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Pathological complete response after preoperative systemic therapy and outcome: relevance of clinical and biological baseline features

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ABSTRACT

Purpose: To evaluate the outcome of patients with breast cancer according to response after primary therapy and according to clinical and biological baseline features.

Patients and methods: We identified patients treated with preoperative therapy and who underwent surgery at the European Institute of Oncology (IEO), Milan, Italy, between 1995 and 2006. The outcome of patients who achieved pathological complete remission (pCR) and patients with residual disease (RD) at final surgery was analyzed.

Results: Of 687 patients treated with preoperative therapy we identified 82 patients who achieved pCR (12%) and 605 patients with RD (88%).

A statistically significant difference in disease-free survival (DFS), distant disease free survival (DDFS), and overall survival (OS) was observed for patients with pCR compared with those who had RD (5 year DFS 73% vs. 59% $p = .029$; 5 year DDFS 81% vs. 72% $p = .085$; 5 year OS 88% vs. 77% $p = .033$). At the multivariate analysis, for patients achieving pCR, large tumor size (> 5 cm) correlated with worse DFS (HR 3.18; 95% CI 1.34-7.51); clinical nodal involvement was associated with poorer DFS and DDFS (HR 6.94; 95% CI 1.62-29.73 and HR 9.87 95%CI 1.29-75.53 respectively).

Conclusions: pCR after preoperative systemic therapy correlated with significant improved outcome. A substantial rate of relapse was observed for patients with large tumours and with clinical nodal involvement at baseline. Further improvement in adjuvant treatment might be warranted.

Introduction

Preoperative chemotherapy might be advantageous in order to acquire early information on disease response. In fact, the response to the primary treatment may be used as a prognostic marker, since it has been demonstrated to be associated with a longer disease free survival (DFS) compared with no-response [1-6]. In particular, the degree of response [pathological complete remission (pCR)] predicts overall outcome in terms of DFS [4]. Several large randomized studies have shown that patients achieving a pCR to chemotherapy have far better long-term survival than those who fail to respond to primary chemotherapy (incomplete responders) [7,8]. In particular, excellent overall survival was observed in a recent report for patients who achieved pCR, irrespective of endocrine responsiveness and HER2 expression [7]. However, a large variation in the outcome of patients achieving a pCR was reported in the past, possibly related to different definitions of pCR and features of patients included.

Furthermore, not all patients who achieve a pCR remain free of recurrence and the identification of patients at high risk of relapse, among those who achieve a pCR, remains most difficult task. Indeed, the selection of factors predictive of responsiveness and related outcome to specific neoadjuvant and adjuvant treatment programs continues to represent a major research issue. Intrinsically different subtypes of breast cancer have been identified in the past years based on gene expression profiles and immunohistochemical (IHC) localization of selected targets which might influence the responsiveness to preoperative therapies and the outcome after surgery [9-12].

The aim of this retrospective study is to evaluate, in a large series of patients who were homogeneously diagnosed and treated in a single institution, the outcome of patients who achieved pCR or presented residual disease (RD) at final surgery, according to the clinical and biological baseline features. We conduct the analyses according to REMARK recommendations [13].

Materials and methods

Patients

For the present study we considered eligible breast cancer patients who underwent radical surgery at the IEO after primary chemotherapy.

Other eligibility criteria for the study included no previous chemotherapy/hormone therapy, performance status 0-2 (ECOG scale) and measurable lesions.

Patients were treated under best known multidisciplinary management. All patients received preoperative chemotherapy (plus/minus endocrine therapy) and adequate local treatment.

Patients were treated with preoperative chemotherapy given in 3-week courses. Patients with partial remission or complete remission were candidates to receive a maximum of 8 courses. The regimens used during the conduct of the study included anthracycline-containing, taxane-containing and navelbine-containing regimens, as previously reported [14].

Postoperative local-regional irradiation (RT) was proposed to all patients who underwent conservative surgery and to patients with cT4 disease and whenever indicated.

The selection of adjuvant systemic treatment was based upon indicators of responsiveness to treatment (endocrine responsiveness of the tumor) and evaluation of risk. For patients with endocrine-responsive disease, adjuvant endocrine therapy alone, according to menopausal status was prescribed (tamoxifen or aromatase inhibitor) for a duration of 5 years in postmenopausal patients, while the combination of tamoxifen for 5 years plus gonadotropin-releasing hormone analogues for at least 2 years in premenopausal patients [15]. For patients who achieved pCR with non-endocrine responsive disease, adjuvant metronomic chemotherapy for 4-6 months was proposed.

Specimen characteristics and assay methods

This is a single institution study. All patients had pathological evaluation performed at diagnostic core biopsy and at final surgery at the IEO.

Surgical specimens were extensively sampled for the evaluation of residual tumor after primary chemotherapy. In cases of lack of gross evidence of tumor the quadrantectomy specimens were entirely embedded in paraffin blocks and examined histologically, as were the tumor-bearing quadrants of the mastectomies. In the latter cases, the other quadrants were also thoroughly evaluated with the examination of at least three tissue blocks.

Pathological complete remissions (pCR) were evaluated according to the criteria of Kuerer et al. [4]. In particular the absence of invasive cancer on both the primary breast tumor and axillary lymph nodes qualified for pCR.

Immunostaining experiments for the localization of ER and PgR, HER2 protein and Ki-67 antigen were performed on consecutive tissue sections from the tumor-containing blocks, as previously reported [14]. The immunostained slides were re-evaluated independently by two of the pathologists. The following primary antibodies were used: the monoclonal antibody (MAb) to ER (clone 1D5; Dako, Glostrup, Denmark at 1/100 dilution), the Mab to PgR (clone 1A6, Dako, at 1/800 dilution), the MIB-1 Mab to the Ki-67 antigen (Immunotech, Marseille, France, 1/1200), and the polyclonal antibody (Dako, 1/3200) to the HER2 protein.

Only nuclear reactivity was taken into account for ER, PgR, and Ki-67 antigen, whereas only an intense and complete membrane staining in >10% of the tumor cells qualified for HER2 overexpression (3+). The results for ER, PgR and Ki-67 were recorded as the percentage of immunoreactive cells over up to 2,000 neoplastic cells. The value of 20% for Ki-67 labelling index (LI) was used as a cut-off in distinguishing tumors with low (<20%) and high (>20%) proliferative fraction [14]. Steroid hormone receptors status was classified as negative (lack of any ER and PgR

immunoreactivity, or <1% immunoreactive tumor cells), incompletely endocrine responsive (ER and/or PgR < 50% of the cells) or highly endocrine responsive (ER and PgR > 50% of the cells)

Study design

We collected information through the institutional clinical database on all consecutive breast cancer patients treated at the European Institute of Oncology, Milan, Italy, between 1995 and 2006.

Data on the patient's medical history, concurrent diseases, type of surgery, histopathological features, and results of staging procedures (blood chemistry, hematological values, bone scan, chest film and upper abdominal ultrasound examination) were reviewed. We subsequently identified those patients treated with preoperative chemotherapy plus or minus concurrent endocrine therapy and we selected patients who achieved pCR and patients with residual disease at final surgery

Main endpoints were disease-free survival (DFS), distant disease-free survival (DDFS) and overall survival (OS). DFS was defined as the length of time from the date of surgery to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer) or death. DDFS was defined as the length of time from the date of surgery to events such as distant recurrence, death from breast cancer, death from causes other than breast cancer (including unknown causes) or the development of a secondary primary invasive cancer. Data were censored on the date of the last follow-up visit.

Statistical analysis methods

Pearson χ^2 test was used to compare the pCR rates among levels of the considered variables.

Plots of the survival curves were drawn using the Kaplan–Meier method. The log-rank test was used to assess the survival difference between groups.

Cox's proportional hazard regression models were used to assess the prognostic significance of clinical and histopathological characteristics of the tumor on the evaluated outcomes. Factors that were significant at a P-value of 0.05 or less at the univariate analysis were entered into the multiple regression models. Results from Cox's models were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All analyses were performed with the SAS software version 8.02 (SAS, Cary, NC, USA). All P-values were two sided.

Results

Data

One thousand five hundred forty seven patients, who received primary therapy for breast cancer and submitted at surgery, were identified. Patients that presented with biopsy done elsewhere (n= 673), metastatic disease at presentation (n=133), other previous tumour (n=16), bilateral tumours (n=36) and male breast cancers (n=2), were excluded, leaving a total of 687 patients evaluable for this analysis.

Eighty-two (12%) patients who achieved pCR and 605 (88%) patients with RD at final surgery were identified (Figure 1).

Table 1 shows the characteristics of the patients evaluated at diagnosis and their association with pCR probability. Those showing a statistically significant association were grade, extent of ER and PgR immunoreactivity and Ki-67 labelling index.

Patients who achieved pCR more frequently presented unendocrine responsive disease, with triple negative breast cancer phenotype, high nuclear grade. 31% of patients who achieved pCR presented at baseline triple negative breast cancer phenotype with Ki-67 expression more than 20% of cells (Table 2).

We reported, in overall population, an increased use of anthracycline and taxane combination in the later years of diagnosis compared to earlier; 56% of patients who were operated in the 2004-2006 received anthracycline and taxane combination compared to 15% of patients operated in the 1995-1999.

The anthracycline and taxane combination was more frequently associated with achievement of pCR as reported in Table 3.

Analysis and presentation

Median follow up was 60.9 months (range 5-152 months).

The Kaplan-Meier curves for DFS and DDFS, according to type of response (pCR and RD) are displayed in Figure 2. The 5 year DFS and DDFS was 73% and 81% in the pCR group compared to 59% and 72% in the RD group ($p=.029$ for DFS and $p=.085$ for DDFS). Figure 3 shows the Kaplan-Meier curve for OS. Better OS was observed for patients who achieved pCR as compared to that of patients with RD, 5 year OS were 88% and 77% in two groups respectively ($p=.033$).

We investigated the prognostic significance of selected subgroups of patients with pCR and patients with RD. We identified three immunohistochemically-defined tumor subtypes: triple negative (ER, PgR and HER2 negative), HER2 positive and non-endocrine-responsive disease (HER2 positive, ER and PgR negative) and endocrine-responsive (ER and or PgR >1% any status of HER2).

Figures 4a and 4b show the Kaplan Meier curves for outcome between three subgroups of patients in patients with pCR and RD. DFS, DDFS were poorer for patients with HER2 positive disease, compared to those with triple negative and endocrine-responsive diseases for patients with pCR and for patients with RD. Significantly worse OS was observed for patients with HER2 positive breast cancer compared to other patients either in pCR group ($p=0.021$) and in RD group ($p<.0001$).

At the univariate analysis, clinical size of tumor greater than 5 cm was significantly associated with poorer DFS (HR 2.95; 95% CI:1.25-6.98), DDFS (HR 3.19; 95% CI: 1.07-9.52) in patients that achieved a pCR. Also clinical lymph node involvement was significantly associated with increased risk of recurrence (HR 4.87; 95%CI 1.45-16.4: and HR 4.9; 95%CI 1.11-21.72 for DFS and DDFS respectively) in patients that achieved pCR.

Multivariate analysis

The independent association between biological variables and the risk of recurrence in the pCR group and in the RD group was analyzed. The results, obtained using Cox proportional hazards regression analysis, are displayed in Tables 4a-b and 5 a-b.

At the multivariate analysis for patients with RD high nuclear grade (HR 1.42; 95% CI 1.01-2), large clinical tumour size (HR 1.40; 95% CI 1.02-1.92), clinical positive nodal status (HR 1.91; 95% CI 1.17-3.12), and Ki-67 more than 20% of the cells (HR 1.69; 95% CI 1.02-2.80), correlated with worse DFS. Ki-67 more than 20% of the cells also correlated with worse DDFS for patients with RD (HR 2.06; 95% CI 1.08-3.92).

At the multivariate analysis for patients who achieved pCR, clinical larger tumor size (> 5 cm) correlated with higher risk of worse DFS (HR 3.18; 95% CI 1.34-7.51).

Clinical nodal involvement was found to be associated with a higher risk of worse DFS and DDFS (HR 6.94; 95% CI 1.62-29.73 and HR 9.87 95%CI 1.29-75.53 respectively)..

Discussion

Several large randomized studies have shown that patients achieving a pCR to primary chemotherapy have far better long-term survival than those who fail to respond to primary chemotherapy (incomplete responders) [1-4]. It has therefore been assumed that pCR is a valid surrogate marker of long-term survival and cure in patients with locally advanced breast cancer treated with preoperative chemotherapy even though the definition of pCR between studies was heterogeneous in the past studies [1]. Only recently a more homogeneous definition of pCR (i.e., the absence of invasive carcinoma in either breast and axilla) has been accepted as a surrogate marker of better survival.

Several major conclusions can be drawn from the present study. Although pCR might identify patients with significantly improved outcome, a substantial risk of relapse still persists for these patients. As previously shown, we reported significantly better outcome in terms of DFS, DDFS and OS after primary chemotherapy for patients who achieved pCR compared to those with residual disease at final surgery. However, the 5 year DFS for patients with a pCR at final surgery was 73%, thus indicating that a non-negligible proportion of patients might experience an event despite the achievement of pCR. These results are consistent with those of previous studies that have reported recurrence rates in the range of 13%–25% [1,4,16,17].

The finding that patients achieving a pCR remain at substantial risk of relapse, was observed in a population subjected to an adjuvant therapy program which might have interfered with the outcome. It is noteworthy that in the present analysis medical oncologists used consistent approaches during the years of reference. The adjuvant treatment proposed was largely based on the degree of nodal involvement, as well as on known prognostic features according to the recent St. Gallen Consensus Conference Guidelines [15]. Consequently, the identification of “niches” of patients at major risk is key for future studies and further tailored adjuvant programs should be developed within these subgroups of patients.

In the present study we showed that the tumour diameter and the nodal clinical status at baseline are clinical features that might identify those patients at higher risk. Other groups showed that a more advanced disease (e.g. clinical stage IIIB/C and cT4d) at baseline might correlate with a worse outcome in patients who achieved pCR if compared with those patients with less advanced disease. [18, 19].

However, in the present study we found an independent prognostic role for both the tumour diameter and clinical nodal status. In particular the tumour measurement might be of clinical value, since easily available and not subject to possible false positive results as opposed to the clinical nodal status.

We hypothesize that large tumour size and clinical nodal involvement at baseline could reflect a higher risk of systemic micrometastatic disease at diagnosis. Theoretically, the ability to achieve a pCR, might indicate high tumor chemosensitivity and therefore eradication of all distant invasive micrometastatic disease, with resulting low recurrence rates.

It might be argued however that with a more advanced disease stage there is a higher probability of micrometastatic clones, a subgroup of which may be resistant to conventional agents, or have different tumour features as compared with the primary tumours. This hypothesis might support further studies using additional agents in the adjuvant setting with a mechanism of action different from those used in the preoperative setting.

It should be emphasized that the subgroups at higher risk identified in the present analysis include a heterogeneous groups of tumors, and that the identification of specific niches of patients amenable to targeted treatments represents a research priority. In particular, in this study we explored the role of HER2 overexpression, steroid hormone receptors and the definition of subgroups (namely luminal, triple negative, HER2 positive) as recently reported [12], but we were not able to identify subgroups with a different outcome after surgery. Possible reasons for these results include the low number of patients included in the analysis and the low number of events registered in studies focusing on a population that achieved a pCR.

In conclusion we demonstrate that the achievement of a pCR after preoperative systemic therapy is correlated with significant improved outcome, although a non-negligible risk of relapse remains, in particular with patients with clinical large tumor size and clinical nodal involvement at baseline. The results of this study provide substantial additional evidence to support the concept that further progress in the adjuvant treatment of breast cancer will require studies dedicated to specific “niches” of patients identified through both clinical and biological features.

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Figure 1: Diagram of the study

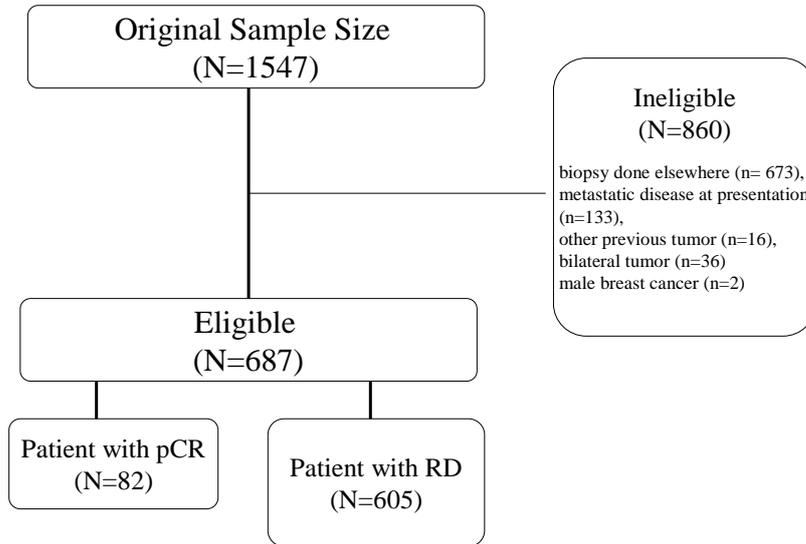


Table 1. Patient characteristics at baseline and observed pCR rates

	All Patients No. of patients	pCR No. of patients (%)	P value*
Age range (years)			
<35	80	13 (16.3)	0.14
35-49	339	46 (13.6)	
50-59	181	17 (9.4)	
60+	87	6 (6.9)	
Menopausal Status			
Premenopausal	322	41 (12.7)	0.55
Postmenopausal	365	41 (11.2)	
Histotype			
IDC	578	63 (10.9)	0.06
ILC	45	0 (0.0)	
Other	44	2 (4.5)	
Unknown	20	17 (85.0)	
Nuclear Grade			
1-2	348	25 (7.2)	<0.0001
3	224	52 (23.2)	
Unknown	115	5 (4.3)	
Clinical T			
T2	391	50 (12.8)	0.43
T3	122	16 (13.1)	
T4	174	16 (9.2)	
Clinical nodal status			
Positive	480	45 (9.4)	0.01
Negative	182	30 (16.5)	
Unknown	25	7 (28.0)	
Endocrine Responsiveness			
Non responsive †	239	64 (26.8)	<0.0001
Incompletely responsive ‡	293	17 (5.8)	
Highly responsive §	141	1 (0.7)	
Unknown	14	0 (0.0)	
HER2			
Overexpressed	114	20 (17.5)	0.30
Not Expressed	352	48 (13.6)	
Unknown	221	14 (6.3)	
Triple Negative Status			
TNBC	115	35 (30.4)	<0.0001
Non-TNBC	351	33 (9.4)	
Unknown	221	14 (6.3)	
Ki-67			
<20%	170	7 (4.1)	0.0002
≥20%	494	73 (14.8)	
Unknown	23	2 (8.7)	

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; TNBC, triple-negative breast cancer.

* Pearson χ^2 test comparing pCR rates among levels of the considered variables. Unknowns were excluded.

† (ER=0% and PgR=0%)

‡ (ER or PgR 0-49 %)

§ (ER≥50% and PgR≥50%)

Table 2. Breast cancer phenotype and pCR rates

ER *	HER2	Ki67 †	No.	pCR No. (%)
Positive	Overexpressed	High	42	3 (7.1)
Positive	Negative	High	155	9 (5.8)
Positive	Overexpressed	Low	3	0 (0.0)
Positive	Negative	Low	79	4 (5.1)
Negative	Overexpressed	High	62	15 (24.2)
Negative	Negative	High	107	33 (30.8)
Negative	Overexpressed	Low	5	1 (20.0)
Negative	Negative	Low	6	1 (16.7)

* Positive: $\geq 1\%$

† High: $\geq 20\%$

(pvalue χ^2 test comparing pCR rates among combined levels of the considered variables): <0.0001

Table 3. Treatment and observed pCR rates

	All Patients No. of patients	pCR No. of patients (%)	P value*
Primary therapy			
Chemotherapy regimens			<0.0001
Antracyclines	352	52 (14.8)	
Antracyclines and taxanes	54	13 (24.1)	
Herceptin	25	5 (20.0)	
Others	256	12 (4.7)	
Concomitant hormone therapy			0.07
Yes	173	14 (8.1)	
No	514	68 (13.2)	
Surgery			<0.0001
Conservative	343	60 (17.5)	
Radical	344	22 (6.4)	
Radiotherapy			0.32
Yes	519	66 (12.8)	
No	168	16 (9.5)	
Adjuvant treatment			<0.0001
Nil	70	34 (48.6)	
Only hormone therapy	295	12 (4.1)	
Only chemotherapy	181	30 (16.6)	
Chemotherapy and hormone therapy	141	6 (4.3)	
Adjuvant trastuzumab			0.07
Yes	26	6 (23.1)	
No	661	76 (11.5)	

* Pearson χ^2 test comparing pCR rates among levels of the considered variables.

Table 4 a. Disease Free Survival (DFS) by characteristics at presentation in patients achieving pathological complete response (pCR) after primary chemotherapy. Univariate and multivariate analysis

	No. of patients with events	Total No. of patients	5-yr DFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Staus						
Premenopausal	11	41	0.79 (0.66-0.92)	0.70	reference	
Postmenopausal	12	41	0.67 (0.50-0.83)		1.18 (0.52-2.67)	
Nuclear grade						
1-2	8	25	0.66 (0.47-0.86)	0.87	reference	
3	15	52	0.74 (0.60-0.87)		0.93 (0.39-2.20)	
Clinical T						
T2	9	50	0.80 (0.68-0.93)	0.01	reference	reference
T3-T4	13	32	0.65 (0.48-0.82)		2.95 (1.25-6.98)	3.18 (1.34-7.51)
Clinical nodal status						
Negative	3	30	0.88 (0.74-1.00)	0.005	reference	reference
Positive	20	45	0.61 (0.46-0.76)		4.87 (1.45-16.4)	6.94 (1.62-29.73)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	4	17	0.71 (0.46-0.96)	0.25	reference	
ER and PgR 0% / HER2 overexpressed	6	16	0.63 (0.39-0.86)		2.19 (0.62-7.78)	
TNBC	8	35	0.81 (0.67-0.95)		0.96 (0.29-3.20)	
Ki-67						
<20%	3	7	0.48 (0.03-0.92)	0.28	reference	
≥20%	20	73	0.75 (0.64-0.85)		0.52 (0.15-1.76)	
Primary chemotherapy regimen						
Antracyclines	17	52	0.71 (0.58-0.84)	0.41	reference	
Antracyclines and taxanes	1	13	0.75 (0.33-1.00)		0.28 (0.04-2.10)	
Others	5	17	0.71 (0.49-0.92)		0.96 (0.35-2.59)	

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariate Cox regression model

‡ Determined by multivariate Cox regression model (only variables significant at a P-value of 0.05 in the univariate model were considered).

Table 4 b. Disease Free Survival (DFS) by characteristics at presentation in patients with RD after primary chemotherapy. Univariate and multivariate analysis

	No. of patients with events	Total No. of patients	5-yr DFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Status						
Premenopausal	125	281	0.59 (0.53-0.65)	0.90	reference	
Postmenopausal	141	324	0.59 (0.53-0.64)		1.02 (0.80,1.29)	
Nuclear grade						
1-2	119	323	0.64 (0.58-0.70)	<.0001	reference	reference
3	98	172	0.43 (0.35-0.51)		1.83 (1.40,2.40)	1.42 (1.01,2.00)
Clinical T						
T2	130	341	0.66 (0.61-0.71)	<.0001	reference	reference
T3-T4	136	264	0.49 (0.43-0.56)		1.84 (1.44,2.34)	1.40 (1.02,1.92)
Clinical nodal status						
Negative	49	152	0.70 (0.61-0.77)	<.0001	reference	reference
Positive	207	435	0.55 (0.50-0.59)		4.87 (1.45,16.40)	1.91 (1.17,3.12)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	86	266	0.66 (0.59-0.72)	<.0001	reference	reference
ER and PgR 0% / HER2 overexpressed	36	52	0.30 (0.17-0.43)		3.25 (2.20,4.81)	2.39 (1.59,3.58)
TNBC	47	80	0.38 (0.26-0.50)		2.78 (1.94,3.98)	2.16 (1.48,3.15)
Ki-67						
<20%	47	163	0.79 (0.72-0.85)	<.0001	reference	reference
≥20%	207	421	0.51 (0.46-0.56)		2.31 (1.68,3.18)	1.69 (1.02,2.80)
Primary chemotherapy regimen						
Antracyclines	143	300	0.59 (0.53-0.64)	0.0031	reference	reference
Antracyclines and taxanes	22	41	0.45 (0.29-0.60)		1.65 (1.05,2.59)	1.64 (1.00,2.69)
Others	101	264	0.61 (0.55-0.68)		0.77 (0.60,1.00)	0.76 (0.53,1.09)

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariable Cox regression model

‡ Determined by multivariable Cox regression model (only variables significant at a P-value of 0.05 in the univariable model were considered).

Table 5 a. Distant Disease Free Survival (DDFS) by characteristics at presentation in patients achieving pathological complete response (pCR) after primary chemotherapy. Univariate and multivariate analysis

	No. of patients with events	Total No. of patients	5-yr DDFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Status						
Premenopausal	6	41	0.84 (0.73-0.96)	0.36	reference	
Postmenopausal	9	41	0.77 (0.64-0.90)		1.62 (0.58-4.55)	
Nuclear grade						
1-2	6	25	0.76 (0.59-0.93)	0.56	reference	
3	9	52	0.81 (0.70-0.92)		0.74 (0.26-2.08)	
Clinical T						
T2	5	50	0.89 (0.80-0.98)	0.03	reference	reference
T3-T4	9	32	0.72 (0.56-0.87)		3.19 (1.07-9.52)	3.57 (1.19-10.69)
Clinical nodal status						
Negative	2	30	0.91 (0.79-1.00)	0.02	reference	reference
Positive	13	45	0.71 (0.58-0.84)		4.9 (1.11-21.72)	9.87 (1.29-75.53)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	3	17	0.80 (0.59-1.00)	0.06	reference	
ER and PgR 0% / HER2 overexpressed	6	16	0.63 (0.39-0.86)		2.97 (0.74-11.89)	
TNBC	4	35	0.88 (0.77-0.99)		0.67 (0.15-2.97)	
Ki-67						
<20%	3	7	0.48 (0.03-0.92)	0.08	reference	
≥20%	12	73	0.83 (0.75-0.92)		0.34 (0.10-1.20)	
Primary chemotherapy regimen						
Antracyclines	9	52	0.82 (0.72-0.93)	0.29	reference	
Antracyclines and taxanes	1	13	0.75 (0.33-1.00)		0.43 (0.06-3.42)	
Others	5	17	0.71 (0.49-0.92)		1.86 (0.62-5.56)	

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariate Cox regression model

‡ Determined by multivariate Cox regression model (only variables significant at a P-value of 0.05 in the univariate model were considered).

Table 5 b. Distant Disease Free Survival (DDFS) by characteristics at presentation in patients with RD after primary chemotherapy. Univariate and multivariate analysis

	No. of patients with events	Total No. of patients	5-yr DDFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Status						
Premenopausal	86	281	0.71 (0.64-0.76)	0.51	reference	
Postmenopausal	89	324	0.74 (0.68-0.79)		0.91 (0.67,1.22)	
Nuclear grade						
1-2	79	323	0.76 (0.71-0.81)	0.0002	reference	reference
3	66	172	0.60 (0.52-0.68)		1.82 (1.31,2.53)	1.27 (0.84,1.91)
Clinical T						
T2	84	341	0.78 (0.73-0.83)	<.0001	reference	reference
T3-T4	91	264	0.64 (0.58-0.70)		1.80 (1.34,2.43)	1.31 (0.89,1.93)
Clinical nodal status						
Negative	34	152	0.80 (0.72-0.86)	0.0044	reference	reference
Positive	132	435	0.70 (0.65-0.74)		1.75 (1.19,2.57)	1.29 (0.76,2.19)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	60	266	0.75 (0.69-0.81)	<.0001	reference	reference
ER and PgR 0% / HER2 overexpressed	26	52	0.48 (0.32-0.62)		3.02 (1.90,4.79)	2.26 (1.40,3.66)
TNBC	29	80	0.55 (0.40-0.68)		2.37 (1.52,3.70)	1.78 (1.11,2.85)
Ki-67						
<20%	28	163	0.88 (0.82-0.93)	<.0001	reference	reference
≥20%	137	421	0.66 (0.61-0.71)		2.52 (1.68,3.80)	2.06 (1.08,3.92)
Primary chemotherapy regimen						
Antracyclines	91	300	0.73 (0.67-0.77)	0.0033	reference	reference
Antracyclines and taxanes	17	41	0.56 (0.39-0.70)		2.03 (1.21,3.40)	1.91 (1.07,3.40)
Others	67	264	0.75 (0.68-0.80)		0.83 (0.60,1.13)	0.81 (0.52,1.26)

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

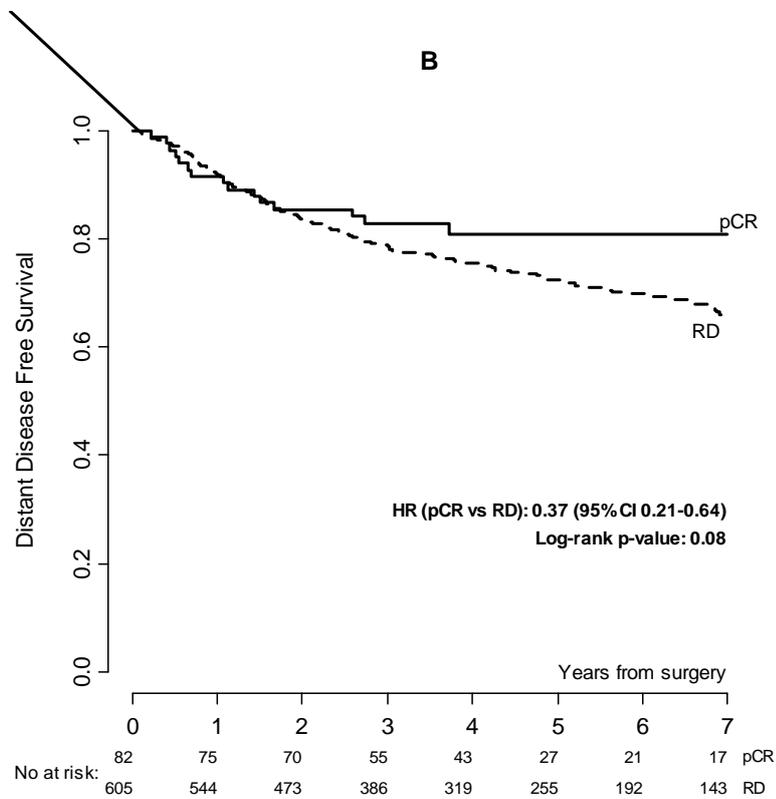
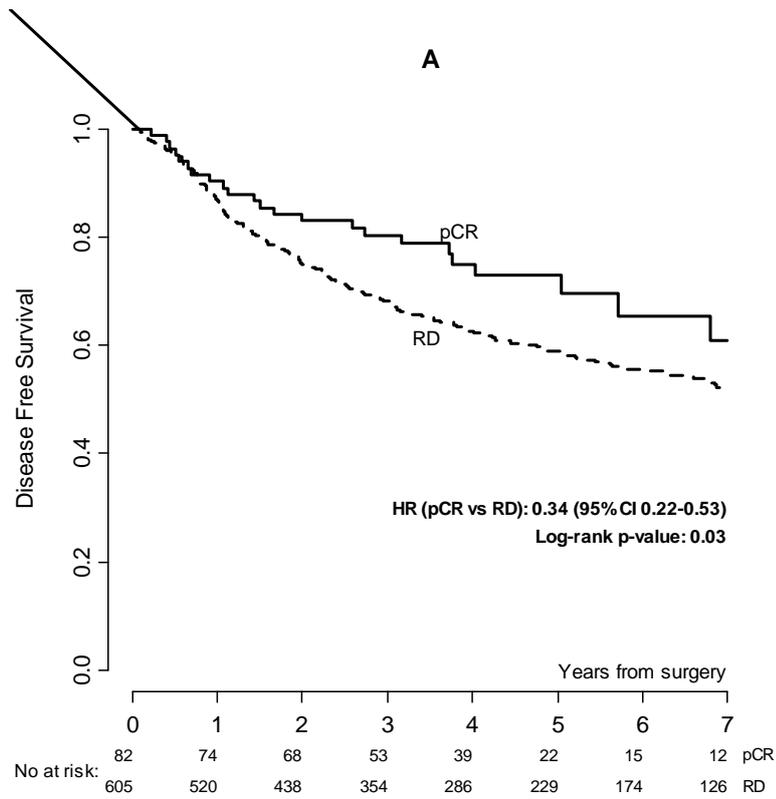
Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariable Cox regression model

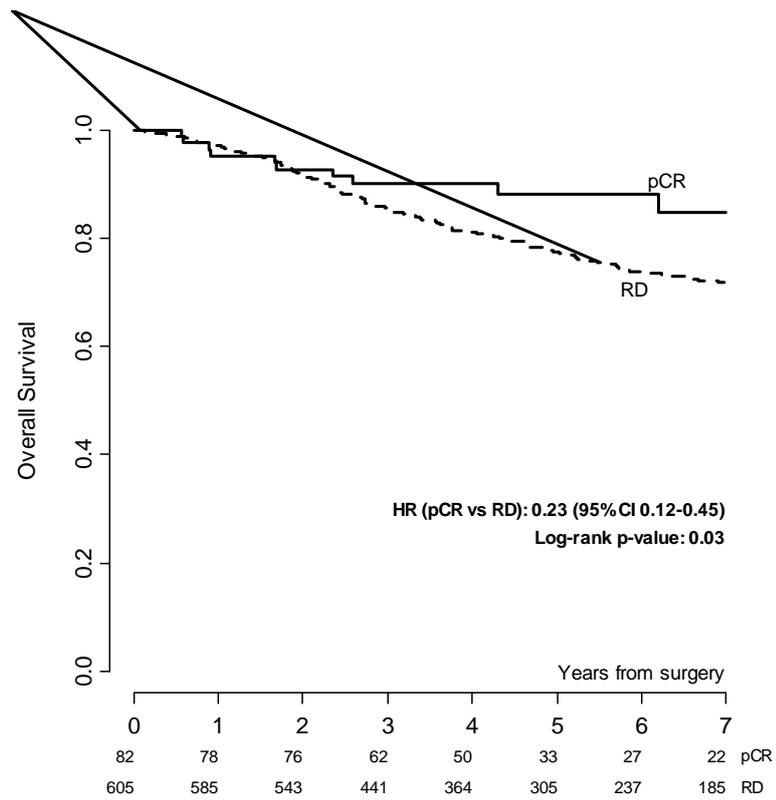
‡ Determined by multivariable Cox regression model (only variables significant at a P-value of 0.05 in the univariable model were considered).

Figure 2. Disease Free Survival (A) and Distant Disease Free Survival (B) by response after primary therapy.



Abbreviations: pCR, Pathological Complete Response; RD, Residual Disease

Figure 3. Overall Survival by response after primary therapy.



Abbreviations: pCR, Pathological Complete Response; RD, Residual Disease

Figure 4 a. Disease Free Survival (A), Distant Disease Free Survival (B) and Overall Survival (C) by ER/PgR/HER2 status in patients achieving pathological complete response (pCR)

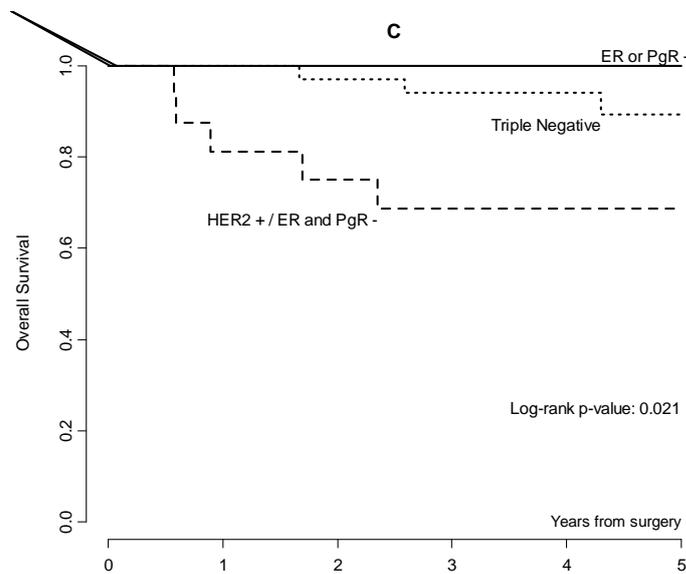
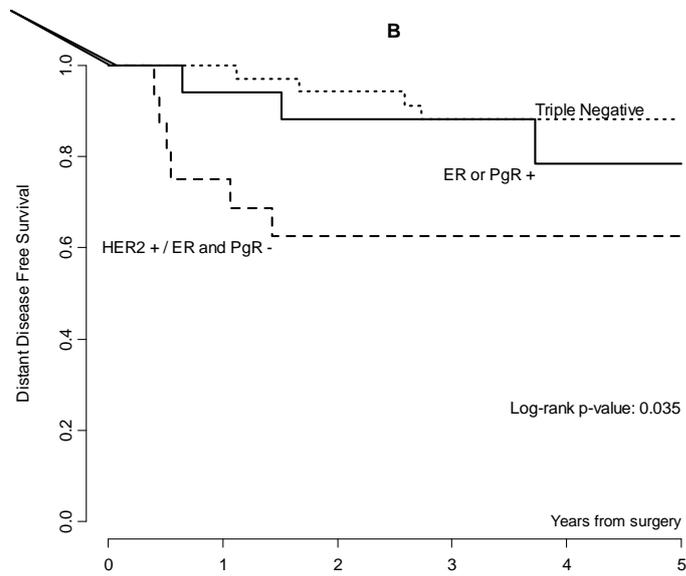
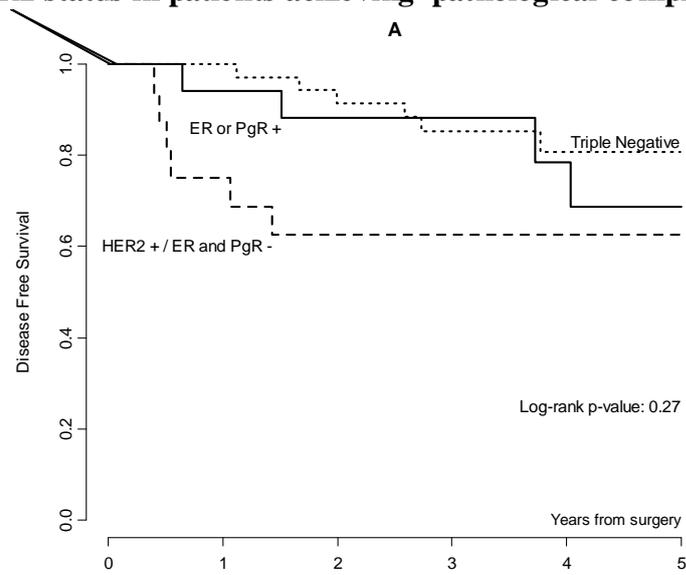
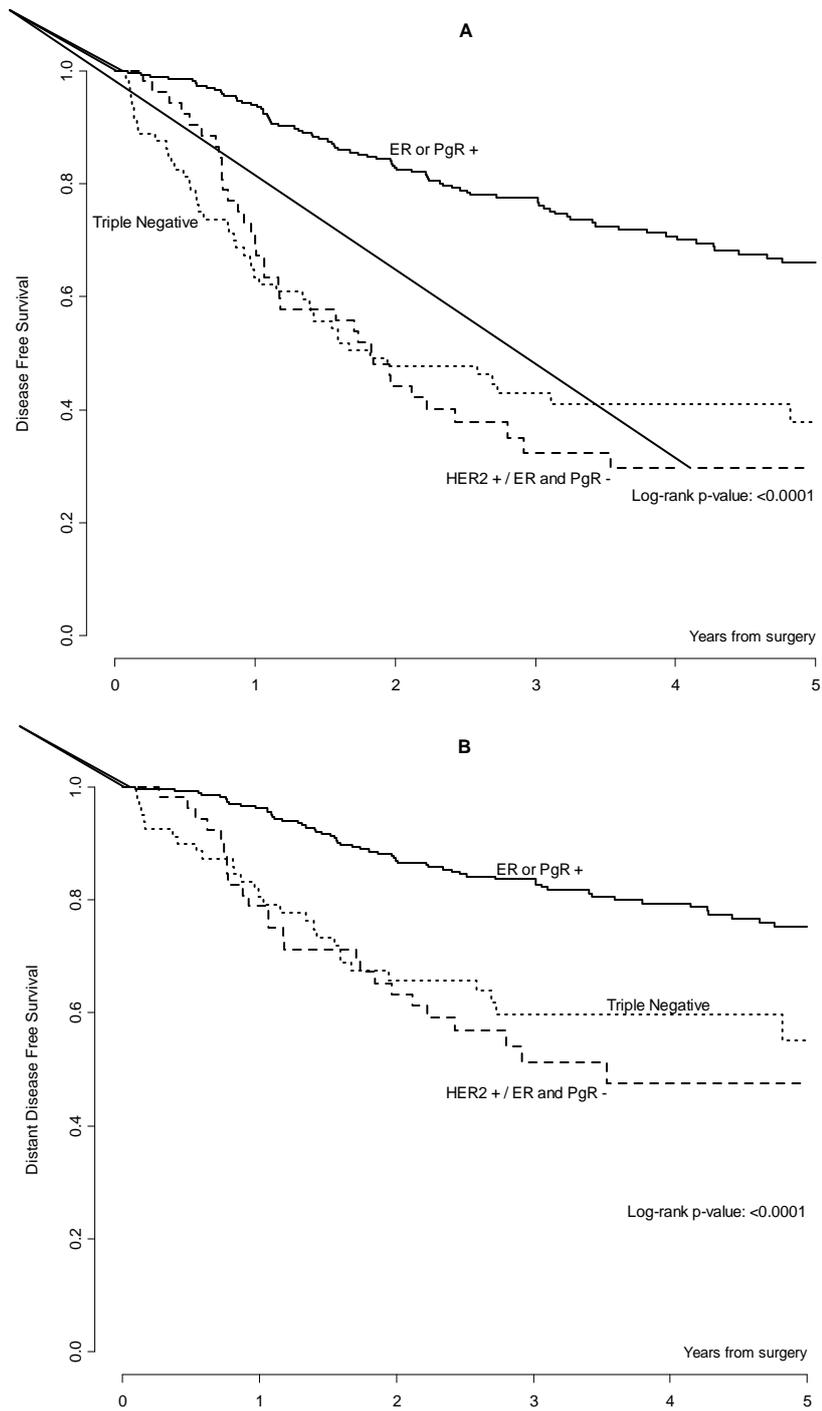


Figure 4 b. Disease Free Survival (A), Distant Disease Free Survival (B) and Overall Survival (C) by ER/PgR/HER2 status in patients with RD after primary chemotherapy



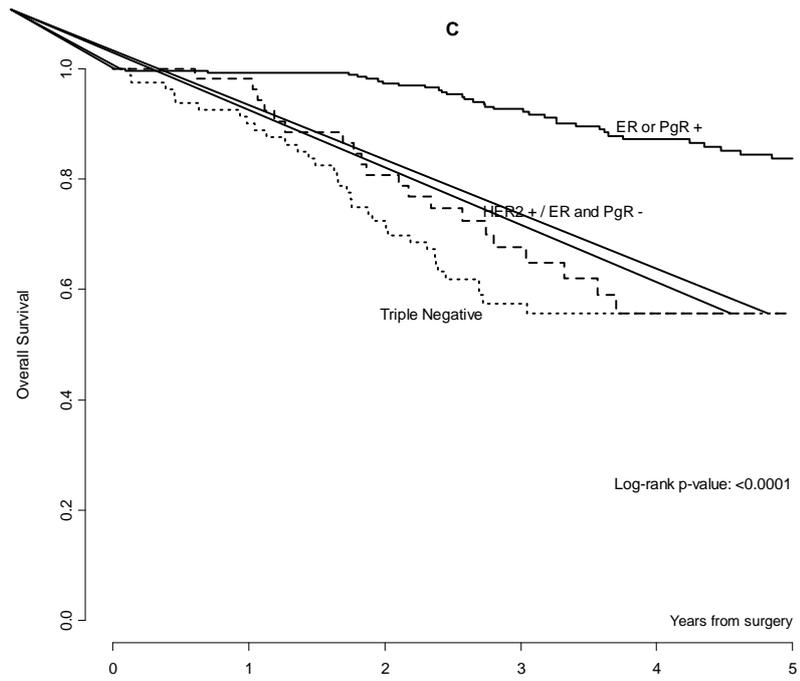


Figure 1: Diagram of the study

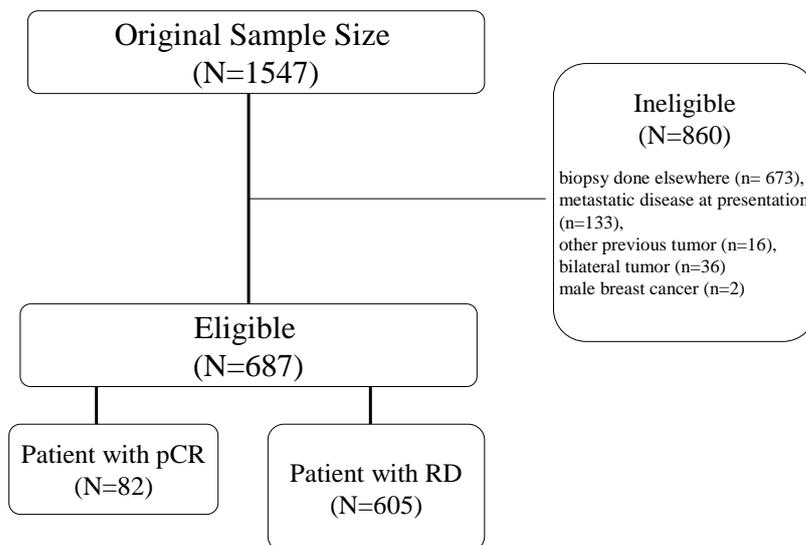
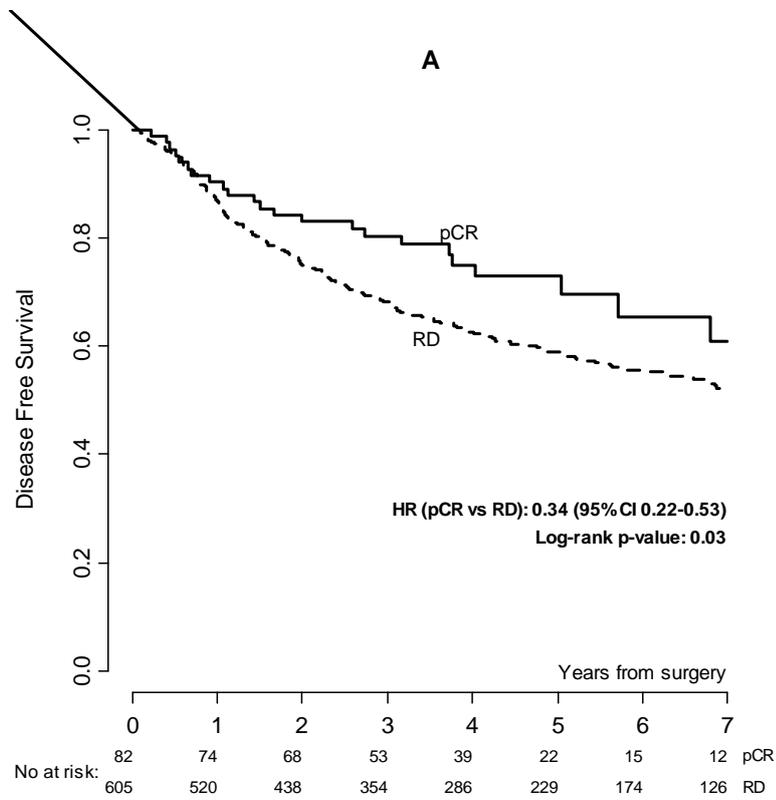
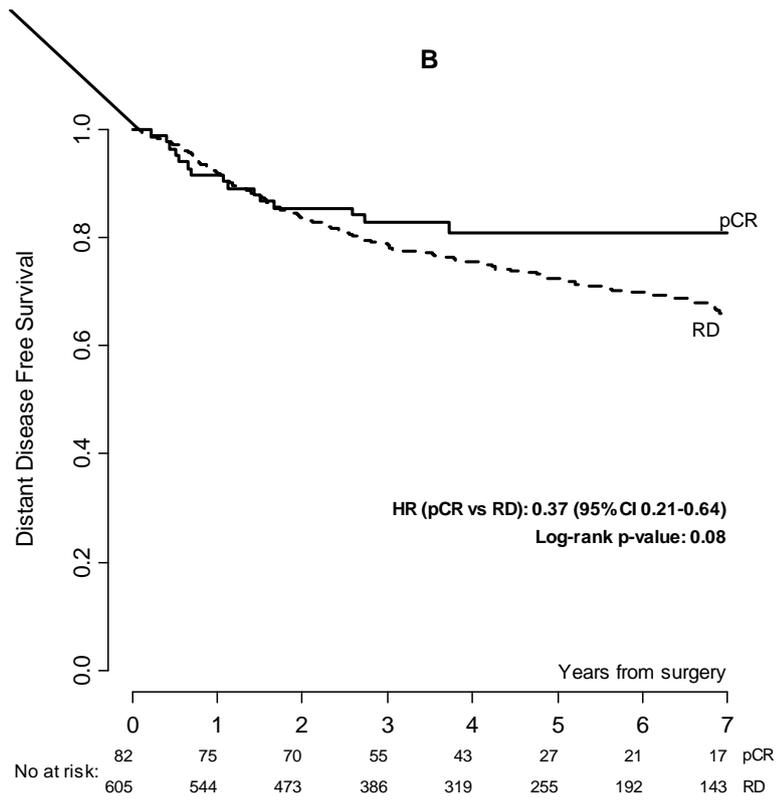


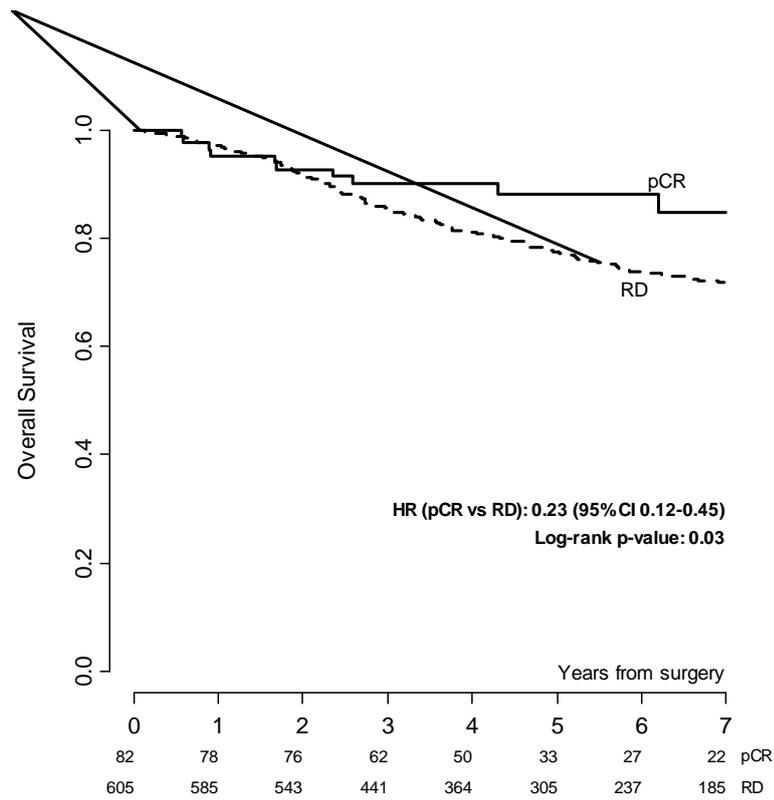
Figure 2. Disease Free Survival (A) and Distant Disease Free Survival (B) by response after primary therapy.





Abbreviations: pCR, Pathological Complete Response; RD, Residual Disease

Figure 3. Overall Survival by response after primary therapy.



Abbreviations: pCR, Pathological Complete Response; RD, Residual Disease

Figure 4 a. Disease Free Survival (A), Distant Disease Free Survival (B) and Overall Survival (C) by ER/PgR/HER2 status in patients achieving pathological complete response (pCR)

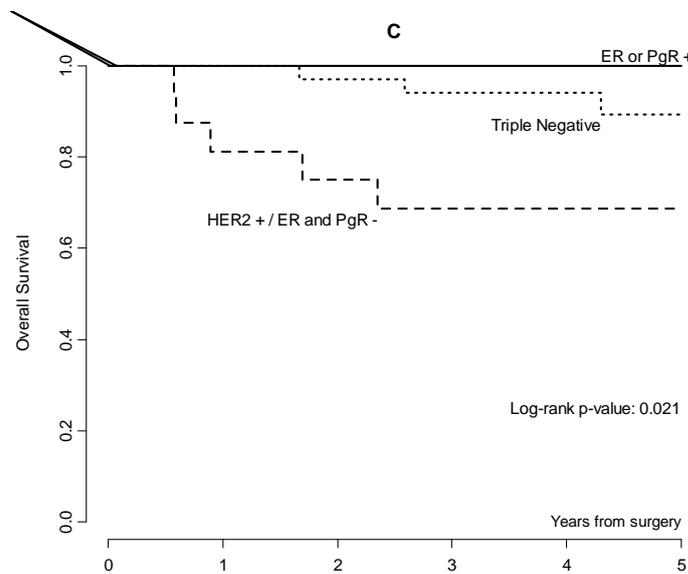
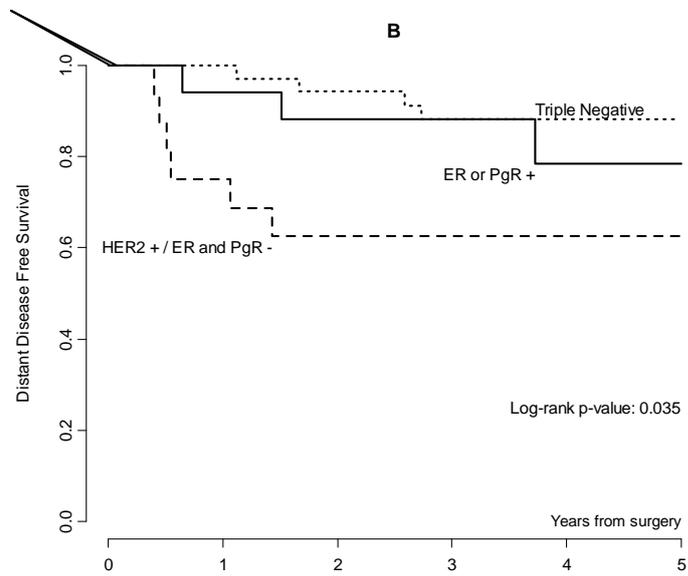
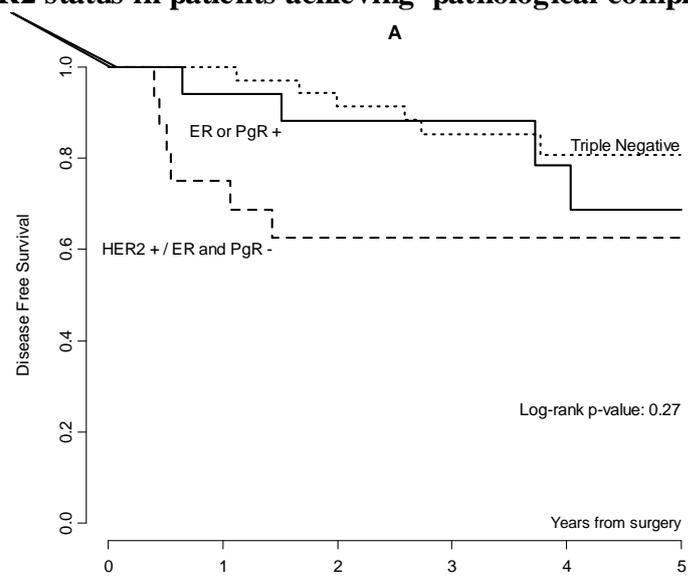
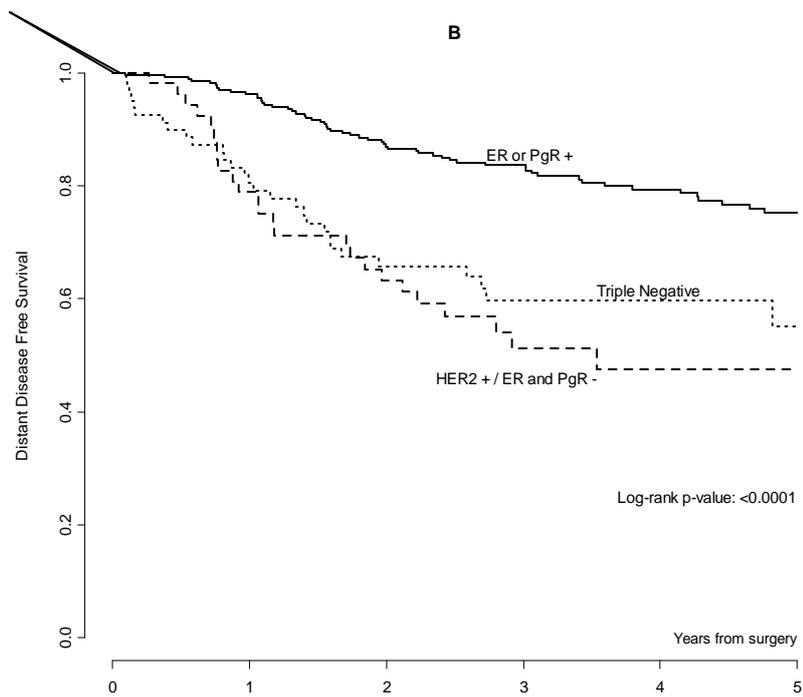
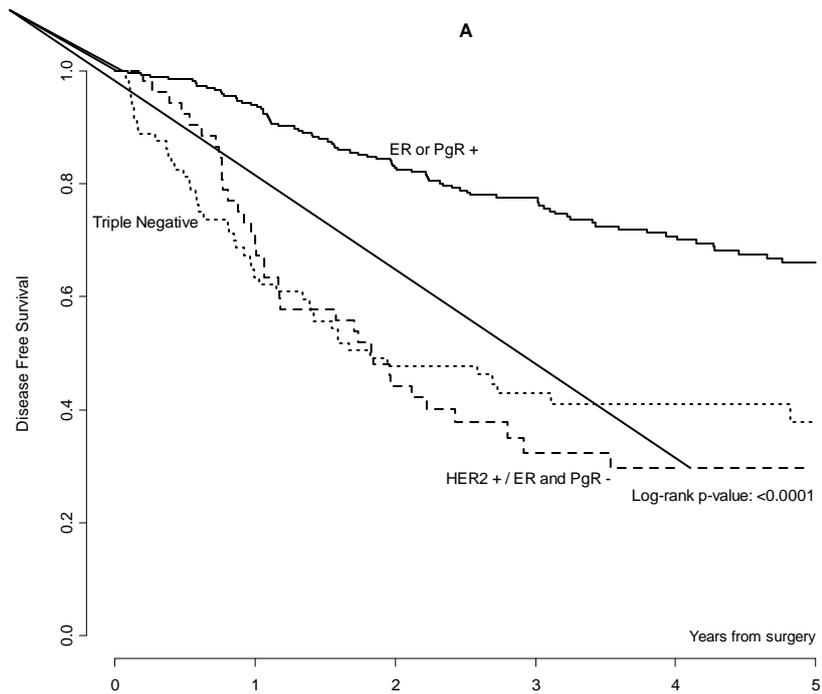


Figure 4 b. Disease Free Survival (A), Distant Disease Free Survival (B) and Overall Survival (C) by ER/PgR/HER2 status in patients with RD after primary chemotherapy



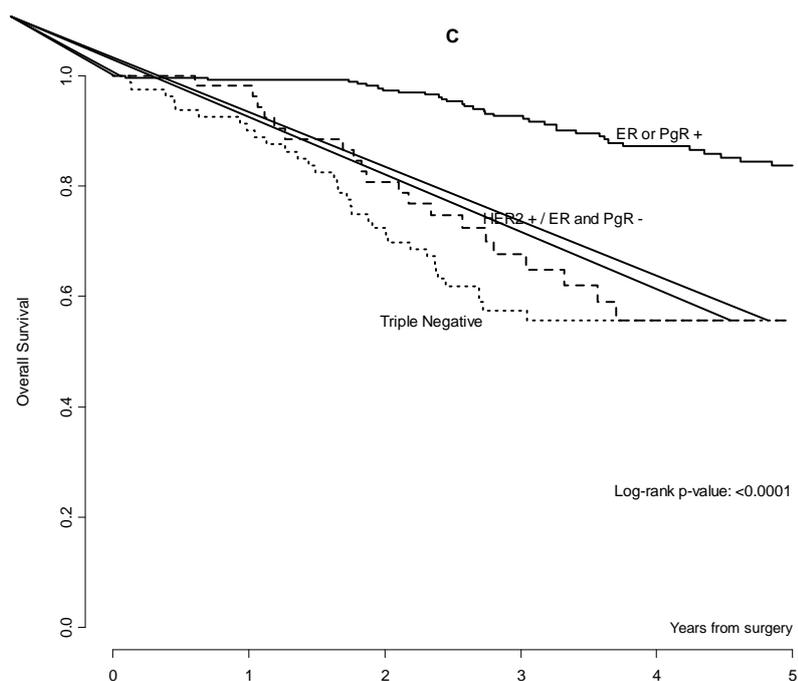


Table 1. Patient characteristics at baseline and observed pCR rates

	All Patients No. of patients	pCR No. of patients (%)	P value*
Age range (years)			
<35	80	13 (16.3)	0.14
35-49	339	46 (13.6)	
50-59	181	17 (9.4)	
60+	87	6 (6.9)	
Menopausal Status			
Premenopausal	322	41 (12.7)	0.55
Postmenopausal	365	41 (11.2)	
Histotype			
IDC	578	63 (10.9)	0.06
ILC	45	0 (0.0)	
Other	44	2 (4.5)	
Unknown	20	17 (85.0)	
Nuclear Grade			
1-2	348	25 (7.2)	<0.0001
3	224	52 (23.2)	
Unknown	115	5 (4.3)	
Clinical T			
T2	391	50 (12.8)	0.43

T3	122	16 (13.1)	
T4	174	16 (9.2)	
Clinical nodal status			
Positive	480	45 (9.4)	0.01
Negative	182	30 (16.5)	
Unknown	25	7 (28.0)	
Endocrine Responsiveness			
Non responsive †	239	64 (26.8)	<0.0001
Incompletely responsive ‡	293	17 (5.8)	
Highly responsive §	141	1 (0.7)	
Unknown	14	0 (0.0)	
HER2			
Overexpressed	114	20 (17.5)	0.30
Not Expressed	352	48 (13.6)	
Unknown	221	14 (6.3)	
Triple Negative Status			
TNBC	115	35 (30.4)	<0.0001
Non-TNBC	351	33 (9.4)	
Unknown	221	14 (6.3)	
Ki-67			
<20%	170	7 (4.1)	0.0002
≥20%	494	73 (14.8)	
Unknown	23	2 (8.7)	

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; TNBC, triple-negative breast cancer.

* Pearson χ^2 test comparing pCR rates among levels of the considered variables. Unknowns were excluded.

† (ER=0% and PgR=0%)

‡ (ER or PgR 0-49 %)

§ (ER≥50% and PgR≥50%)

Table 2. Breast cancer phenotype and pCR rates

ER *	HER2	Ki67 †	No.	pCR No. (%)
Positive	Overexpressed	High	42	3 (7.1)
Positive	Negative	High	155	9 (5.8)
Positive	Overexpressed	Low	3	0 (0.0)
Positive	Negative	Low	79	4 (5.1)
Negative	Overexpressed	High	62	15 (24.2)
Negative	Negative	High	107	33 (30.8)
Negative	Overexpressed	Low	5	1 (20.0)
Negative	Negative	Low	6	1 (16.7)

* Positive: ≥1%

† High: ≥20%

(pvalue χ^2 test comparing pCR rates among combined levels of the considered variables): <0.0001

Table 3. Treatment and observed pCR rates

	All Patients No. of patients	pCR No. of patients (%)	P value*
Primary therapy			
Chemotherapy regimens			
Antracyclines	352	52 (14.8)	<0.0001
Antracyclines and taxanes	54	13 (24.1)	
Herceptin	25	5 (20.0)	
Others	256	12 (4.7)	
Concomitant hormonotherapy			
Yes	173	14 (8.1)	0.07
No	514	68 (13.2)	
Surgery			
Conservative	343	60 (17.5)	<0.0001
Radical	344	22 (6.4)	
Radiotherapy			
Yes	519	66 (12.8)	0.32
No	168	16 (9.5)	
Adjuvant treatment			
Nil	70	34 (48.6)	<0.0001
Only hormonotherapy	295	12 (4.1)	
Only chemotherapy	181	30 (16.6)	
Chemotherapy and hormonotherapy	141	6 (4.3)	
Adjuvant trastuzumab			
Yes	26	6 (23.1)	0.07
No	661	76 (11.5)	

* Pearson χ^2 test comparing pCR rates among levels of the considered variables.

Table 4 a. Disease Free Survival (DFS) by characteristics at presentation in patients achieving pathological complete response (pCR) after primary chemotherapy. Univariate and multivariate analysis

	No. of patients with events	Total No. of patients	5-yr DFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Staus						
Premenopausal	11	41	0.79 (0.66-0.92)	0.70	reference	
Postmenopausal	12	41	0.67 (0.50-0.83)		1.18 (0.52-2.67)	
Nuclear grade						
1-2	8	25	0.66 (0.47-0.86)	0.87	reference	
3	15	52	0.74 (0.60-0.87)		0.93 (0.39-2.20)	
Clinical T						
T2	9	50	0.80 (0.68-0.93)	0.01	reference	reference
T3-T4	13	32	0.65 (0.48-0.82)		2.95 (1.25-6.98)	3.18 (1.34-7.51)
Clinical nodal status						
Negative	3	30	0.88 (0.74-1.00)	0.005	reference	reference
Positive	20	45	0.61 (0.46-0.76)		4.87 (1.45-16.4)	6.94 (1.62-29.73)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	4	17	0.71 (0.46-0.96)	0.25	reference	
ER and PgR 0% / HER2 overexpressed	6	16	0.63 (0.39-0.86)		2.19 (0.62-7.78)	
TNBC	8	35	0.81 (0.67-0.95)		0.96 (0.29-3.20)	
Ki-67						
<20%	3	7	0.48 (0.03-0.92)	0.28	reference	
≥20%	20	73	0.75 (0.64-0.85)		0.52 (0.15-1.76)	
Primary chemotherapy regimen						
Antracyclines	17	52	0.71 (0.58-0.84)	0.41	reference	
Antracyclines and taxanes	1	13	0.75 (0.33-1.00)		0.28 (0.04-2.10)	
Others	5	17	0.71 (0.49-0.92)		0.96 (0.35-2.59)	

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariate Cox regression model

‡ Determined by multivariate Cox regression model (only variables significant at a P-value of 0.05 in the univariate model were considered).

Table 4 b. Disease Free Survival (DFS) by characteristics at presentation in patients with RD after primary chemotherapy. Univariate and multivariate analysis

	No. of patients with events	Total No. of patients	5-yr DFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Status						
Premenopausal	125	281	0.59 (0.53-0.65)	0.90	reference	
Postmenopausal	141	324	0.59 (0.53-0.64)		1.02 (0.80,1.29)	
Nuclear grade						
1-2	119	323	0.64 (0.58-0.70)	<.0001	reference	reference
3	98	172	0.43 (0.35-0.51)		1.83 (1.40,2.40)	1.42 (1.01,2.00)
Clinical T						
T2	130	341	0.66 (0.61-0.71)	<.0001	reference	reference
T3-T4	136	264	0.49 (0.43-0.56)		1.84 (1.44,2.34)	1.40 (1.02,1.92)
Clinical nodal status						
Negative	49	152	0.70 (0.61-0.77)	<.0001	reference	reference
Positive	207	435	0.55 (0.50-0.59)		4.87 (1.45,16.40)	1.91 (1.17,3.12)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	86	266	0.66 (0.59-0.72)	<.0001	reference	reference
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TNBC	47	80	0.38 (0.26-0.50)		2.78 (1.94,3.98)	2.16 (1.48,3.15)
Ki-67						
<20%	47	163	0.79 (0.72-0.85)	<.0001	reference	reference
≥20%	207	421	0.51 (0.46-0.56)		2.31 (1.68,3.18)	1.69 (1.02,2.80)
Primary chemotherapy regimen						
Antracyclines	143	300	0.59 (0.53-0.64)	0.0031	reference	reference
Antracyclines and taxanes	22	41	0.45 (0.29-0.60)		1.65 (1.05,2.59)	1.64 (1.00,2.69)
Others	101	264	0.61 (0.55-0.68)		0.77 (0.60,1.00)	0.76 (0.53,1.09)

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariable Cox regression model

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	No. of patients with events	Total No. of patients	5-yr DDFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Status						
Premenopausal	6	41	0.84 (0.73-0.96)	0.36	reference	
Postmenopausal	9	41	0.77 (0.64-0.90)		1.62 (0.58-4.55)	
Nuclear grade						
1-2	6	25	0.76 (0.59-0.93)	0.56	reference	
3	9	52	0.81 (0.70-0.92)		0.74 (0.26-2.08)	
Clinical T						
T2	5	50	0.89 (0.80-0.98)	0.03	reference	reference
T3-T4	9	32	0.72 (0.56-0.87)		3.19 (1.07-9.52)	3.57 (1.19-10.69)
Clinical nodal status						
Negative	2	30	0.91 (0.79-1.00)	0.02	reference	reference
Positive	13	45	0.71 (0.58-0.84)		4.9 (1.11-21.72)	9.87 (1.29-75.53)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	3	17	0.80 (0.59-1.00)	0.06	reference	
ER and PgR 0% / HER2 overexpressed	6	16	0.63 (0.39-0.86)		2.97 (0.74-11.89)	
TNBC	4	35	0.88 (0.77-0.99)		0.67 (0.15-2.97)	
Ki-67						
<20%	3	7	0.48 (0.03-0.92)	0.08	reference	
≥20%	12	73	0.83 (0.75-0.92)		0.34 (0.10-1.20)	
Primary chemotherapy regimen						
Antracyclines	9	52	0.82 (0.72-0.93)	0.29	reference	
Antracyclines and taxanes	1	13	0.75 (0.33-1.00)		0.43 (0.06-3.42)	
Others	5	17	0.71 (0.49-0.92)		1.86 (0.62-5.56)	

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariate Cox regression model

‡ Determined by multivariate Cox regression model (only variables significant at a P-value of 0.05 in the univariate model were considered).

Table 5 b. Distant Disease Free Survival (DDFS) by characteristics at presentation in patients with RD after primary chemotherapy. Univariate and multivariate analysis

	No. of patients with events	Total No. of patients	5-yr DDFS probability (95% CI)	p-value*	HR †	HR ‡
Menopausal Status						
Premenopausal	86	281	0.71 (0.64-0.76)	0.51	reference	
Postmenopausal	89	324	0.74 (0.68-0.79)		0.91 (0.67,1.22)	
Nuclear grade						
1-2	79	323	0.76 (0.71-0.81)	0.0002	reference	reference
3	66	172	0.60 (0.52-0.68)		1.82 (1.31,2.53)	1.27 (0.84,1.91)
Clinical T						
T2	84	341	0.78 (0.73-0.83)	<.0001	reference	reference
T3-T4	91	264	0.64 (0.58-0.70)		1.80 (1.34,2.43)	1.31 (0.89,1.93)
Clinical nodal status						
Negative	34	152	0.80 (0.72-0.86)	0.0044	reference	reference
Positive	132	435	0.70 (0.65-0.74)		1.75 (1.19,2.57)	1.29 (0.76,2.19)
ER/PgR/HER2 status						
ER or PgR ≥ 1%	60	266	0.75 (0.69-0.81)	<.0001	reference	reference
ER and PgR 0% / HER2 overexpressed	26	52	0.48 (0.32-0.62)		3.02 (1.90,4.79)	2.26 (1.40,3.66)
TNBC	29	80	0.55 (0.40-0.68)		2.37 (1.52,3.70)	1.78 (1.11,2.85)
Ki-67						
<20%	28	163	0.88 (0.82-0.93)	<.0001	reference	reference
≥20%	137	421	0.66 (0.61-0.71)		2.52 (1.68,3.80)	2.06 (1.08,3.92)
Primary chemotherapy regimen						
Antracyclines	91	300	0.73 (0.67-0.77)	0.0033	reference	reference
Antracyclines and taxanes	17	41	0.56 (0.39-0.70)		2.03 (1.21,3.40)	1.91 (1.07,3.40)
Others	67	264	0.75 (0.68-0.80)		0.83 (0.60,1.13)	0.81 (0.52,1.26)

NOTE. Bold text indicates significant variables. Total number of patients in the tables varies because of unknown values.

Abbreviations: HR, Hazard Ratio; TNBC, triple-negative breast cancer.

* log-rank test

† Determined by univariable Cox regression model

‡ Determined by multivariable Cox regression model (only variables significant at a P-value of 0.05 in the univariable model were considered).