p=0.414). Conclusion: IBR following total mastectomy in patients with ER-negative disease after NT is associated with a worse rate of local relapses. More insight in mechanisms of wound healing and extent of surgery is required to further investigate this observation.*

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Key Words: Immediate breast reconstruction, non-endocrine responsive patients, invasive breast cancer, locoregional recurrence.

Mastectomy with immediate breast reconstruction (IBR) is a treatment option for patients with breast cancer (BC) when breast-conserving surgery is not feasible.

IBR has been associated with patient satisfaction (1, 2), improvement in quality of life (3) and no detrimental effect on survival outcomes (4).

As yet, very few data have been published upon IBR in BC patients treated with neoadjuvant chemotherapy (NT) (5), especially for restricted to hormone receptor negative tumors and within studies with biologically heterogeneous populations.

Evidence suggests that extended breast surgery may induce stimulation of residual cancer cells through angiogenic cytokine release (6, 7).

We hypothesized that breast surgery followed by IBR might further stimulate abnormal cell proliferation through growth factor release due to extensive surgical manipulation, compared to total mastectomy-alone. This effect might be more striking in a sub-population with endocrine non-responsive disease. Moreover the possible correlation with NT has never been widely investigated.

In the present study, non-endocrine responsive BC patients were submitted to IBR after total mastectomy and NT, and were compared to patients who did not receive IBR (control group) retrospectively to assess locoregional recurrence, distant metastases and survival outcomes.

Patients and Methods

Patients, inclusion criteria and treatment approaches. From 1995 to 2006, at the European Institute of Oncology, Milan, a total of 133 non-endocrine responsive BC patients received NT (taxanes plus anthracyclines alone), total mastectomy and complete axillary dissection. Fifty-nine patients of the whole cohort were submitted to IBR, 28 with prosthesis, 27 with expander (after removal, 13 were submitted to reconstruction with prosthesis, one with transverse rectus abdominus myocutaneous (TRAM) flap; no data were available for 13 patients) and 4 immediately with TRAM flap reconstruction, respectively.

Only patients with invasive BC hormone receptor-negative underwent mastectomy after NT were eligible for analysis; no previous diagnosis of BC was permitted. Patients with distant metastases and supraclavicular lymph nodes were not eligible and patients with inflammatory BC were excluded. Eligible patients were those who could receive contralateral reduction mastoplasty and mastopexy.

Indication for IBR was planned on a case by case basis during a weekly multidisciplinary panel of experts, including oncologists, radiologists, cytopathologists, surgeons and reconstructive surgeons; guidelines for IBR after neoadjuvant therapy did not exist. Patient preference, panel opinion and the cosmetic outcome were carefully taken into consideration; in our Institute the reconstructive procedure is discussed as routine within BC treatment. Clinical tumor size and nodal status (cN) were the categories basically assessed to select or not patients for IBR. Tumors less than or equal to T3 and negative cN were preferred. Systemic treatments and human epidermal growth factor receptor 2 (HER2) status did not hamper the decision process for IBR.

The indication for adjuvant radiotherapy was based on lymph node status and tumor size, both assessed pre- and post-mastectomy. IBR did not represent a contraindication for subsequent radiotherapy, however high risk of capsular contracture existed and flap reconstructions were usually preferred when RT was indicated.

Concerning chemotherapy as adjuvant, metronomic cyclophosphamide (50 mg *per os* (*p.o.*) daily) and methotrexate (2.5 mg *p.o.*) twice daily on day 1 and day 4 weekly) were given. All patients were followed every six months with clinical and radiological controls. Mammography on the contralateral breast was performed every year, bilateral breast ultrasound every six months, liver ultrasound every year and biological markers every six months.

Statistical methods. Differences in the distribution of subject characteristics between groups were evaluated by the Chi-square test.

The endpoints evaluated were disease-free survival (DFS), overall survival (OS), cumulative incidence of local or regional recurrence (CI-LR) and distant metastases (CI-DM).

DFS was defined as the time from surgery to events such as relapse (including ipsilateral breast recurrence), appearance of a second primary cancer (including contralateral breast cancer) or death, whichever occurred first. OS was defined as the time from surgery until the date of death (from any cause). The DFS and OS functions were estimated using the Kaplan–Meier method. The CI-LR and CI-DM were defined as the time from the date of surgery to a local or regional recurrence and a distant metastasis, respectively. The CI-LR and CI-DM functions were estimated according to methods described by Kalbfleisch and Prentice (8), taking into account the competing causes of recurrence.

Table I. *Demographic, clinical and pathological characteristics and local and systemic treatments of the 133 patients, categorized as either not receiving or receiving an immediate breast reconstruction (IBR).*

	Without IBR (N=74) N (%)	With IBR (N=59) N (%)	*p*-Value*
Age class (years)			
<35	3 (4)	19 (32)	<0.001
35-49	25 (34)	28 (48)	
50-59	34 (46)	9 (15)	
60-69	9 (12)	2 (3)	
70+	3 (4)	1 (2)	
Menopausal status			
Pre-menopausal	28 (38)	40 (68)	<0.001
Post-menopausal	46 (62)	19 (32)	
Histotype			
Ductal	65 (88)	56 (95)	0.197
Lobular	4 (5)	1 (2)	
Other	5 (7)	2 (3)	
Multicentric/Multifocal			
No	55 (74)	48 (81)	0.335
Yes	19 (26)	11 (19)	
Clinical nodal status			
Unknown	12 (16)	9 (15)	0.036
Negative	57 (77)	39 (66)	
Positive	5 (7)	11 (19)	
Clinical T			
Unknown	2 (3)	6 (10)	<0.001
T1-T2	11 (15)	22 (37)	
T3	17 (23)	22 (37)	
T4	44 (59)	9 (15)	
Perivascular invasion			
Absent	33 (45)	26 (44)	0.417
Focal	12 (16)	11 (19)	
Moderate	8 (11)	2 (3)	
Extensive	21 (28)	20 (34)	
HER2 overexpressed			
Unknown	10 (13)	9 (15)	0.334
Intense and complete	34 (46)	22 (37)	
Not Expressed	30 (41)	28 (48)	
KI-67			
Unknown	5 (7)	1 (2)	0.402
<14%	12 (16)	7 (12)	
>=14%	57 (77)	51 (86)	
Adjuvant local and systemic treatment			
Radiotherapy	53 (72)	21 (36)	<0.001
Chemotherapy	70 (95)	54 (91)	0.483
Trastuzumab	7 (9)	7 (12)	0.653

*Unknown are not considered in the *p*-value calculation.

The prognostic impacts of IBR on DFS, OS, cumulative incidence of locoregional recurrence and cumulative incidence of distant metastases were estimated by the multivariable Cox proportional hazards regression model, controlled for age at diagnosis, clinical tumor size (cT) and cN. Model-based hazard ratios (HR) with 95% confidence intervals (CI) were presented.

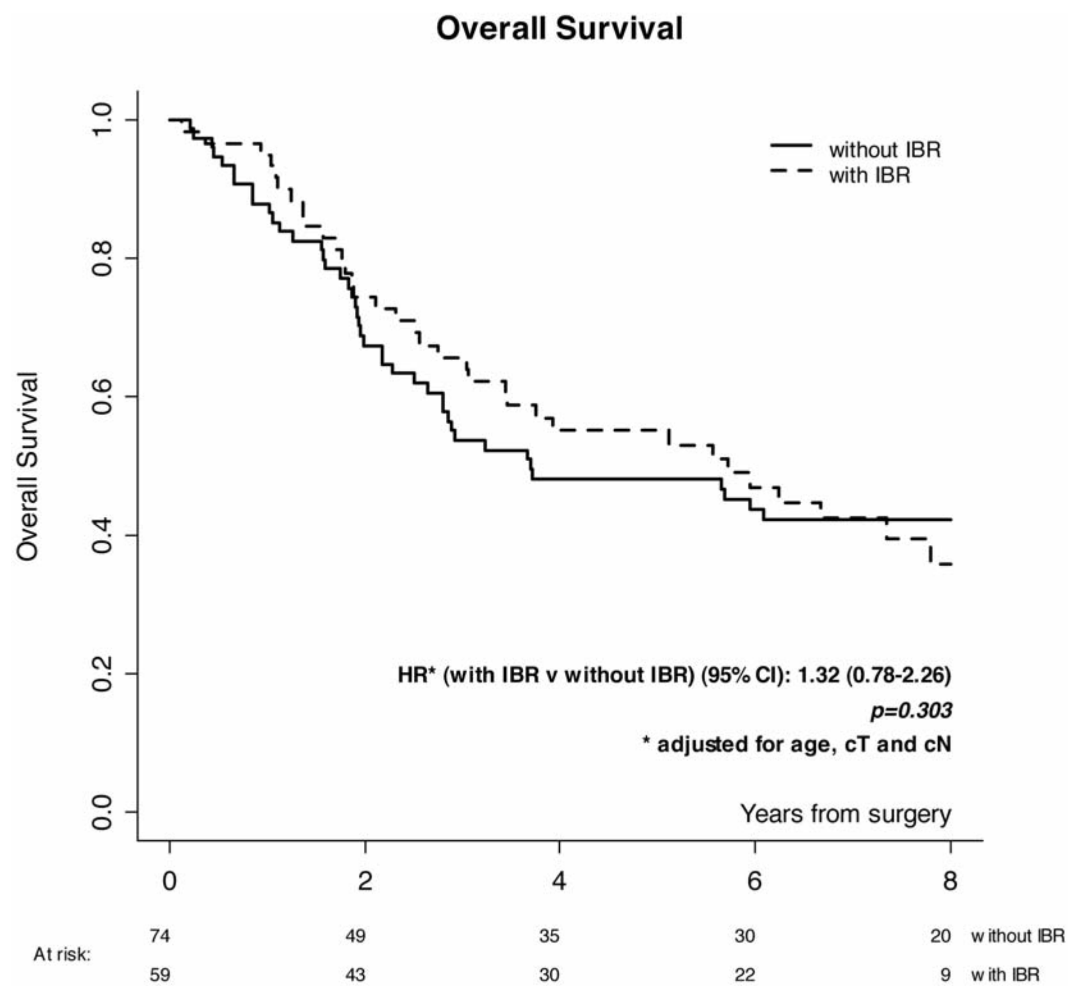

Figure 1. *Overall survival, by IBR status. Hazard ratio (HR), 95% confidence interval (CI) and p-value, adjusted for age, cT and cN, are reported.*

The analyses were carried-out with the SAS software (SAS Institute, Cary, NC, USA). All reported *p*-values are two-sided.

Results

Demographic, clinical and pathological characteristics and local and systemic treatments of the 133 patients are shown in Table I, categorized as either receiving (N=59) or not (N=74) IBR.

No significant differences between the IBR group and no-IBR group could be found in terms of histologic type, presence of multicentric/multifocal lesions, perivascular invasion, HER2 overexpression and Ki-67 score. Patients receiving IBR were on average significantly younger than patients not receiving IBR ($p<0.001$). Accordingly, menopausal status was significantly associated. The percentage of patients with positive cN was higher in the IBR group (7% in the no IBR group *vs*. 19% in IBR group, $p=0.036$), while patients without IBR were more frequently diagnosed as clinical T4 (59% in the no IBR group *vs*. 15% in IBR group, $p<0.001$).

Fifty-three patients in the no-IBR group (72%) and 21 patients in the IBR group (36%) received radiotherapy ($p<0.001$); 70 (95%) and 54 (91%) received chemotherapy in the no-IBR and IBR group, respectively ($p=0.483$). Only 7 patients (9%) and 7 patients (12%) received trastuzumab in the no IBR and IBR group, respectively ($p=0.653$).

Two patients with pathological complete response to NT were observed in the IBR group (2%) *vs*. none in the no-IBR group. Twenty-six (44%) partial responses were observed in the IBR group *vs*. 30 (41%) in the no-IBR group. The difference in response rates between the two groups was not statistically significant ($p=0.236$).

After a median follow-up of 8.2 years, 53 (72%) and 43 (73%) first events were observed in the no-IBR group (10

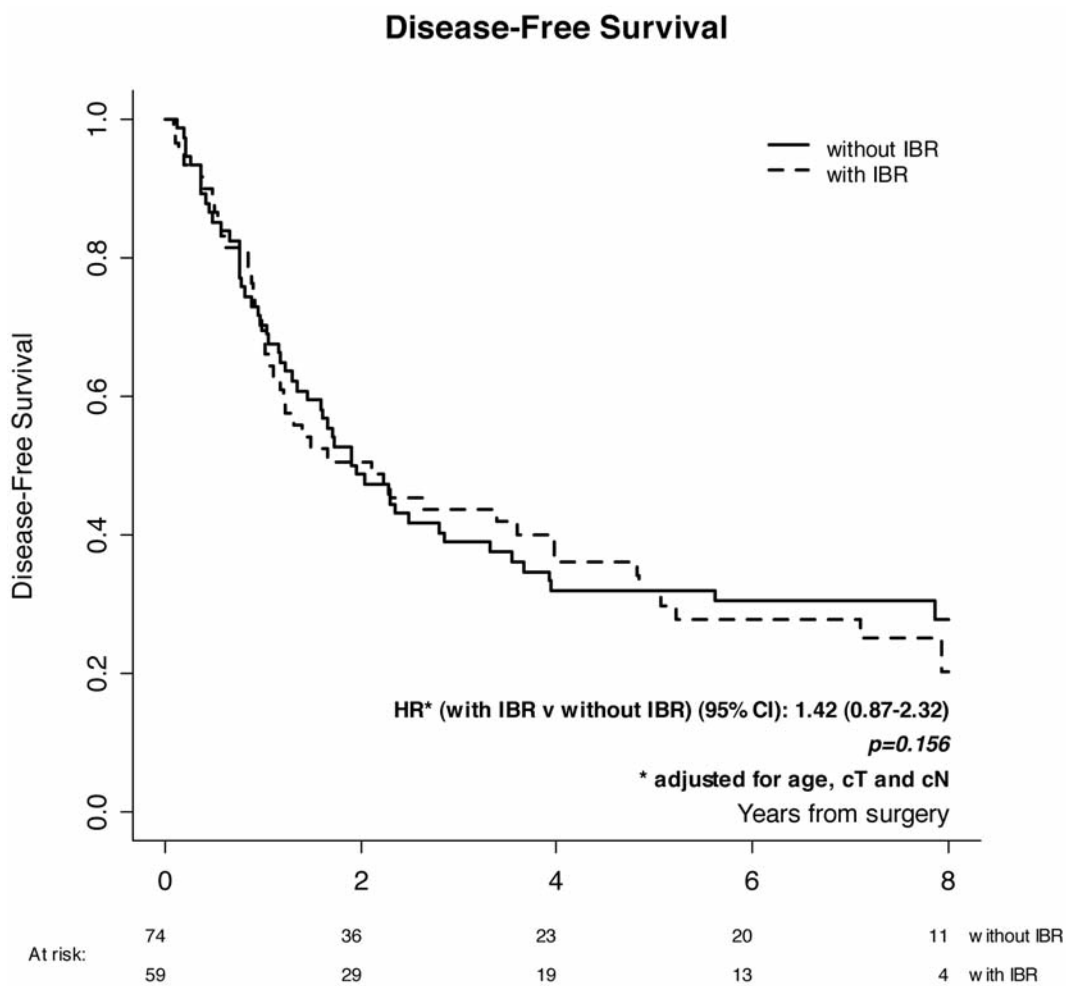

Figure 2. *Disease-free survival, by IBR status. Hazard ratio (HR), 95% confidence interval (CI) and p-value, adjusted for age, cT and cN, are reported.*

local and regional events, 33 distant metastases and 10 other events) and the IBR group (13 local and regional events, 27 distant metastases and 3 other events), respectively. Forty-four (59%) and 35 (59%) patients died during the follow-up in the no-IBR group and the IBR group respectively.

The Kaplan–Meier curves for OS and DFS and the cumulative incidence of locoregional recurrences and distant metastases, according to IBR status, are displayed in Figures 1 to 4. HR estimated from multivariable analyses, adjusted for age, cT and cN, are also presented.

The 5-year OS proportions were 48% (95%CI=36%-59%) in the no-IBR group and 55% (95%CI=41%-67%) in the IBR group (Figure 1). The 5-year DFS proportions were 32% (95%CI=22%-43%) in the no IBR group and 32% (95%CI=20%-44%) in the IBR group (Figure 2). The estimated hazards of death and of first event were greater in the IBR group than in the no IBR group (HR for death=1.32 and HR for first event=1.42) but they were not statistically significant (p=0.303 for OS and p=0.156 for DFS).

The 5-year cumulative incidences of local or regional recurrences were 14% (95%CI: 6%-22%) in the no-IBR group and 21% (95%CI=10%-31%) in the IBR group (Figure 3). The estimated hazard of loco-regional event was significantly greater in the IBR group than in the no-IBR group (HR=2.77, p=0.045). The observed difference between the two incidence curves was mainly due to an increase of early local and regional relapses (*i.e.* observed within two years after surgery) in the IBR group.

The 5-year cumulative incidences of distant metastases were 42% (95%CI: 31%-53%) in the no-IBR group and 46% (95%CI=32%-59%) in the IBR group (Figure 4). The estimated hazard of distant metastases was not significantly greater in the IBR group than in the no IBR group (HR=1.29, p=0.414).

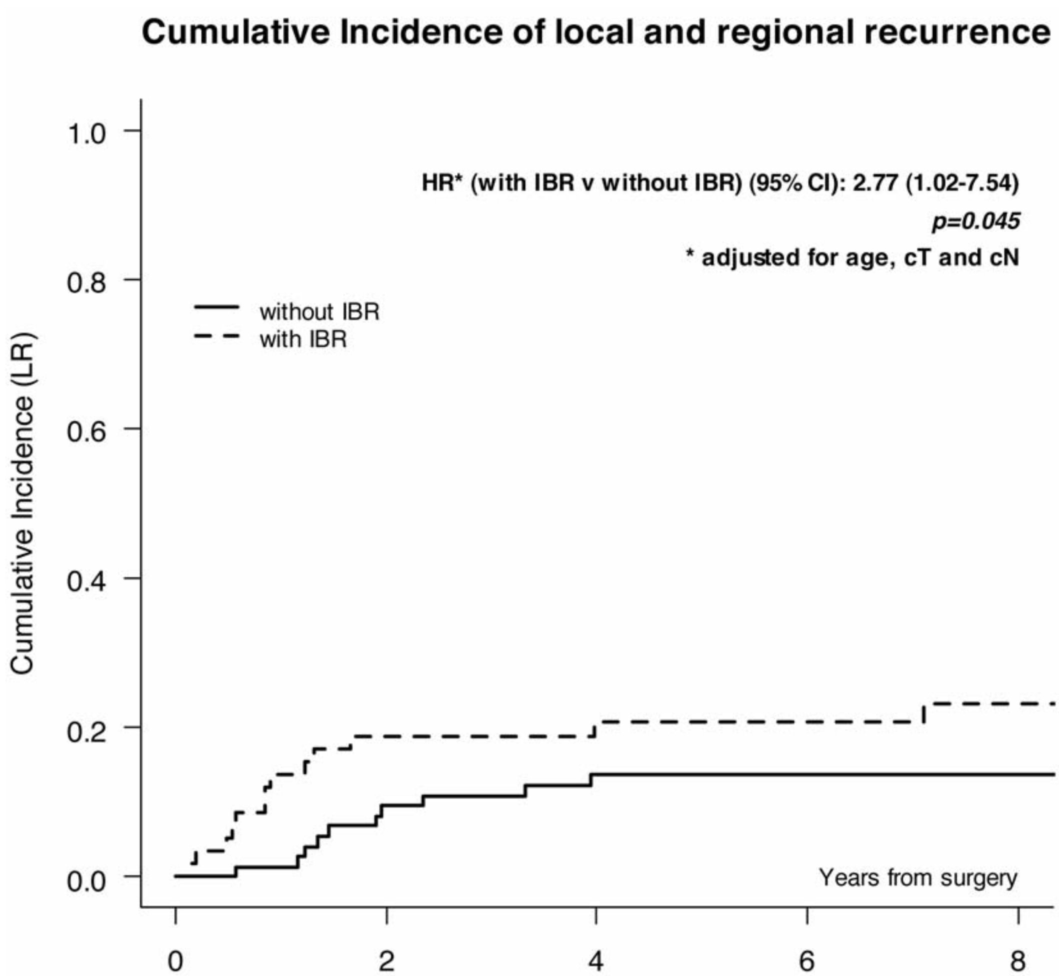

Figure 3. *Cumulative incidence of local and regional recurrence, by IBR status. Hazard ratio (HR), 95% confidence interval (CI) and p-value, adjusted for age, cT and cN, are reported.*

Although not significant, the use of radiotherapy did not seem to improve the non-favorable trend for the IBR group (Figure 5).

Discussion

In our series of 133 BC patients submitted to total mastectomy after NT, 59 of whom underwent IBR, the reconstructive procedure seems to be associated to a worse rate of locoregional recurrences with borderline significance, while significantly negative conclusions with regard to survival outcomes were not observed.

To our knowledge, this is the largest published series addressing the role of IBR after preoperative treatment, no previous study in patients with and without IBR has explored such topic in ER negative tumors.

Extensive surgical manipulation (mastectomy plus IBR) might be theoretically disadvantageous as hypothesized above, certainly tumor biology is not a secondary concern. To this end, Kneubil *et al*. assessed the incidence of locoregional recurrence in a large series of consecutive BC patients according to pathological features and demonstrated higher 5-year cumulative incidence of locoregional recurrence (11%) for triple-negative tumors (ER negative, progesterone receptor (PgR)-negative and HER2-negative) (9). In our analysis nearly two-thirds of the study population was triple-negative.

Interestingly, the incidence rate of loco-regional recurrence was greater in patients with IBR than in patients without IBR within the first two years after reconstruction, while remained similar among the two groups afterwards (Figure 3). This observation is in agreement with the difference, slightly in favour, of the group without IBR we

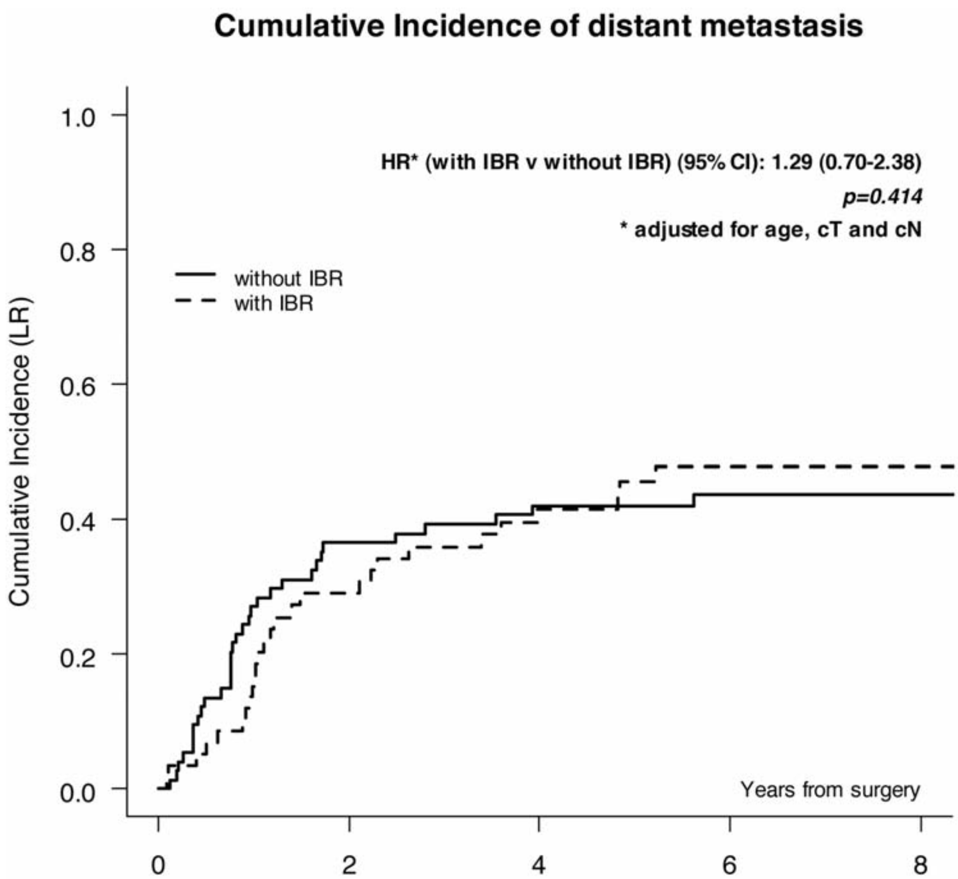

Figure 4. *Cumulative incidence of distant metastasis, by IBR status. Hazard ratio (HR), 95% confidence interval (CI) and p-value, adjusted for age, cT and cN, are reported.*

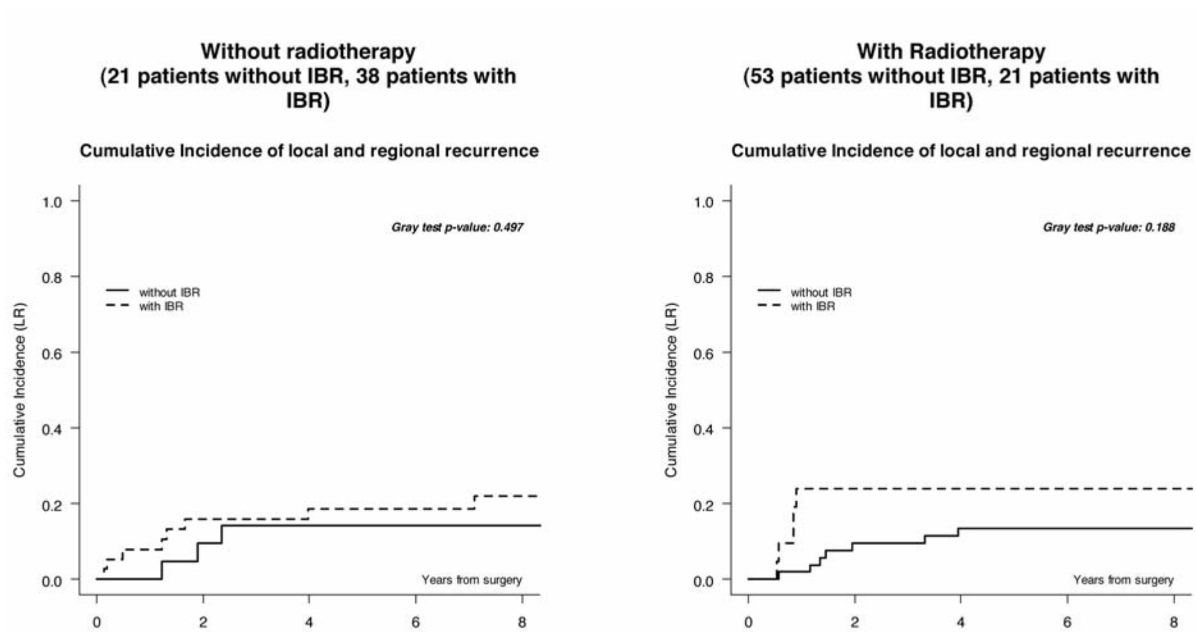

Figure 5. *Cumulative incidence of locoregional recurrence: stratified analysis for radiotherapy.*

observe in DFS (Figure 2). Furthermore, these data are in line with Sandelin *et al*. (10) who documented that most recurrences occurred within 24 months after IBR.

Of interest, the cumulative incidence of distant metastases between the two groups (Figure 4) was higher for the IBR group after 5 years and the difference was steadily retained until 8 years after reconstruction; however, without any statistical significance.

Intriguingly, the clinical response to intravenous chemotherapy as neoadjuvant did not influence the decision of performing IBR, since both groups did not show meaningful differences in response rates.

The impact of radiotherapy on IBR is still a controversial issue. Evidence supports the treatment with a breast prosthesis without affecting the dosage schedule and/or increased morbidity (11, 12). In our analysis, one third of the IBR group patients received radiation therapy implying that the higher cumulative incidence of locoregional events in the IBR group is likely due to the low dosages received. Therefore, we believe that patient selection for IBR is crucial and cT, for instance, must be previously carefully evaluated. The reconstructive surgeon should confer with others team members a treatment suitable for the stage of cancer and other characteristics at diagnosis.

One of the strengths of our study is the long follow-up time with a median of 8.2 years and the biologically-homogenous series, referring to hormone receptor negative status. Conversely, the retrospective nature of such study, the two not well-matched groups and the lack of data of final reconstruction for 13 patients are intrinsic drawbacks. The unbalanced indication of radiotherapy in the two groups (knowing the role of radiotherapy to decrease the risk of LR) has also to be considered.

The potential advantages and disadvantages of IBR and the optimal timing and method of radiation could be better assessed in prospective studies; however, a retrospective controlled study, such as the one presented in this paper, based on data collected on all patients consecutively operated in a single institution and where all patients were actively followed-up, could yield useful and reliable prognostic information in breast cancer patients who underwent IBR.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Received July 3, 2014
Revised August 4, 2014
Accepted August 6, 2014