Master of Medicine

Long-term outcome of breast cancer patients after neoadjuvant chemotherapy

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of the University of Ulsan
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Long-term outcome of breast cancer patients after neoadjuvant chemotherapy

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A Dissertation

Submitted to

the Graduate School of the University of Ulsan

In partial Fulfillment of the Requirements

for the Degree of

Master of Medicine

by

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Ulsan, Korea

August 2020

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August 2020

Abstract

Background

Neoadjuvant chemotherapy (NCT) has become the standard of care for operable early-stage breast cancer (BC). Pathologic complete response (pCR) after NCT as well as subtype and age are good prognostic factors for long-term survival. We aimed to identify factors associated achieving pCR and the role of pCR as a prognostic indicator after NCT.

Patients and methods

Total 1,643 patients with BC undergone NCT between 2008 and 2014 were analyzed. Baseline characteristics of patient and tumor, pCR rate and long-term survival outcome were evaluated. Factors associated with achieving pCR, prognostic impact of pCR on overall, each subgroup were analyzed. Disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS) were evaluated.

Results

Median age at diagnosis was 45 years (range: 20–80); median follow-up period was 65.5 months (range: 7–147). The overall pCR (ypT0/is ypN0) rate was 17.3%. Tumor size, grade, proliferative index (Ki-67%) and BC subtypes were associated with achieving pCR. Patients with pCR displayed favorable outcome in DFS, DMFS and OS. Among pCR group, age and other known factors were not associated with outcome. On the contrary, among patients with residual disease, young (<40yr) patients exhibited the significantly worst outcome than older non-pCR group. Other risk factors of tumor size, LN involvement, BC subtype were independently associated with outcome in non-pCR group. Among patients exhibiting recurrence after achieving pCR (24/284), more than 70% presented with distant metastasis.

Conclusion

Grade, proliferative index, tumor size and BC subtype were associated with achieving pCR after NCT. Patients who achieved pCR after NCT showed better DFS, DMFS, and OS.

Favorable outcome sustained regardless of other known risk factors. pCR achievement was a good prognostic indicator in both young and old groups. Young age, high initial tumor burden, HR-/HER2+, TNBC were associated with worse outcome in patients with residual disease after NCT. Additional adjuvant systemic therapy should be considered for patients with residual disease after NCT.

Keywords: Breast neoplasm, Neoadjuvant chemotherapy, Pathologic complete response, Subtypes, Age, Survival

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Introduction

Neoadjuvant chemotherapy (NCT) has become the standard of care for patients with operable early-stage breast cancer. Previously, NCT was used in a limited population of breast cancer patients with advanced stage as the timing of chemotherapy showed no difference in oncologic outcome.[1, 2] Neoadjuvant chemotherapy strategy has several advantages over adjuvant chemotherapy that it provides the opportunity to increase the possibility of breast conservation surgery and to reduce the extent of axillary surgery by down-staging of the tumor.[3, 4] Additionally, the response to specific given cytotoxic drugs can be monitored *in vivo*, providing an opportunity for patients unresponsive to NCT to receive alternative chemotherapy regimens.[1]

In South Korea, the proportion of young breast cancer patients is higher than that in western countries and the median age at diagnosis was 51.5 years (range 16 - 99) in 2016 .[5, 6] Young breast cancer patients tend to present advanced stage at diagnosis compared to older patients diagnosed from screening. Yet, apart from the advanced stage, cancers in younger group have worse prognosis owing to more aggressive nature of the tumor. Studies have revealed similar gene expression patterns in young age breast cancer patients with worse prognosis compared to elderly counterparts.[7] This is more pronounced in very young (<35yrs) breast cancer patients with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2−) subtypes.[8, 9] Innate resistance to endocrine therapy and decreased adherence to anti-estrogen treatment have been suggested to be the cause.[10]

Pathologic complete response (pCR) after NCT is a known favorable prognostic indicator and is widely used as an endpoint in NCT clinical trials.[11, 12] However, controversial results exist in HR+/HER2- population among whom the pCR rate is low, that pCR does not correlate with recurrence nor survival.[13] Also, the definition of pCR differs in each study requiring careful interpretation.[14, 15]

In this retrospective study, we aimed to evaluate factors associated with pCR and its role as a

prognostic indicator among the whole population and in each breast cancer subtype and age group.

Materials and methods

Patient selection

Between 2008 and 2014, 1,930 patients were diagnosed with breast cancer and treated with neoadjuvant chemotherapy at AMC. Patients with stage IV disease, bilateral breast cancer, and those previously diagnosed with cancer in other site(s) were excluded. Patients with a follow-up period of less than 6 months were also excluded. A total of 1,643 patients were finally analyzed.

Clinical pathological and survival data were retrieved from the Asan Medical Center breast cancer surgery database. It is a web-based database that has been maintained prospectively by surgical oncologists and contains information on all consecutive patients who have undergone breast cancer surgery at the Asan Medical Center since 1989. Clinicopathological data including age at diagnosis, tumor grade, HR status, HER2 status, Ki-67 level (cutoff ≥50%), type of breast and axillary surgery, clinical stage, type of neoadjuvant chemotherapy regimen, and achievement of pCR were obtained. All tumor characteristic factors were from treatment-naïve time-point, clinical TNM stage and IHC profile from core-needle biopsy (CNB) specimen. Chemotherapeutic regimen was decided within the multidisciplinary clinic consist of medical and surgical oncologist, radiologist, radio-oncology and pathologist after thorough discussion. Anthracycline- and/or taxane regimen were given to patients according to pre-treatment tumor biology. pCR was defined as absence of residual invasive disease in the breast and axilla or presence only of noninvasive residual carcinoma in the breast (ypT0/Tis ypN0).[15)]

Recurrence and survival data were updated by reviewing electronic medical records (EMR) , the National Health Insurance Service and survey through direct phone-call to the patients. Disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS) were analyzed. DFS was defined as time from surgery to any locoregional or distant metastasis during the follow-up period. DMFS was defined as time from surgery to distant metastasis. OS was defined as time from surgery to death of any cause. Our study was approved by the Institutional Review Board (IRB no. 2017-1341) of Asan Medical Center (AMC), Seoul, Korea.

Objectives

We aimed to evaluate factors associated with pCR and its role as a prognostic indicator among the whole population and in each breast cancer subtype and age group. Factors associated with outcome in both pCR and non-pCR group were analyzed. Recurrence pattern after pCR observed in small number of patients, was also described.

Statistical analysis

The baseline characteristics of all patients were analyzed by descriptive statistics. Clinicopathological characteristics were compared between the pCR and no pCR groups using Chi-square or Fisher's exact tests followed by multivariate logistic regression analysis. Survival curves were presented using the Kaplan-Meier method, and the significance of survival differences was analyzed using the log-rank test. The Cox proportional hazards model was used to evaluate the independent prognostic effect of the variables in two groups. Adjusted variables included age at diagnosis, tumor size, lymph node status, histologic grade, hormone receptor status, HER2 status, Ki-67 status, and pCR achievement. The cutoff value for statistical significance was set at P <0.05. All statistical analyses were performed using SPSS ver. 22.0 (IBM Corp., Armonk, NY).

Results

Patient demographics and pCR rate

Median follow-up period was 65.5 months (range: 7–147). Median age at diagnosis was 45 years (range: 20–80) and 28% (40/1643) were <40 years (Table1). 30.7% had tumor size >5cm and 69.6% (1,144/1643) presented with clinical LN positive disease. Total population consist of 42.7% (702/1643) HR+, 31.9% (523/1643) HER2+ breast cancers. 85.1% of patients were treated with anthracycline containing regimen. Among 513 HER2+ patients, 23.5% were given anti-HER2 therapy preoperatively as anti-HER2 therapy during NCT and 63.7% received as adjuvant treatment. (data not shown). Overall pCR (ypT0/is and ypN0) rate was 17.3%. Node pCR was observed in 49.4% (812/1643). ypT0, ypTis, ypT residual in the primary breast tumor was 13.9%, 6.4% and 79.7% respectively.

Factors associated with achieving pathologic complete response

While pCR rate was similar between young (<40yr) and old (≥40yr) patients (17.8% and 17.1%, respectively; *P*=0.718), diverse pCR rate was observed according to breast cancer subtypes (Table2). pCR rates in HR+/HER2-, HR+/HER2+, HR-/HER2+ and triple negative (TNBC) were 7.3% (51/695), 14.3% (36/249), 31.2% (83/264) and 26.1% (114/433) respectively (*P*<0.001). Factors associated with pCR in whole population is described in Table2. Tumors with smaller size (<5cm), high proliferative index (Ki67≥50%) were independently associated to achieve pCR. HR+/HER2+, HR-/HER2+ and TNBC subtypes were more likely to achieve pCR than HR+/HER2- (odds ratio, OR 1.645, 4.538 and 2.817, P<0.001). Also, patients treated with chemotherapeutic regimen other than anthracycline- nor taxane based regimen were less likely to achieve pCR.

Long term outcome after neoadjuvant chemotherapy

Consistent with previously known, patients with pCR showed better 5-year DFS, DMFS, and OS (93.2% vs 77.1%, 94.3% vs 80.2% and 95.5% vs 84.6%, respectively) (Figure 1A). In multivariable

Cox regression survival analysis, younger age (<40yr) greater tumor size (>5cm), LN positivity and HR negativity was associated with worse outcome. Notably, achieving pCR was the most powerful prognostic factor (DFS hazard ratio, HR 4.07, P<0.001) than other known prognostic factors (Table 3).

Subgroup analysis according to breast cancer subtypes were done subsequently. 1) Among HR+/HER2− subtype, patients with pCR displayed better 5-year DFS (96.1% vs 84.3%, log rank=0.042), but no significant difference in DMFS nor OS was observed (Figure 1B). Similarly, in Cox regression analysis, pCR was a prognostic indicator of DFS and DMFS with greatest impact (HR 3.72 and 4.22 respectively). Lymph node metastasis was the only factor independently associated with worse DFS, DMFS and OS in this subgroup. Younger age was an independent prognostic factor of DFS in this subtype and yet, not in DMFS and OS(Table 4). 2) In patients with HR+/HER2+ breast cancer, although better DFS, DMFS, OS was observed numerically, pCR achievement was not a significant prognostic indicator (Figure 1C, Table 5). Moreover, none of the known prognostic factors were associated with DFS, DMFS nor OS in this subgroup. 3) In HR−/HER2+ subgroup, pCR achievement was the most powerful prognostic factor of DFS, DMFS, and OS (Figure 1D, 1E). In the multivariable analysis however, known prognostic factors were not associated with DFS, DMFS nor OS (Table6). 4) In TNBC group, similar to other subgroups, pCR was the most powerful prognostic factor affecting DFS, DMFS, and OS even with sequential increase in hazard ratio (Figure 1E). Initial tumor size (>5cm) and LN metastasis was also independent risk factors affecting DFS, DMFS and OS (Table7). The hazard ratio even showed sequential increase between DFS, DMFS and OS. Young age (<40yr) patients with TNBC displayed worse DFS, yet no difference in DMFS and OS was observed.

Subgroup analysis by age at diagnosis (<40yrs vs ≥40yrs) showed that pCR achievement was an independent prognostic factor in both age groups (Figure 2 A-B, Tables 8-9). In both age groups, pCR had the greatest hazard ratio than other risk factors including tumor size, LN involvement and HR positivity, throughout DFS, DMFS and OS. Hazard ratio of pCR was greater in younger age group than in old age group.

Patients were then divided into four groups by age combined with breast cancer subtype. The

survival curve of young/pCR and old/pCR group overlapped (Figure 2C). On the contrary, among patients with residual disease, the survival curve spread apart widely with young_non-pCR group displaying the worst outcome than old/non-pCR group. Five-year DFS, DMFS, and OS of the 'young/pCR', 'old/pCR', 'old/non-pCR' and 'young_non-pCR' are illustrated in Figure2C (P<0.001).

Cox regression analysis was performed among patients with pCR to assess factors associated with outcome after achieving pCR. In particular, tumor size (>5cm) was the only factor associated with outcome after achieving pCR (Table 10). The initial tumor size (>5cm) was significantly prognostic for all DFS, DMFS and OS in this group (HR 3.18, 3.94 and 6.07 respectively, Table10). On the contrary, among patients with residual disease, tumor size, LN involvement, age and breast cancer subtype were all significantly associated with outcome (Table 11).

Among 284 patients who achieved pCR, 24 cases had recurrence and 70.8% (17/24) presented with distant metastasis (Table12). In patients with distant metastasis. 5 cases had brain metastasis, followed by lung (n=3), bone and liver metastasis in one case each. 70.6% (12/17) of distant metastasis occurred in patients with HR- subtype. Disease free interval was relatively short, with median 25.7 months (Figure3)

Discussion

In this study, we observed pCR after NCT was the strongest independent prognostic indicator than all the other conventional prognostic factors. Notably, as young age itself indicates worse prognosis, we observed young age patients with residual disease present the worst outcome than the older patients with residual disease. Yet, among patients who achieved pCR, young age group and older group had similar outcome. Furthermore, other risk factors for example, LN metastasis and breast cancer subtype, did not affect outcome in this pCR group, except for initial tumor size (>5cm). This indicates the overall impact of achieving pCR in long term outcome.

From a pooled analysis of eight prospectively randomized controlled trials by Loibl et al. [13] in 2015, they reported that while significant survival difference is observed in the youngest age group(<40yr) according to pCR status, survival benefit in older age groups did not reach a significant difference in terms of pCR status. Our study showed similar result that the magnitude of pCR on long term outcome was, although significantly better, smaller in older age group than the younger counterpart. They also found that the effect of pCR on the prognosis was not significant in the HR+/HER2− group, and age was the only determining factor, especially in low grade luminal A-like breast cancer. Also in 2016, Villarreal-Garza et al. [16] analyzed 1,639 patients treated with preoperative chemotherapy. HR+ breast cancer patients achieving pCR after NCT showed no significant survival benefit in disease free survival. In those with HR+ subtype with residual disease, younger patients (<40yr) showed worse DFS than those older (>40yr) without pCR. However, HR+/HER2− group in our study, pCR status along with age and LN involvement were indeed significantly associated with outcome. Spring et al. [17] analyzed young age breast cancer patients (< 40 yrs) undergone NCT. They observed patients who achieved pCR showed significant long term DFS advantage and regardless of subtype including HR+/HER2- Subtype. The different observations between each study on HR+ Subtype could be addressed in several aspects. Heterogeneous study population in each study could yield different result. As endocrine therapy is a critical systemic strategy for HR+ Subtype, adherence to adjuvant endocrine

therapy in HR+ patients may have caused the different outcome apart from achieving pCR. Also, the rate of pCR is relatively low and the number of events were small which may affect the statistical power. The late recurrence (recurrence after 5-10yrs) should be taken into account for this HR+ population needing further follow-up.

In the HR+/HER2+ group, patients with pCR did not have survival benefit. Other known prognostic indicators also failed to reach statistical significance. A possible explanation for this is that our study cohort includes patients to whom preoperative target therapy was not given. In our study, only 26.1% of HR+/HER2+ patients received neoadjuvant target therapy resulting in low pCR rate (14.3%). Additionally, number of HR+/HER2+ cases in the study population was relatively small (n=249), with small number of events (recurrence, n=41). Unlike HR+/HER2+ Subtype, significant survival benefit from achieving pCR was observed in HR-/HER2+ group in our study. While pCR indicated favorable outcome in terms of DFS, DMFS and OS, other known factors did not significantly affect outcome. Limited number of patients were given anti-HER2 therapy preoperatively likewise, yet HR negativity itself drives better response to NCT resulting in higher pCR rate (31.2%). The TNBC group in our study, also showed significant survival benefit according to pCR status. Although with smaller impact, younger age and initial tumor burden (size, LN involvement) were also independently associated with outcome in this population.

Our findings suggest that achieving complete remission after NCT itself is a strong independent indicator of a favorable prognosis. And when pCR takes place, magnitude of other known factors affecting survival outcome become minimal. Consistent with our finding, Weiss et al. [18] after analyzing 721 patients who obtained pCR, reported that there was no difference in DFS by chemotherapy regimen nor breast cancer subtype among patients who had already obtained pCR. Our finding is also similar that pCR is prognostic in HR+/HER2- Subtype implying necessity of better surrogate to predict response to NCT, to decide whether to give NCT or perform upfront surgery especially in locally advanced stage.

Another important observation in this study is the outcome of the patients with residual disease. In patients without pCR, age as well as other known prognostic factors remained significantly associated with outcome. We have seen the data of CREATE-X trial, which provided evidence to give additional adjuvant capecitabine for patients with residual disease in HER2- subtype.[19] The benefit of adjuvant capecitabine was greatest among TNBCs. Taking into account the greater risk of recurrence in patients with residual disease, we should consider additional systemic treatment strategy for this population according to each subtype. Benefit of adding GnRH agonist and/or CDK inhibitor for HR+/HER2- Subtype would be worthy of investigating. Adding adjuvant immune checkpoint inhibitor for high risk TNBCs after NCT are being investigated. For HER2+ breast cancers, we already have evidence from clinical trial KATHERINE, to give adjuvant TDM-1 when residual disease after neoadjuvant chemo and anti-HER2 therapy.[20] Yet, the risk among the non-pCR group should definitely be stratified then, evidence regarding the risk should be built.

Not only the non-pCR group but also patients who exhibited pCR, do present with recurrences. The recurrence pattern in patients with pCR differs from that reported in a previous study.[21, 22] We observed that ipsilateral and/or regional-only recurrence was observed in 29.2% (7/24) of this group while 70.8% (17/24) of them presented with distant metastasis. While commonly known metastatic site are bone and lung, in this study population 29.4% (5/24) of the metastasis were found in brain. Also multiple distant organ involvement were found in 5 cases. These data suggest that recurrence after pCR may be present with more aggressive phenotype. After surgery, a thorough risk assessment should be done in all patients, including ones with pCR, along with careful follow-up and surveillance.[23] For patients with residual disease, escalation of adjuvant systemic strategy should be implemented especially in younger patients with greater tumor burden. The adjuvant treatment should obviously be decided as per breast cancer subtype based on evidence established in each clinical settings.[13, 16, 17]

This study has innate limitation as a retrospective study, that the study population are

heterogeneous in terms of patient, tumor, given therapy etc. which makes difficult to interpret the causes and consequences. Also the adjuvant treatment were taken into account quite restrictedly during survival analyses which could have affected the outcome. Yet, despite this limitation, our study has several strengths. It included a large number of Asian patients treated with NCT, whose long-term outcome was rarely reported in previous retrospective studies.[24] We demonstrated subgroup analyses comprehensive manner to translate relevant implications. Also the survival update was done immensely thoroughly, using direct phone calls and national healthcare system to enhance the quality of the data.

Conclusion

Patients with pCR after NCT showed better outcome. pCR exhibited the greatest impact on survival than other known prognostic indicators. While young age patients with pCR displayed similar outcome with old age patients, young age patients with residual disease presented with the worst outcome. Patients with residual disease after NCT should be considered to undergo adjuvant systemic therapy followed by comprehensive risk assessment. Young age patients who presented with high clinical stage at diagnosis are high risk group who may require additional adjuvant treatment. Evidence to decide the best adjuvant treatment in each clinical setting needs to be furtherly investigated. At the same time, a robust platform should be established to decide the best neoadjuvant strategy, especially for HR+ Subtype.

Table 1. Baseline characteristics of total patients (n=1,643)

Factors		numbers	%
Age*	<40	460	28.0
	≥40	1,183	72.0
Tumor grade*	Grade I–II	1,015	61.9
	Grade III	624	38.1
Tumor size*	≤5 cm	1,138	69.3
	>5 cm	505	30.7
Pre-treatment nodal status*	No regional metastasis	499	30.4
	Regional lymph node metastasis	1,144	69.6
Proliferation Index*	Ki67 <50%	722	47.0
	Ki67 ≥50%	871	53.0
Hormone receptor*	Negative	702	42.7
	Positive	941	57.3
HER2 overexpression*	Negative	1,118	68.1
	Positive	523	31.9
Subtype by IHC*	HR+/HER2−	695	42.4
	HR+/HER2+	249	15.2
	HR−/HER2+	264	16.1
	TNBC	433	26.4
Clinical Stage*	1	25	1.5
	2	984	59.9
	3	633	38.6
Chemotherapy regimen	Anthracycline only	450	27.4
	Anthracycline + taxane	948	57.7
	Taxane based	175	10.7
	Others	70	4.3
Radiation therapy	No	290	17.7
	Yes	1,353	82.3
Type of breast surgery	Breast conservation	844	51.4
	Total mastectomy	798	48.6
Axillary Dissection	Sentinel lymph node biopsy only	781	47.6
	Axillary dissection	861	52.4
pCR achievement (ypT0/Tis, ypN0)	no pCR	1,359	82.7%
	pCR	284	17.3%
pCR tumor	ypT0	228	13.9%
	ypTis	105	6.4%
	ypT residual	1,310	79.7%
pCR node	ypN residual	831	50.6%
	ypN0	812	49.4%

*; pretreatment data

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; HR, hormone receptor; pCR, pathologic complete response; TNBC, triple negative breast cancer

Table 2. pCR rate and factors associated with pCR achievement

		Univariable analysis					Multivariable analysis			
		PCR achievement								
		no pCR		pCR			Odds	95% CI		
		n	%	n	%	*P*-value	Ratio	min	max	*P*-value
Age*	Age <40	378	82.20%	82	17.80%	0.718	Ref.			
	Age ≥ 40	981	82.90%	202	17.10%		1.004	0.737	1.367	0.981
Tumor Grade*	Grade I–II	894	88.10%	121	11.90%	<0.001	Ref.			
	Grade III	463	74.20%	161	25.80%		1.512	1.127	2.028	0.006
Tumor size*	≤5 cm	916	80.50%	222	19.50%	<0.001	0.534	0.385	0.742	<0.001
	>5 cm	443	87.70%	62	12.30%		Ref.			
Nodal status*	No regional metastasis	413	82.80%	86	17.20%	0.971	Ref.			
	Regional node metastasis	946	82.70%	198	17.30%		0.897	0.613	1.313	0.576
Hormone receptor*	Negative	505	71.90%	197	28.10%	<0.001		N/A		
	Positive	854	90.80%	87	9.20%					
HER2 overexpression*	Negative	955	85.40%	163	14.60%	<0.001		N/A		
	Positive	402	76.90%	121	23.10%					
Proliferation Index*	Ki67 <50%	698	90.40%	74	9.60%	<0.001	Ref.			
	Ki67 ≥50%	661	75.90%	210	24.10%		2.205	1.616	3.008	<0.001
Chemotherapy regimen*	Anthracycline only	379	84.20%	71	15.80%	<0.001	7.486	1.733	32.332	0.007
	Anthracycline + taxane	785	82.80%	163	17.20%		9.277	2.206	39.013	0.002
	Taxane based	127	72.60%	48	27.40%		14.324	3.298	62.212	0
	Others	68	97.10%	2	2.90%		ref			0.001
Subtype by IHC*	HR+/HER2−	644	92.70%	51	7.30%	<0.001				0
	HR+/HER2+	213	85.50%	36	14.30%		1.645	1.024	2.642	0.04
	HR−/HER2+	181	68.60%	83	31.20%		4.538	3.008	6.847	0
	TNBC	319	73.70%	114	26.10%		2.817	1.899	4.178	0

*; pretreatment data

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; HR, hormone receptor; pCR, pathologic complete response; TNBC, triple negative breast cancer

Table 3. Multivariable analysis of factors associated with long-term survival in all patients

	DFS				DMFS				OS			
Variables (*reference*)	*P*-value	Hazard ratio	95% CI min.	95% CI max.	*P*-value	Hazard ratio	95% CI min.	95% CI max.	*P*-value	Hazard ratio	95% CI min.	95% CI max.
no pCR (*pCR*)	<0.001	4.07	2.66	6.22	<0.001	4.97	3.02	8.19	<0.001	5.65	3.20	9.95
Grade III (*grade I–II*)	0.223	0.86	0.67	1.10	0.314	0.88	0.67	1.14	0.797	0.96	0.73	1.28
Tumor size >5 cm (*≤5 cm*)	0.004	1.39	1.11	1.74	<0.001	1.70	1.34	2.15	<0.001	1.90	1.47	2.46
Lymph node metastasis(*negative*)	<0.001	2.17	1.64	2.86	<0.001	2.90	2.06	4.07	<0.001	3.21	2.17	4.73
Ki 67 ≥50% (*Ki 67 <50%*)	0.157	1.18	0.94	1.48	0.005	1.44	1.12	1.85	0.026	1.37	1.04	1.81
HER2+ (*negative*)	0.083	0.81	0.64	1.03	0.097	0.80	0.62	1.04	0.03	0.73	0.56	0.97
HR− (*positive*)	<0.001	2.48	1.94	3.17	<0.001	2.62	2.01	3.42	<0.001	3.21	2.39	4.32
Age at diagnosis: <40 years (*≥40 years*)	<0.001	1.58	1.27	1.98	0.002	1.47	1.15	1.87	0.066	1.29	0.98	1.69

DFS, disease-free survival; DMFS, distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; HER2, human epidermal growth factor receptor 2; HR; hormone receptor; CI, confidence interval

Table 4. Multivariable analysis of factors associated with long-term survival in HR+/HER2− group

	DFS				DMFS				OS			
Variables (*reference*)	*P*-value	Hazard ratio	95% CI min.	95% CI max.	*P*-value	Hazard ratio	95% CI min.	95% CI max.	*P*-value	Hazard ratio	95% CI min.	95% CI max.
no pCR (pCR)	0.026	3.72	1.17	11.84	0.046	4.22	1.03	17.36	0.126	3.03	0.73	12.59
Grade III (grade I–II)	0.152	1.39	0.89	2.18	0.202	1.38	0.84	2.28	0.205	1.44	0.82	2.53
Tumor size >5 cm (≤5 cm)	0.517	1.14	0.77	1.67	0.072	1.48	0.97	2.25	0.054	1.62	0.99	2.64
Lymph node metastasis(negative)	<0.001	2.57	1.56	4.22	<0.001	3.51	1.86	6.61	<0.001	4.86	2.09	11.30
Ki 67 ≥50% (Ki 67 <50%)	0.19	1.29	0.88	1.89	0.023	1.63	1.07	2.50	0.011	1.92	1.16	3.19
Age at diagnosis: <40 years (≥40 years)	0.011	1.65	1.12	2.43	0.132	1.41	0.90	2.19	0.592	1.16	0.68	1.98

DFS, disease-free survival; DMFS distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval

Table 5. Multivariable analysis of factors associated with long-term survival in HR+/HER2+ group

	DFS				DMFS				OS			
Variables (*reference*)	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.
no pCR (pCR)	0.137	2.46	0.75	8.05	0.274	1.95	0.59	6.45	0.127	4.76	0.64	35.35
Grade III (grade I–II)	0.293	0.68	0.33	1.40	0.171	0.55	0.24	1.29	0.458	0.72	0.30	1.73
Tumor size >5 cm (≤5 cm)	0.464	1.28	0.66	2.47	0.215	1.56	0.77	3.12	0.052	2.21	0.99	4.94
Lymph node metastasis(negative)	0.864	1.07	0.49	2.33	0.093	2.86	0.84	9.70	0.378	1.77	0.50	6.31
Ki 67 ≥50% (Ki 67 <50%)	0.192	1.53	0.81	2.87	0.09	1.86	0.91	3.82	0.129	1.90	0.83	4.32
Age at diagnosis: <40 years (≥40 years)	0.335	1.36	0.73	2.53	0.496	1.28	0.63	2.57	0.755	1.13	0.51	2.50

DFS, disease-free survival; DMFS, distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval

Table 6. Multivariable analysis of factors associated with long-term survival in HR−/HER2+ group

	DFS				DMFS				OS			
Variables (*reference*)	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.
pCR (non pCR)	<0.001	3.83	1.81	8.12	<0.001	4.70	2.00	11.06	0.001	4.55	1.79	11.55
Grade III (grade I-II)	0.175	0.71	0.43	1.17	0.406	0.80	0.47	1.36	0.73	0.91	0.52	1.59
Tumor size >5 cm (≤5 cm)	0.114	1.51	0.91	2.50	0.083	1.61	0.94	2.75	0.073	1.68	0.95	2.95
Lymph node metastasis(negative)	0.153	1.68	0.82	3.44	0.066	2.22	0.95	5.22	0.031	3.11	1.11	8.68
Ki 67 ≥50% (Ki 67<50%)	0.295	1.32	0.78	2.24	0.051	1.78	1.00	3.19	0.653	1.14	0.64	2.03
Age at diagnosis: <40 years (≥40 years)	0.055	1.74	0.99	3.07	0.074	1.73	0.95	3.16	0.307	1.41	0.73	2.72

DFS, disease-free survival; DMFS distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval

Table 7. Multivariable analysis of factors associated with long-term survival in TNBC group

	DFS				DMFS				OS			
Variables (*reference*)	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.
pCR (non pCR)	<0.001	4.65	2.41	8.96	<0.001	6.78	2.95	15.60	<0.001	7.49	3.02	18.59
Grade III (grade I–II)	0.21	0.79	0.55	1.14	0.386	0.84	0.57	1.24	0.62	0.90	0.60	1.35
Tumor size >5 cm (≤5 cm)	0.015	1.58	1.10	2.29	0.002	1.85	1.26	2.72	0.001	2.03	1.36	3.02
Lymph node metastasis(negative)	<0.001	2.23	1.45	3.41	<0.001	2.60	1.61	4.22	<0.001	2.77	1.65	4.64
Ki 67 ≥50% (Ki 67 <50%)	0.633	0.91	0.62	1.34	0.987	1.00	0.66	1.53	0.918	1.02	0.66	1.59
Age at diagnosis: <40 years (≥40 years)	0.035	1.48	1.03	2.12	0.092	1.39	0.95	2.05	0.241	1.27	0.85	1.91

DFS, disease-free survival; DMFS distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval

Table 8. Multivariable analysis of factors associated with long-term survival in patients aged below 40 years

	DFS				DMFS				OS			
Variables (*reference*)	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.
pCR (non pCR)	<0.001	4.86	2.34	10.11	<0.001	5.41	2.33	12.54	<0.001	5.52	2.19	13.87
Grade III (grade I–II)	0.003	0.53	0.35	0.81	0.026	0.60	0.38	0.94	0.472	0.83	0.51	1.37
Tumor size >5 cm (≤5 cm)	0.111	1.35	0.93	1.95	0.01	1.70	1.14	2.53	0.002	2.02	1.29	3.16
Lymph node metastasis(negative)	0.072	1.45	0.97	2.18	0.006	1.99	1.22	3.25	0.002	2.50	1.39	4.50
Ki 67 ≥50% (Ki 67 <50%)	0.553	1.12	0.77	1.64	0.227	1.30	0.85	1.99	0.181	1.40	0.86	2.28
HER2 overexpression (negative)	0.419	0.85	0.57	1.27	0.612	0.89	0.58	1.38	0.333	0.78	0.47	1.29
HR positive (negative)	<0.001	3.10	2.04	4.70	<0.001	3.31	2.09	5.24	<0.001	3.63	2.13	6.19

DFS, disease-free survival; DMFS distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval

Table 9. Multivariable analysis of factors associated with long-term survival in patients aged 40 years and above

	DFS				DMFS				OS			
Variables (*reference*)	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.
pCR (non pCR)	<0.001	3.56	2.11	5.98	<0.001	4.58	2.46	8.51	<0.001	5.69	2.77	11.70
Grade III (grade I–II)	0.47	1.12	0.83	1.51	0.699	1.07	0.77	1.47	0.841	1.04	0.74	1.46
Tumor size >5 cm (≤5 cm)	0.019	1.40	1.06	1.84	0.001	1.67	1.24	2.25	<0.001	1.84	1.34	2.53
Lymph node metastasis(negative)	<0.001	3.02	2.03	4.49	<0.001	3.92	2.42	6.34	<0.001	3.85	2.28	6.49
Ki 67 ≥50% (Ki 67 <50%)	0.262	1.18	0.89	1.57	0.014	1.48	1.08	2.03	0.079	1.35	0.97	1.89
HER2 overexpression (negative)	0.058	0.75	0.56	1.01	0.06	0.74	0.53	1.01	0.048	0.71	0.50	1.00
HR positive (negative)	<0.001	2.26	1.67	3.07	<0.001	2.39	1.72	3.32	<0.001	3.05	2.13	4.36

DFS, disease-free survival; DMFS distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor

Table 10. Multivariable analysis of factors associated with long-term survival in patients who achieved pCR

	DFS				DMFS				OS			
Variables (reference)	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.	*P*-value	Hazard ratio	95% CI min.	max.
Subtypes												
HR+/HER2+(reference)	0.399				0.852				0.611			
HR+/HER2+	0.727	1.34	0.26	6.81	0.634	1.55	0.25	9.50	0.569	0.49	0.04	5.59
HR−/HER2+	0.474	1.65	0.42	6.56	0.668	1.43	0.28	7.46	0.815	1.23	0.22	6.75
HR−/HER2−	0.121	3.03	0.75	12.25	0.395	2.10	0.38	11.55	0.405	2.14	0.36	12.73
Grade III (grade I–II)	0.151	0.53	0.22	1.26	0.112	0.42	0.14	1.22	0.03	0.24	0.07	0.87
Tumor size >5 cm (≤5 cm)	0.008	3.18	1.35	7.52	0.008	3.94	1.43	10.84	0.003	6.07	1.85	19.88
Lymph node metastasis(negative)	0.282	1.74	0.64	4.75	0.162	2.91	0.65	13.00	0.287	2.31	0.49	10.79
Ki 67 ≥50% (Ki 67 <50%)	0.05	0.41	0.17	1.00	0.903	0.93	0.28	3.05	0.857	0.88	0.22	3.55
Age at diagnosis: <40 years (≥40 years)	0.742	1.16	0.47	2.86	0.59	1.33	0.47	3.79	0.416	1.63	0.50	5.29

DFS, disease-free survival; DMFS distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor

Table 11. Multivariable analysis of factors associated with long-term survival in patients with residual disease

	DFS				DMFS				OS			
Variables (*reference*)	*P*-	Hazard	95% CI		*P*-	Hazard	95% CI		*P*-	Hazard	95% CI	
	value	ratio	min.	max.	value	ratio	min.	max.	value	ratio	min.	max.
Subtypes												
HR+/HER2+(reference)	<0.001				<0.001				<0.001			
HR+/HER2+	0.785	0.95	0.66	1.37	0.705	0.92	0.61	1.40	0.922	1.02	0.65	1.62
HR−/HER2+	<0.001	1.92	1.36	2.70	<0.001	1.99	1.37	2.88	<0.001	2.23	1.49	3.35
HR−/HER2−	<0.001	2.64	1.97	3.54	<0.001	2.85	2.08	3.91	<0.001	3.65	2.57	5.20
Grade III (grade I-II)	0.287	0.87	0.68	1.12	0.505	0.91	0.70	1.19	0.929	1.01	0.76	1.35
Tumor size >5 cm (≤5 cm)	0.029	1.29	1.03	1.62	<0.001	1.58	1.24	2.02	<0.001	1.74	1.34	2.27
Lymph node metastasis(negative)	<0.001	2.16	1.62	2.87	<0.001	2.86	2.03	4.04	<0.001	3.23	2.18	4.80
Ki 67 ≥50% (Ki 67 <50%)	0.043	1.27	1.01	1.61	0.003	1.47	1.14	1.91	0.023	1.39	1.05	1.84
Age at diagnosis: <40 years (≥40 years)	<0.001	1.57	1.24	1.97	0.007	1.41	1.10	1.82	0.182	1.21	0.92	1.60

DFS, disease-free survival; DMFS distant metastasis-free survival; OS, overall survival; pCR, pathologic complete response; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor

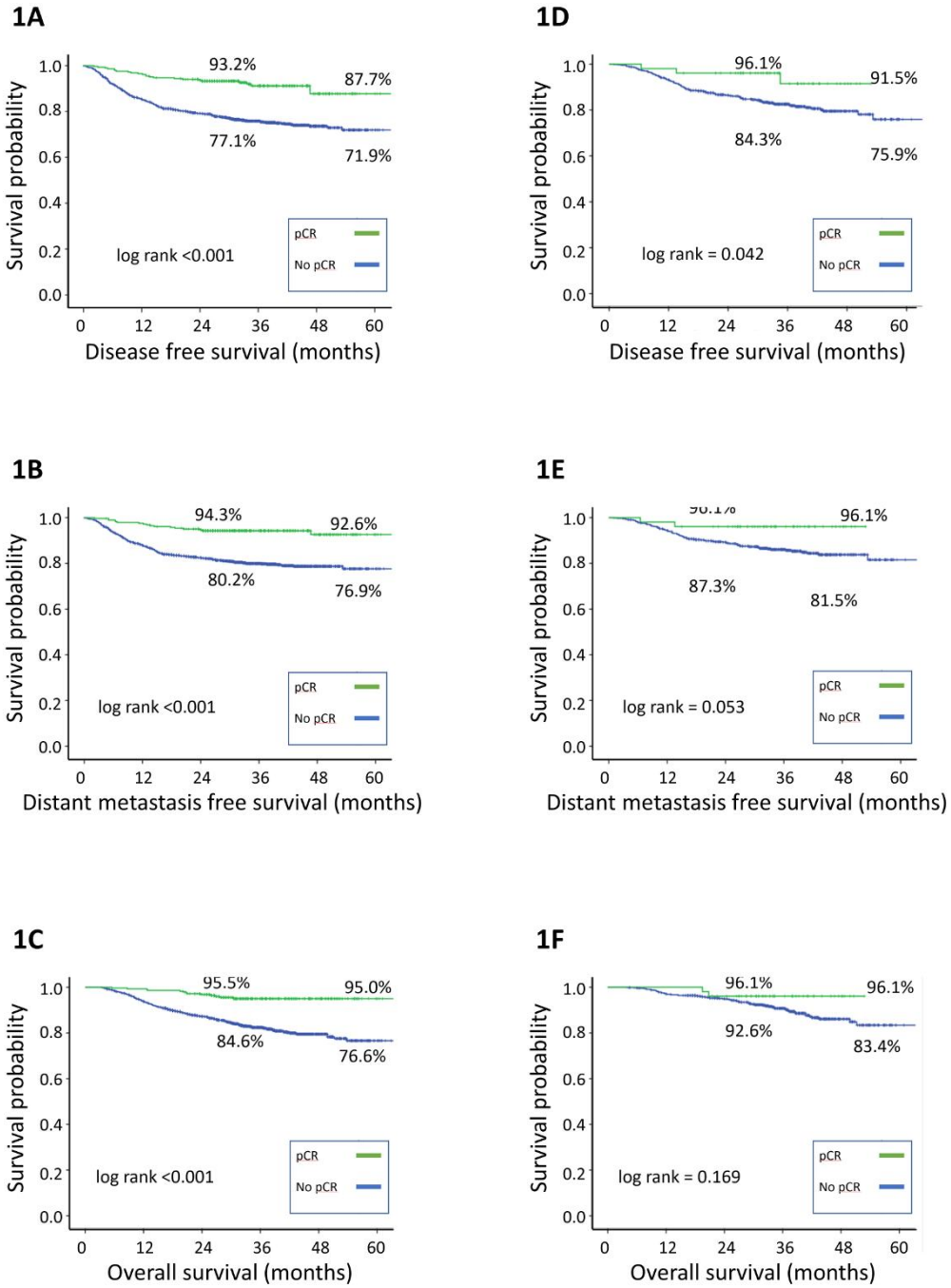
Table 12. Site and type of first recurrence of patients achieved pCR (n=24)

Locoregional only, 29.2% (7/24)	**N**	**%**	**Subtype**	**Clinical stage**	**Age**	**Disease free interval (months)**	**Death (recurrence to death, months)**
IBTR	5	71.4	HR-/HER2+	cT1 N2	47	19.5	Alive
			HR-/HER2+	cT3 N0	51	64.2	Alive
			HR−/HER2−	cT2 N0	32	93.4	Alive
			HR−/HER2−	cT2 N0	50	25.8	Alive
			HR−/HER2−	cT2 N1	61	35.7	Alive
Chest wall	1	14.3	HR+/HER2-	cT2 N1	35	27.7	Alive
Axillary node	1	14.3	HR−/HER2−	cT4 N3	56	9.0	Alive
Distant metastasis, 70.8% (17/24)	**N**	**%**	**Subtype**	**Clinical stage**	**Age**	**Disease free interval (months)**	**Death (recurrence to death, months)**
Distant lymph nodes	2	11.8	HR+/HER2-	cT3 N3	44	27.1	Alive
			HR−/HER2−	cT3 N1	57	41.0	14.0
Bone	1	5.9	HR+/HER2-	cT3 N3	48	12.9	26.0
Lung	3	17.6	HR−/HER2−	cT2 N1	36	18.4	21.8
			HR−/HER2−	cT3 N1	38	24.3	36.6

			HR−/HER2−	cT2 N1	60	6.0	5.0
Liver	1	5.9	HR-/HER2+	cT2 N2	51	4.3	Alive
			HR−/HER2−	cT2 N0	37	48.9	2.8
			HR+/HER2+	cT2 N1	50	28.9	Alive
Brain	5	29.4	HR+/HER2+	cT1 N3	51	25.7	16.2
			HR-/HER2+	cT3 N1	52	13.6	12.0
			HR-/HER2+	cT1 N3	67	10.0	Alive
			HR-/HER2+	cT3 N0	34	48.0	5.5
			HR−/HER2−	cT3 N1	35	12.7	4.6
Multiple (more than 3 organs)	5	29.4	HR+/HER2+	cT3 N1	38	93.3	Alive
			HR-/HER2+	cT3 N2	50	37.4	10.2
			HR-/HER2+	cT2 N3	50	22.5	2.8

HR, hormone receptor ; HER2, human epidermal growth factor receptor 2

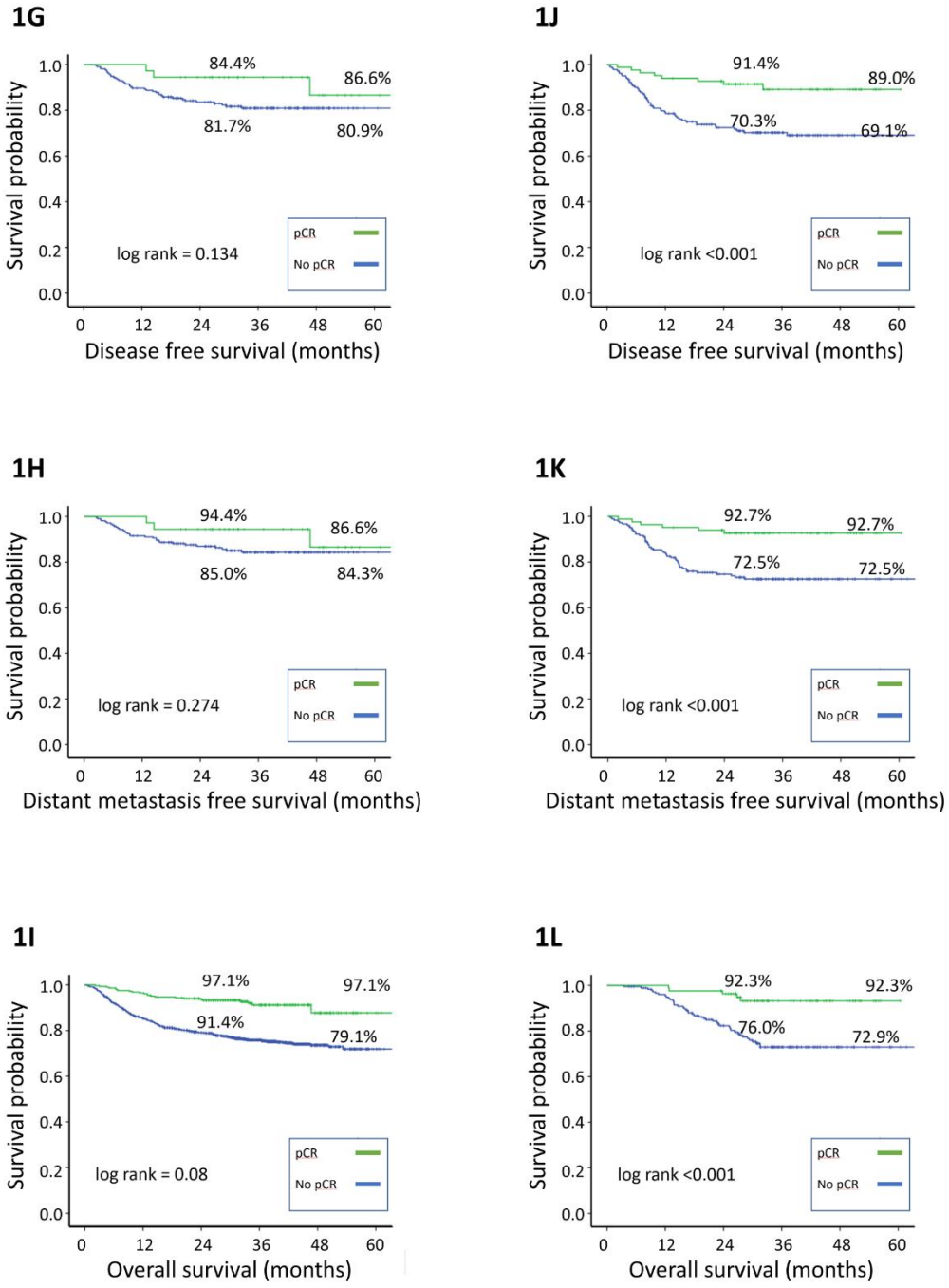
Figure 1. Kaplan-Meier curves by achievement of pCR



In all Patients

In HR+/HER2-

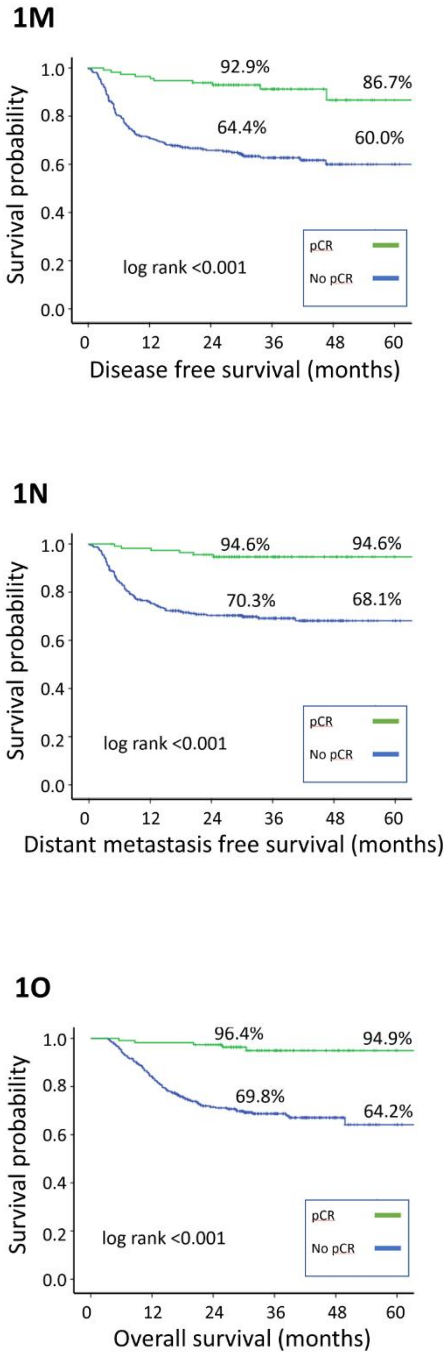
Figure 1. Kaplan-Meier curves by achievement of pCR



In HR+/HER2+

In HR-/HER2+

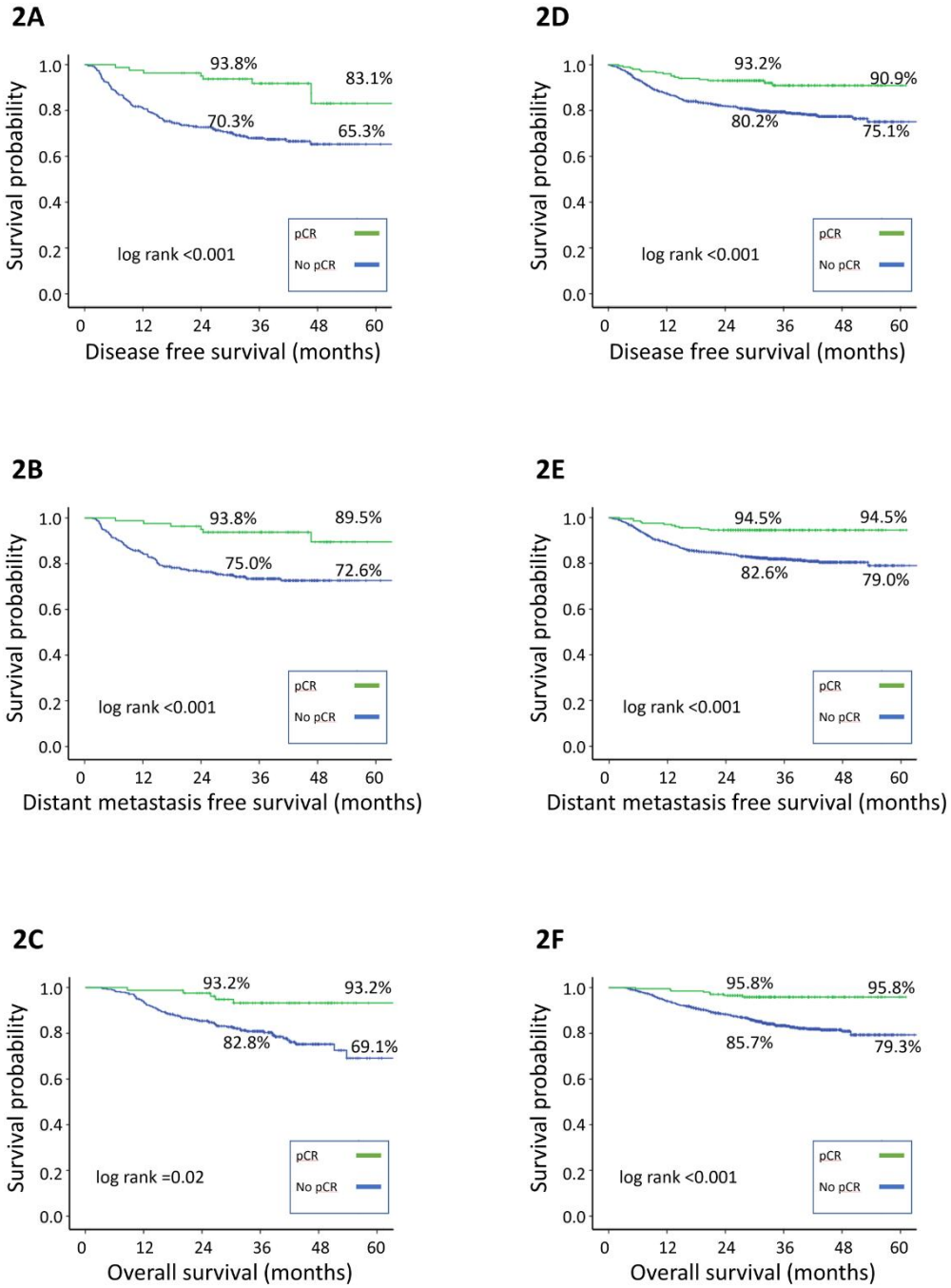
Figure 1. Kaplan-Meier curves by achievement of pCR



In HR-/HER2-

HR: hormone receptor, HER2: human epidermal growth factor receptor2

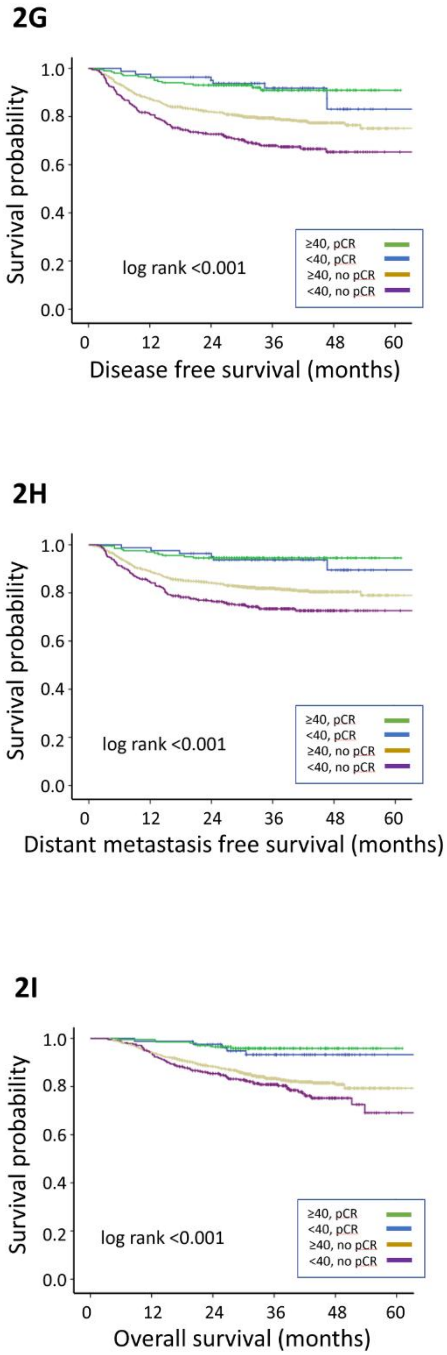
Figure 2. Kaplan-Meier curves by achievement of pCR



In patients age under 40

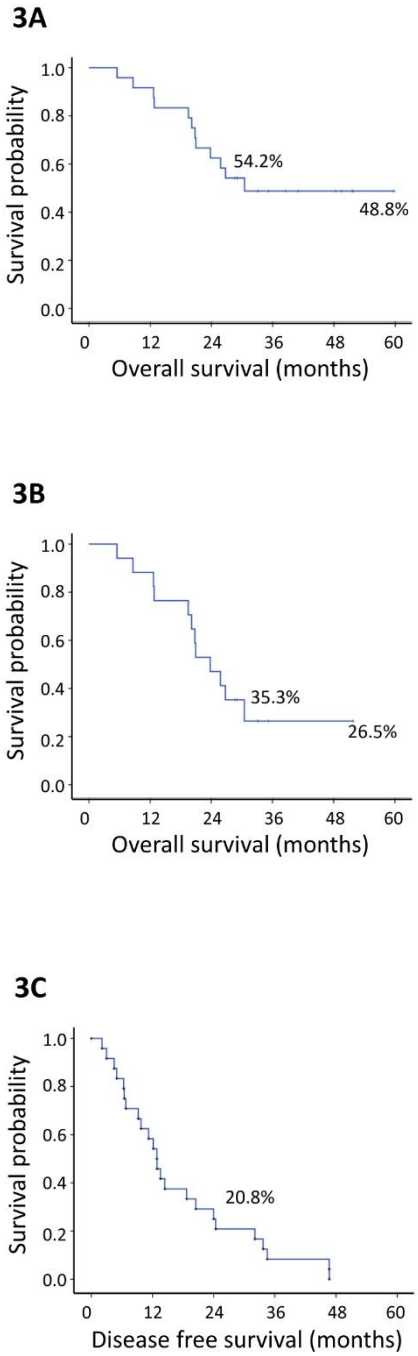
In patients age 40 and over

Figure 2. Kaplan-Meier curves by achievement of pCR



In all patients by combined age and achievement of pCR

Figure 3. Kaplan-Meier curves in patients with recurrence after achievement of pCR



3A. Overall survival of patients with recurrence after achievement of pCR

3B. Overall survival of patients with distant metastasis after achievement of pCR

3C. Disease free survival of patients with recurrence after achievement of pCR

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국문요약

수술 전 항암치료를 시행한 유방암환자의 장기예후분석

목적

선행 항암 치료는 현재 진행된 유방암 및 특정 유방암 아형에서 표준치료로 자리 잡았다. 선행항암 치료이후 완전관해에 도달한 환자들은 기존의 연구들에서 좋은 장기예후결과를 보인다. 한국 유방암 환자들은 서양과 비교하였을때 비교적 젊은 나이에 진단을 받는 경우가 많고 공격적인 특성을 보여 이러한 환자군에서는 좋지 않은 예후를 보여준다. 본 연구에서는 이 환자군에서의 치료 후 장기생존을 분석하고자 한다.

방법

서울아산병원에서는 2008년부터 본격적으로 유방암 환자들의 선행항암 치료를 시행하였으며 이 논문은 2008년부터 2014년까지 본원에서 유방암을 진단받고 선행항암 치료를 시행한 여성에서의 장기 예후를 분석 하였다. 세부분석으로는 선행항암 치료 이후 완전관해여부와 각 유방암의 네 가지 아형 및 진단 당시 나이를 40세 기준으로 두군으로 나누어 후향적 코호트 분석을 시행하였다.

결과

총 1643명의 환자들이 포함되었으며 중위 생존추적기간은 65개월, 진단당시 중위나이는 45세 였다. 286명 (17.3%) 의 환자들에서 선행항암 이후 완전관해에 도달하였고 생존추적기간동안 총 346명 (20.9%) 의 재발 환자와 246명 (17.3%) 의 사망이 확인되었다. 전체 환자군 및 각 유방암의 네가지 아형 및 두 나이군 (40세 기준) 으로 나눈 완전관해를 도달한 환자들에서 좋은 무병생존률을 보였다. 이는 수용체양성, HER2 과발현 아형이외 모든 환자군에서 단변량, 다변량에서 모두 의미있는 생존률 향상을 보였다. 반면 완전관해에 도달한 군에서는 진단당시 환자의 나이가 더 이상 예후를 결정하는 요인이 아니었으며 다변량 분석에서 완전관해 여부가 가장 강력한 예후인자로 확인 되었다. 완전관해를 이룬 군에서는 재발양상이 일반적인 유방암 환자군과 차이를 보였는데 70.8% 환자에서 첫 재발로 원격전이가 발견되었다. 또한 완전관해를 이루지 못하고 수술이후 잔존암이 있는 경우에는 삼중음성 아형과 임파

선 전이가 있는경우 특히 높은 위험률을 보이며 좋지 않은 예후를 결정하는 요인으로 확인되었다.

결론

선행항암 치료 이후 완전관해를 이룬 환자들은 좋은 장기 생존률을 보이며 기존에 위험인자로 알려져 있는 요인들을 모두 상쇄할 만큼 영향력이 있는 것으로 확인되었다. 완전관해를 이룬 젊은 환자군에서 추가적인 보조치료의 영향은 낮을 것이며 반면 잔존암이 있는 경우 삼중음상, 임파선 전이, 젊은 환자들에서 공격적인 추가 보조치료를 적극적으로 고려해야 하겠다.