



Prediction of axillary pathologic response with breast pathologic complete response after neoadjuvant chemotherapy

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Received: 6 March 2019 / Accepted: 26 March 2019 / Published online: 7 May 2019
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Abstract

Purpose Many breast cancer patients receive sentinel lymph node biopsy after neoadjuvant chemotherapy (NAC). We evaluated the axillary pathologic complete response (pCR) in relation to achievement of breast pCR.

Methods We evaluated 1044 patients who were diagnosed with invasive breast cancer and were treated with NAC followed by curative surgery at the Samsung Medical Center between January 2008 and December 2016. The pathologic node-positive rates in breast pCR patients were compared for different breast cancer subtypes and clinical nodal stages.

Results Axillary pCR was achieved in 51.9% of the patients after NAC. In this case, the axillary pCR was associated with a biologic subtype ($P < 0.0001$), initial clinical tumor stage ($P < 0.0001$), clinical nodal stage ($P = 0.0071$), and breast pCR ($P < 0.0001$). In particular, axillary pCR correlated more than 80% with breast pCR (87.1%) or clinical nodal stage N0 (81.0%). Patients with breast pCR had 96.4% axillary pCR in clinical nodal stage N0, 86.1% in N1, and 84.7% in N2/N3.

Conclusion Our study may help to predict node-positive rates in patients with breast pCR after NAC according to clinical node stage. Patients with a high probability of achieving pCR might be suitable candidates for more minimal surgery.

Keywords Axillary pathologic complete response · Neoadjuvant chemotherapy

Introduction

Neoadjuvant chemotherapy (NAC) is increasingly used for patients with operable breast cancer to allow for de-escalation of surgery [1, 2]. To avoid axillary lymph node dissection (ALND) in NAC, it is preferable to perform sentinel

lymph node (SLN) surgical procedure, which results in fewer problems and lower morbidity [1, 3, 4].

Specifically, the pathologic complete response (pCR) rate in NAC is increasing in HER2+ breast cancer and triple-negative breast cancer (TNBC). Survival of breast cancer patients with pCR is better than with those with non-pCR.

Some evidence has suggested that the nodal stage after NAC reflects patient prognosis more accurately than the initial axillary status [5]. Therefore, ALND may not be needed for patients with a complete response (CR). These patients are able to avoid postoperative morbidities, such as lymphedema, arm pain, and reduced arm movement [6, 7]. Patients who achieve a pCR have significantly better survival rates compared to those with residual disease.

If we can predict which patients will develop axillary pCR, we can prevent ALND or perform the more minimal SLN biopsy (SLNB). In addition, axillary and breast pCR after a course of NAC are associated with improved oncologic survival [8]. While pCR in these patients improves survival, an important emerging question is whether SLNB surgery can be avoided in these patients. Therefore, we investigated the factors predictive of axillary pCR and

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established a way to calculate the probability of axillary pCR with and without breast pCR after NAC by breast cancer subtype.

Materials and methods

This study was a registered medical record review of a prospectively collected database. Of those, 1169 patients who were diagnosed with invasive breast cancer and treated with NAC followed by curative surgery at Samsung Medical Center between January 2008 and December 2016 were selected. Patients were eligible if they completed all cycles of the planned dosage of NAC. Patients with clinical T4, supraclavicular, or internal mammary lymph node metastasis, pregnancy-related breast cancer, BRCA 1/2 mutation, and inappropriate chemotherapy were excluded. Finally, 1044 patients were eligible and included in the study (Fig. 1).

Most patients received anthracycline- and/or taxane-based regimens. These regimens included anthracycline plus cyclophosphamide, followed by anthracycline-based, taxane-based, or trastuzumab regimens. Adjuvant radiotherapy was performed in all patients followed by breast conserving surgery.

The clinical stage was evaluated by physical examination, breast magnetic resonance imaging (MRI), mammography, and breast ultrasonography (US). The clinical lymph node stage (cN0) was defined as normal axillary lymph nodes on physical examination, breast US, or MRI. If enlarged axillary lymph nodes were detected on breast US or MRI, but no tumor cells were found in fine needle aspiration cytology, the node was also classified as cN0. The ypN0 classification was assigned to no micrometastatic or no macrometastatic nodal disease in SLNB or ALND. Breast pCR was defined as no invasive breast cancer (ypT0 or ypTis) on the final pathologic results.

SLNB was performed with technetium-99m sulfur colloid diluted in normal saline solution and/or vital blue dye

(0.8% indigo carmine). The site and timing of the agent administration were at the physician's discretion. As applicable, the radiolabeled colloid was injected 2 to 6 h before the scheduled surgery, and/or 5 ml of 0.8% indigo carmine was injected periareolarly, and the breast was massaged for 5 min. For the sulfur-colloid injection, a handheld gamma detection probe was used to scan the axilla transcutaneously and identify the most radioactive area. All radioactive and/or blue LNs and palpable LNs were excised and submitted as SLNs. All of the patients underwent surgery within 6 weeks of NAC completion. The type of breast surgery was selected according to the preferences of the surgeon and the patient.

Proportions were compared between groups using the χ^2 test, and 2-sided 95% binomial CIs were calculated for estimated proportions using the Wilson score method. All statistical analyses were performed using the IBM SPSS Statistics for Windows, version 23 software (IBM Corp., Armonk, NY, USA). Differences were assumed to be significant when the *P* value was less than 0.05. This study adhered to ethical tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB File No. 2017-09-051). The need for informed consent was waived because of the low risk posed by this investigation.

Results

In this study, the median age of patients at the time of surgery was 45.6 years old. The demographic and clinicopathological characteristics of the patients included in this study are listed in Table 1. Axillary pCR was achieved in 51.9% ($n = 542$), and breast pCR was achieved in 28.2% ($n = 294$) of the patients who underwent surgery after NAC. Overall, axillary pCR with breast pCR was achieved in 87.1% ($n = 256$) of the patients who underwent surgery. Only 38 patients (12.9%) with breast pCR did not have axillary pCR (Fig. 2).

According to biologic subtype, there were more both breast and axillary pCRs in hormone receptor (HR)+/HER2+, HR−/HER2+, and TNBC than HR+/HER2− (Table 2). Axillary pCR was associated with a biologic subtype ($P < 0.0001$), initial clinical low tumor stage ($P = 0.0071$), initial clinical low nodal stage ($P < 0.0001$), and breast pCR ($P < 0.0001$) (Table 3). Among biologic subtypes, there were more axillary pCRs in hormone HR+/HER2+, HR−/HER2+, and TNBC than HR+/HER2−. Eighty-one percent of the breast cancer patients with clinical stage N0 had axillary pCR, and 87.1% of the patients with breast pCR had axillary pCR.

Table 4 shows the extent of nodal status by pathologic nodal category for each group of patients. Further evaluation of the group of patients with cN0 and breast pCR

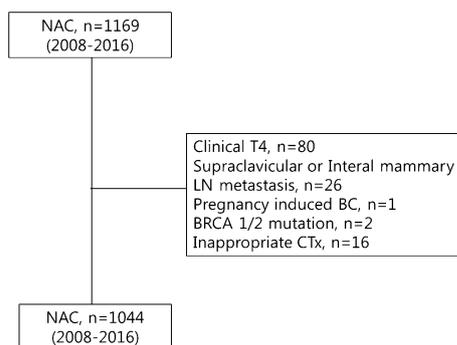
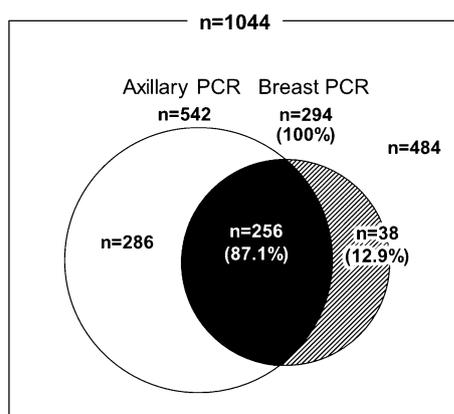


Fig. 1 Flowchart of study patients

Table 1 Clinicopathological and treatment characteristics of patients

Characteristics	No.	%
Age (years)		
Median	45.4 ± 9.4	
Range	21–72	
Clinical T stages		
cT1	50	4.8
cT2	618	59.2
cT3	376	36.0
Clinical N stages		
cN0	200	19.2
cN1	125	12.0
cN2–3	719	68.8
Clinical tumor subtypes		
HR+/HER2–	338	32.4
HR+/HER2+	162	15.5
HR–/HER2+	186	17.8
Triple negative	358	34.3
Ki-67		
High (≥ 20)	818	78.3
Low (< 20)	226	21.7
Response		
Residual breast disease	750	71.8
Breast pCR	294	28.2
Pathologic node status after neoadjuvant chemotherapy		
N0	542	51.9
N1	275	26.3
N2–3	227	21.8
Total	1044	100.0

HR hormone receptor, pCR pathologic complete response, TNBC triple negative breast cancer

**Fig. 2** Association of the incidence rate of axillary pCR on achieving breast pCR

showed that the rate of ypN1 disease was 3.6% and the rate of ypN2/3 disease was 0% across all biologic subtypes. For those with cN1 disease and breast pCR, the rate of residual nodal disease was 13.9 percent. Most had ypN1 disease (11.1%) and 2.8% cases had ypN2/3 disease. For those with cN2/3 disease and breast pCR, the rates of residual nodal disease were 15.3%, most had ypN1 disease (11.4%), and 3.9% had ypN2/3 disease. For patients with breast pCR, the rates of ypN0 disease did not differ significantly across the biologic subtypes for those with cN0 ($P=0.652$), cN1 ($P=0.198$), or cN2/3 ($P=0.564$) disease.

Among patients with residual breast disease, those with HR+/HER2– disease had higher rates of residual nodal disease (41.3% for cN0 disease, 81.6% for cN1 disease, and 79.5% for cN2/3 disease) compared to HR+/HER2+ disease (31.8% for cN0, 54.6% for cN1, and 61.1% for cN2/3 disease), HR–/HER2+ disease (9.3% for cN0, 50.0% for cN1, and 64.1% for cN2/3 disease), and TNBC (9.3% for cN0, 50.0% for cN1, and 64.1% for cN2/3 disease). For patients with no breast pCR, the rates of ypN0 disease differed significantly across the biologic subtypes for those with clinically node-positive disease.

Discussion

Predicting pCR after NAC in breast cancer patients with breast cancer is important for understanding and improving patient outcomes, as well as for identifying patients for whom aggressive surgery might be omitted as a treatment option. We performed a registered medical record review of a prospectively collected database and made a predictive model based on the clinicopathological tumor characteristics to estimate the probability of achieving axillary pCR. Our study demonstrated an extremely low rate of axillary pCR in patients who presented with clinically N0 breast cancer were treated with NAC and achieved breast pCR. A recent study of 116 patients with HER2+ disease or TNBC and clinical N0 status on physical examination and breast sonography at presentation, who achieved breast pCR, found that 100% of them had negative lymph nodes [9]. Moreover, some studies have argued for the possible omission of axillary surgery in patients with clinical N0 HER2+ breast cancer or TNBC who achieved breast pCR, because nodal positivity rates are extremely low in this population [9, 10]. However, these studies included only clinical N0 and clinical N1 breast cancer patients, regardless of any initial cytologically proven axillary metastasis. Our study defined cN0 as normal or enlarged axillary lymph nodes on US or MRI, but no tumor cells on initial cytologic examination.

Patients with HR–/HER2+ breast cancer, HR+/HER2+, and TNBC had 65.0% (121 of 186), 58.6% (95 of 162), and 60.3% (216/358) axillary pCR rates, respectively, but

Table 2 Both breast and axillary pCR rates treated with neoadjuvant chemotherapy according to biologic subtypes

Variables	Both breast and axillary pCR (<i>n</i> = 256)	Residual disease (<i>n</i> = 788)	Total (<i>n</i> = 1044)	<i>P</i> values
Biologic subtypes				< 0.0001
HR+/HER2–	32 (9.5)	306 (90.5)	338 (100.0)	
HR+/HER2+	45 (27.8)	117 (72.2)	162 (100.0)	
HR–/HER2+	75 (40.3)	111 (59.7)	186 (100.0)	
TNBC	104 (29.1)	254 (70.9)	358 (100.0)	

Table 3 Tumor characteristic of 1044 patients treated with neoadjuvant chemotherapy according to axillary pCR

Variables	Axillary pCR (<i>n</i> = 542)	No axillary pCR (<i>n</i> = 502)	Total (<i>n</i> = 1044)	<i>P</i> values
Biologic subtypes				< 0.0001
HR+/HER2–	110 (32.5)	228 (67.5)	338 (100.0)	
HR+/HER2+	95 (58.6)	67 (41.4)	162 (100.0)	
HR–/HER2+	121 (65.0)	65 (35.0)	186 (100.0)	
TNBC	216 (60.3)	142 (39.7)	358 (100.0)	
Clinical tumor stages				0.0071
cT1	29 (58.0)	21 (42.0)	50 (100.0)	
cT2	342 (55.3)	276 (44.7)	618 (100.0)	
cT3	171 (45.5)	205 (54.5)	376 (100.0)	
Clinical nodal stages				< 0.0001
cN0	162 (81.0)	38 (19.0)	200 (100.0)	
cN1	56 (44.8)	69 (55.2)	125 (100.0)	
cN2/3	324 (45.0)	395 (55.0)	719 (100.0)	
Breast response				< 0.0001
Breast pCR	256 (87.1)	38 (12.9)	294 (100.0)	
Residual breast disease	286 (38.1)	464 (61.9)	750 (100.0)	

patients with HR+/HER2– breast cancer had 32.5% (110 of 338) axillary pCR rates. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial for patients with HER2+ tumors showed differential nodal responses based on tumor biology. The overall nodal pCR was 41.1%, but varied from 21.1% in patients with HR+/HER2– tumors, to 49.4% in patients with TNBC, to 64.7% in patients with HER2+ disease ($P < 0.0001$) [11]. This association was greater for patients with HR– disease (HR 0.29) than for those patients who had an HR+ disease (HR 0.52) [12]. Although biologic tumor subtype was associated with pCR, for patients with breast pCR, the rates of ypN0 disease did not differ significantly across biologic subtypes for those with cN0, cN1, and cN2/3 disease. A recent study showed that in patients with breast pCR and pathologic positive nodes, the rates of ypN2/3 were not significantly different across biologic subtypes for those with cN0 ($P = 0.42$) or cN1 ($P = 0.78$) disease [10].

Many studies have evaluated ways to predict the axillary response to NAC in node-positive patients with breast cancer [13–16]. The axillary pCR offers a better oncologic outcome for patients. In addition, a recent study demonstrated that

pCR, defined as no residual invasive cancer in the breast and axillary nodes, provided a better association with improved outcomes compared to the eradication of an invasive tumor from the breast alone [17]. Therefore, the evaluation of axilla pCR in the context of breast pCR is more important than the evaluation of axillary pCR alone.

Although our study was performed in a single comprehensive cancer institution located in Korea and the number of patients was relatively small, our study included many node-positive patients whose diagnoses were confirmed by cytology. Therefore, the results from the small number of participating patients are still meaningful and allowed us to confidently draw important conclusions. Additionally, this study was not a prospective randomized clinical trial, and for that reason, the distribution of patients might be uneven and can be presumed to have had some effect on the results of the regional control.

In conclusion, our study might help to predict nodal positive rates in patients with breast pCR after NAC according to clinical node stage. Patients with a high probability of achieving pCR might be candidates for more minimal surgery. In patients with clinical N0 who achieved

Table 4 Extent of pathologic nodal disease according to breast pCR and clinical nodal stage

Clinical nodal stages	ypN0 (%)	ypN1 (%)	ypN2/3 (%)	Total nos.
Breast pCR				
Breast pCR				294
Biologic subtype of cN0	54 (96.4)	2 (3.6)	0	56
HR+/HER2–	8 (100.0)	0	0	8
HR+/HER2+	3 (75.0)	1 (25.0)	0	4
HR–/HER2+	16 (100.0)	0	0	16
TNBC	27 (96.4)	1 (3.6)	0	28
Biologic subtype of cN1	31 (86.1)	4 (11.1)	1 (2.8)	36
HR+/HER2–	4 (80.0)	1 (20.0)	0	5
HR+/HER2+	5 (100.0)	0	0	5
HR–/HER2+	16 (94.1)	1 (5.9)	0	17
TNBC	6 (66.7)	2 (22.2)	1 (11.1)	9
Biologic subtype of cN2/3	171 (84.7)	23 (11.4)	8 (3.9)	202
HR+/HER2–	20 (77.0)	3 (11.5)	3 (11.5)	26
HR+/HER2+	37 (86.0)	6 (14.0)	0	43
HR–/HER2+	43 (76.8)	3 (6.1)	3 (6.1)	49
TNBC	71 (84.5)	11 (13.1)	2 (2.4)	84
No breast pCR				
No breast pCR				750
Biologic subtype of cN0	108 (75.0)	24 (16.7)	12 (8.3)	144
HR+/HER2–	27 (58.7)	13 (28.3)	6 (13.0)	46
HR+/HER2+	15 (68.2)	3 (13.6)	4 (18.2)	22
HR–/HER2+	11 (91.7)	1 (8.3)	0	12
TNBC	55 (86.0)	7 (10.9)	2 (3.1)	64
Biologic subtype of cN1	25 (28.1)	35 (39.3)	29 (32.6)	89
HR+/HER2–	7 (18.4)	14 (36.8)	17 (44.7)	38
HR+/HER2+	5 (45.4)	4 (36.4)	2 (18.2)	11
HR–/HER2+	7 (50.0)	4 (28.6)	3 (21.4)	14
TNBC	6 (23.1)	13 (50.0)	7 (26.9)	26
Biologic subtype of cN2/3	153 (29.6)	187 (36.2)	177 (34.2)	517
HR+/HER2–	44 (20.5)	73 (34.0)	98 (45.5)	215
HR+/HER2+	30 (38.9)	34 (44.2)	13 (16.9)	77
HR–/HER2+	28 (35.9)	28 (35.9)	22 (28.2)	78
TNBC	51 (34.7)	52 (35.4)	44 (29.9)	147

breast pCR, nodal positivity rates were low (3.6%), and omission of axillary surgery can be considered.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose in relation to the production of this study.

Ethical approval This study adhered to ethical tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB File No. 2017-09-051).

Informed consent The need for informed consent was waived because of the low risk posed by this investigation.

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