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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Effect of Age on Outcomes After Neoadjuvant Chemotherapy for Breast Cancer

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ABSTRACT

Background. Younger women (age ≤ 40 years) with breast cancer undergoing neoadjuvant chemotherapy (NAC) have higher rates of pathologic complete response (pCR); however, it is unknown whether axillary or breast downstaging rates differ by age. In this study, we compared pCR incidence and surgical downstaging rates of the breast and axilla post NAC, between patients aged ≤ 40, 41–60, and ≥ 61 years.

Methods. We identified 1383 women with stage I–III breast cancer treated with NAC and subsequent surgery from November 2013 to December 2018. pCR and breast/axillary downstaging rates were assessed and compared across age groups.

Results. Younger women were significantly more likely to have ductal histology, poorly differentiated tumors, and BRCA mutations; 35% of tumors were hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–), 36% were HER2-positive (HER2+), and 29% were triple negative (TN), with similar subtype distribution across age groups ($p = 0.6$). Overall, pCR rates did not differ by age, however among patients with TN tumors ($n = 394$), younger women had higher pCR rates (52% vs. 35% among those aged 41–60 years and 29% among those aged ≥ 61 years; $p = 0.007$) and were more likely to have tumors with high tumor-infiltrating lymphocyte (TIL) concentrations ($p < 0.001$). Downstaging to breast-conserving surgery (BCS) eligibility post NAC among initially BCS-ineligible patients was similar across age groups; younger women chose BCS less often ($p < 0.001$). Among cN1 patients ($n = 813$), 52% of women ≤ 40 years of age avoided axillary lymph node dissection (ALND) with NAC, versus 39% and 37% in the older groups ($p < 0.001$).

Conclusions. Younger women undergoing NAC for axillary downstaging were more likely to avoid ALND across all subtypes; however, overall pCR rates did not differ by age. Despite equivalent breast downstaging and BCS eligibility rates across age groups, younger women were less likely to undergo BCS.

Keywords Breast Cancer · Neoadjuvant chemotherapy · Young women · Breast cancer subtypes · pCR

The incidence of early-onset breast cancer, defined as diagnosis at age ≤ 40 years, has steadily increased since the 1990s.[1] Younger women often present with more advanced disease and have tumors with more aggressive features, such as higher nuclear grade, lymphovascular invasion, and human epidermal growth factor receptor 2 (HER2) overexpression or triple- negative (TN) status (lacking HER2 and estrogen receptor [ER] and progesterone receptor [PR] expression).[2,3] Young women diagnosed with breast cancer have, on average, a higher risk of recurrence and death compared with older women.[4,5] These biological differences and inferior survival outcomes highlight the importance of personalizing treatment for this high-risk population.

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Despite overall worse outcomes, data from clinical trials suggest that younger age is associated with a higher likelihood of achieving a pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC).[6] NAC has become the standard of care for locally advanced and early-stage breast cancer among more aggressive subtypes, including TN and HER2-positive (HER2+). NAC is also used to treat patients with large tumors or nodal disease to facilitate breast-conserving surgery (BCS) and less-extensive axillary surgery. While a pCR after NAC is associated with improved disease-free and overall survival,[7] the absence of pCR guides adjuvant treatment recommendations for patients with TN or HER2+ disease. In a pooled analysis of eight neoadjuvant trials, women aged <40 years were more likely to obtain a pCR compared with women aged 40–49 years and those aged ≥50 years (21% vs. 18% and 14%, respectively; $p < 0.001$). The superior pCR rate seen in young women was driven by higher rates in those with HER2-negative (HER2−) tumors (TN or hormone receptor [HR]-positive [HR+]/HER2−), suggesting that the influence of age on achieving a pCR may differ by biological subtype.

Whether women aged ≤40 years, who often present with larger tumors and nodal disease, are more likely to achieve breast or axillary downstaging with NAC compared with older women is unknown. We therefore compared rates of pCR and of downstaging of the breast and axilla after modern NAC, between breast cancer patients aged ≤40 years and those in older age groups.

METHODS

Study Population and Treatments

After Institutional Review Board approval, consecutive patients with stage I–III breast cancer treated with NAC and subsequent surgery between November 2013 and December 2018 were identified from a prospectively maintained institutional database. Patients who had an indication for systemic chemotherapy because of tumor biology, receptor subtype, or clinical stage (nodal status, tumor size) were considered for NAC. Preoperative genomic testing was not used to select patients for NAC. We excluded male patients and those who received neoadjuvant endocrine therapy. The cohort was divided into three age groups: age ≤40 years, 41–60 years, and ≥61 years.

Clinicopathologic data were recorded. Clinical and pathologic stages were assigned according to the 8th edition of the American Joint Committee on Cancer staging system.[8] HR+ status was defined by a threshold of >1% staining in accordance with current guidelines.[9] Patients were categorized as HR+ if they were ER-positive and/or PR-positive. HER2 overexpression was defined as 3+ by immunohistochemistry or gene amplification by fluorescence in situ hybridization.[10] Based on these definitions, tumors were divided into three subtypes: HR+/HER2−, HER2+, and HR−/HER2− (TN).

Surgeons prospectively assessed eligibility for breast conservation prior to and at completion of NAC based on physical examination and imaging findings with no set size cut-off. Upon completion of NAC, patients underwent definitive breast surgery, except in cases of occult breast cancer, which we routinely manage with whole-breast radiotherapy.

Clinical nodal status was prospectively assessed by the surgeon before and after NAC. Patients with cN1 disease (defined as palpable and mobile ipsilateral axillary lymphadenopathy with biopsy-proven nodal metastasis) who converted to cN0 (defined as no palpable lymphadenopathy) on physical examination after NAC were eligible for sentinel lymph node biopsy (SLNB); SLNB was performed using dual lymphatic mapping. For cN1 patients with no residual palpable adenopathy after NAC, axillary lymph node dissection (ALND) was omitted if three or more sentinel lymph nodes (SLNs) were identified and all were pathologically negative, and ALND was performed for any positive SLN (including macrometastases, micrometastases, and isolated tumor cells). cT4 and cN2/3 patients were considered ineligible for SLNB irrespective of their response to NAC and underwent ALND, as the accuracy of SLNB in this setting is yet to be established.

For TN tumors, we evaluated the concentration of stromal tumor-infiltrating lymphocytes (TILs) in pre NAC core biopsy specimens. Cases were scored by two dedicated breast pathologists on hematoxylin and eosin-stained sections according to the recommendations of the International TILs Working Group.[11,12] TIL-high tumors were defined as those containing >40% TILs.

Statistical Analysis

The primary outcome of interest was pCR. Overall pCR was defined as the absence of invasive carcinoma in the breast and axillary lymph nodes (ypT0/Tis, N0). The rate of breast pCR was calculated among patients presenting with cT1–T4 tumors, and nodal pCR was determined among all node-positive patients at presentation (cN1–N3). Rates of overall, breast, and nodal pCR were compared across age groups, in the overall cohort and within each tumor subtype.

Rates of breast and axillary downstaging were also assessed and compared across age groups. BCS-ineligible patients on presentation who became BCS-eligible after NAC were considered to have breast downstaging. We excluded patients with occult breast cancer or multicentric

or cT4 disease at presentation, as they would be precluded from surgical downstaging. Patients who experienced axillary downstaging were those who initially presented with biopsy-proven cN1 disease and converted to cN0 after NAC. cT4 and cN2/3 patients were excluded, as the accuracy of SLNB in this setting is yet to be established.

Clinical and pathological characteristics were compared between patients aged ≤40 years, 41–60 years, and ≥61 years using Student's *t*-test or the Wilcoxon rank-sum test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables. We compared the clinical and pathological characteristics of individuals who did and did not achieve overall pCR, including age group, histology, histological grade, lymphovascular invasion, cT stage, cN stage, receptor status, and NAC regimen. Factors significant at a type I error rate of 0.05 were included in a multivariable logistic regression analysis to account for confounding. To account for missing data on lymphovascular invasion (for 24% of individuals), we conducted a sensitivity analysis using multiple imputation through the *mice* package in R 3.6.3 (R Core Development Team, Vienna, Austria) assuming that data were missing at random. Multivariable analysis was conducted using the imputed data, and results were compared with the original analysis. Additional statistical analysis included univariate analyses of rates of pCR, overall and according to subtype, and breast and axillary downstaging after NAC stratified by age group.

RESULTS

Patient Characteristics

Among 1383 patients meeting the inclusion criteria, 22% were aged ≤40 years, 56% were aged 41–60 years, and 22% were aged ≥61 years. Table 1 details patient, tumor, and treatment characteristics of the study cohort by age group. Thirty-five percent of patients had HR+/HER2− cancers, 36% had HER2+ tumors, and 28.5% were TN, with similar subtype distribution across age groups ($p = 0.6$). Women aged ≤40 years were significantly more likely to have ductal histology, poorly differentiated tumors, and BRCA mutations compared with older women.

Most patients received both anthracycline and taxol ($n = 1268$, 92%), with younger women more often receiving this regimen (95% vs. 94% in those aged 41–60 years and 84% in those age ≥61 years; $p < 0.001$). Carboplatin was included in a minority of NAC regimens (12%) and was most often used in the setting of TN breast cancer (TNBC; 33% in women aged ≤40 years, 27% in women aged 41–60 years, and 16% in women aged ≥61 years; $p = 0.059$). The majority of HER2+ patients (99.9%) received neoadjuvant dual anti-HER2 therapy with trastuzumab and pertuzumab.

Rates of Pathologic Complete Response (pCR)

Thirty-four percent of all patients achieved a pCR after NAC. Compared with patients who had HR+/HER2− tumors, patients with TN and HER2+ tumors had higher rates of overall pCR (55% and 38%, respectively, vs. 9.4% among HR+/HER2− patients; $p < 0.001$), as well as breast and nodal pCR. Rates of overall, breast, and nodal pCR did not differ among age groups (Fig. 1a).

However, among patients with TN tumors ($n = 394$), women aged ≤40 years more frequently achieved overall pCR (52% vs. 35% of those aged 41–60 years and 29% of those aged ≥61 years; $p = 0.007$), breast pCR (56% vs. 37% of those aged 41–60 years and 33% of those aged ≥61 years; $p = 0.003$) and nodal pCR (70% vs. 51% of those aged 41–60 years and 39% of those aged ≥61 years; $p = 0.006$) [Fig. 1b]. No differences in rates of pCR by age were identified among other subtypes (Fig. 1c, d).

Factors Associated with pCR

On univariate analysis of factors associated with pCR in the entire cohort, ductal histology, poor differentiation, presence of lymphovascular invasion, lower clinical tumor stage, nodal stage at presentation, and TN or HER2+ receptor status were associated with achievement of pCR (Table 2). There was no association between NAC regimen or age group and pCR. On multivariable analysis, poor differentiation ($p < 0.001$), lymphovascular invasion ($p < 0.001$), and receptor subtype ($p < 0.001$) remained independently associated with pCR. These results did not change substantially in a sensitivity analysis accounting for missing data (data not shown).

Breast and Axillary Downstaging Rates

Among 649 BCS-ineligible breast cancer patients with potential for downstaging as determined by their treating surgeon, 72% ($n = 467$) became BCS-eligible after NAC; the rate of conversion to BCS eligibility was similar across age groups (Fig. 2a). Among BCS-eligible patients post NAC, patients aged ≤40 years were less likely to choose BCS (45% vs. 65% of those aged 41–60 years and 81% of those aged ≥61 years; $p < 0.001$) (Fig. 2b).

Among biopsy-proven cN1 patients at presentation ($n = 813$), 94% of women aged ≤40 years became cN0 after NAC and underwent SLNB, compared with 89% and 85% in the older age groups, respectively ($p = 0.02$) (Fig. 2c). In these patients ($n = 726$), rates of nodal pCR

TABLE 1 Patient, tumor, and treatment characteristics of the study cohort by age group

Characteristic	Entire cohort [$n = 1383$]	Age $\leq$ 40 years [$n = 300$]	Age 41–60 years [$n = 772$]	Age $\geq$61 years [$n = 311$]	p Value
Age, years	50 (42–59)	36 (32–38)	50 (46–55)	66 (63–70)	<0.001
Tumor size, cm	4.0 (2.5–6.0)	4.0 (3.0–6.0)	4.0 (2.5–6.0)	3.9 (2.8–6.0)	0.80
Race					
White	849 (66.6)	168 (61)	467 (66)	214 (74)	0.005
Black	194 (15)	39 (14)	117 (16)	38 (13)	
Asian/Pacific Islander	149 (12)	39 (14)	82 (12)	28 (10)	
Other	83 (6.5)	28 (10)	46 (6)	9 (3)	
Unknown	108	26	60	22	
Clinical tumor stage					<0.001
T0 (occult)	11 (0.8)	2 (0.7)	5 (0.60)	4 (1.3)	
T1	197 (14)	42 (14)	110 (14)	45 (14)	
T2	766 (55)	167 (56)	423 (55)	176 (57)	
T3	271 (20)	74 (25)	156 (20)	41 (13)	
T4	136 (9.8)	14 (4.7)	78 (10)	44 (14)	
Clinical nodal stage					>0.90
N0	449 (32)	97 (32)	255 (33)	97 (31)	
N1	813 (59)	180 (60)	447 (58)	186 (60)	
N2–N3	121 (8.7)	23 (7.7)	70 (9.1)	28 (9.0)	
Histology					0.001
Ductal	1244 (92)	287 (97)	687 (91)	270 (89)	
Lobular or mixed	99 (7.3)	7 (2.4)	63 (8.3)	29 (9.5)	
Other	16 (1.2)	2 (0.7)	8 (1.1)	6 (2.0)	
Unknown	24	4	14	6	
Histologic grade					0.034
Well-differentiated	21 (1.5)	0 (0)	14 (1.8)	7 (2.3)	
Moderately differentiated	391 (28)	78 (26)	216 (28)	97 (31)	
Poorly differentiated	964 (70)	221 (74)	536 (70)	207 (67)	
Lymphovascular invasion	406 (39)	96 (42)	226 (38)	84 (36)	0.40
Unknown	7	1	6	0	
Tumor subtype					0.60
HR+/HER2−	487 (35)	106 (35)	271 (35)	110 (35)	
HER2+	502 (36)	111 (37)	269 (35)	122 (40)	
TN	394 (28.5)	83 (28)	232 (30)	79 (25)	
BRCA1/2 mutation status					<0.001
Positive	98 (11)	46 (18)	49 (9.8)	3 (2.6)	
Negative	672 (77)	207 (79)	401 (80)	64 (55)	
Unknown result or VUS	108 (12)	9 (3.4)	50 (10)	49 (42)	
Not tested/missing	505	38	272	195	
Pathologic tumor stage					0.57
T0	399 (29)	97 (33)	219 (29)	82 (27)	
Tis	99 (7.2)	21 (7.0)	58 (7.6)	19 (6.2)	
T1	574 (42)	125 (42)	324 (42)	125 (41)	
T2	232 (17)	44 (15)	124 (16)	64 (21)	
T3	59 (4.3)	10 (3.4)	36 (4.7)	13 (4.2)	
T4	11 (0.80)	1 (0.30)	6 (0.80)	4 (1.3)	
Not assessed or occult	11	2	5	4	
Pathologic nodal stage					0.20

TABLE 1 (continued)

Characteristic	Entire cohort [$n = 1383$]	Age ≤ 40 years [$n = 300$]	Age 41–60 years [$n = 772$]	Age ≥61 years [$n = 311$]	p Value
N0	828 (60)	188 (63)	460 (60)	180 (58)	
N1	344 (25)	81 (27)	191 (25)	72 (23)	
N2–N3	208 (15)	30 (10)	121 (16)	57 (18)	
Neoadjuvant chemotherapy					<0.001
ACT-based	1268 (92)	286 (95)	722 (94)	260 (84)	
Taxane-based	95 (6.9)	14 (4.7)	42 (5.5)	39 (13)	
CMF	9 (0.7)	0 (0)	0 (0)	9 (2.9)	
Other	5 (0.4)	0 (0)	3 (0.4)	2 (0.6)	
NAC included carboplatin	172 (12)	47 (16)	98 (13)	27 (8.7)	0.029
Final breast surgery[a]					<0.001
BCS	586 (43)	88 (30)	332 (43)	166 (54)	
Unilateral mastectomy	388 (28)	62 (21)	210 (27)	116 (38)	
Bilateral mastectomy	398 (29)	148 (50)	225 (29)	25 (8.1)	
Final axillary surgery					
SLNB	722 (52)	186 (62)	393 (51)	149 (48)	<0.001
ALND	661 (48)	114 (38)	379 (49)	162 (52)	<0.001

Categorical data are presented as n (%) and continuous data are presented as median (interquartile range)

[a]Eleven patients with occult primary breast cancer did not undergo primary breast surgery

HR hormone receptor, *HER2* human epidermal growth factor receptor 2, *TN* triple-negative, *BRCA1/2* breast cancer gene 1 or 2, *VUS* variant of unknown significance, *ACT* doxorubicin and cyclophosphamide followed by a taxane *CMF* cyclophosphamide, methotrexate, 5-fluorouracil, *pCR* pathologic complete response, *NAC* neoadjuvant chemotherapy, *BCS* breast-conserving surgery, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

on SLNB were highest among women aged ≤40 years (55% vs. 43% of those aged 41–60 years and 43% of those aged ≥61 years; $p = 0.001$). Fifty-two percent of women aged ≤40 years who initially presented with cN1 disease avoided ALND after NAC compared with 38% and 37% in the older age groups, respectively ($p = 0.001$) (Fig. 2d).

Association BRCA Mutation Status, Stromal Tumor-Infiltrating Lymphocytes, and pCR Among Patients with Triple-Negative Breast Cancer

Among women with TNBC and known BRCA status ($n = 312$), women aged ≤40 years were more likely to have a deleterious BRCA mutation compared with women in the older age groups (29% vs. 15% of those aged 41–60 years and 2.5% of those age ≥61 years; $p = 0.001$). Among BRCA carriers, women aged ≤40 years achieved a pCR more often than older women (67% vs. 44% of those aged 41–60 years and 0% of those aged ≥61 years; $p = 0.058$), although this analysis was carried out in a small sample, and the difference was not statistically significant.

Stromal TILs were measured in 341 women with TNBC (Table 3), of whom 16% ($n = 55$) had tumors with TILs composing >40% of the tumor stroma (i.e., 'TIL-rich'). TIL-rich tumors were significantly more common among women aged ≤40 years (25% vs. 17% of those aged 41–60 years and 4.3% of those aged ≥61 years; $p = 0.001$). Within the entire cohort, pCR was significantly more frequent among patients with TIL-rich tumors (56% vs. 35%; $p = 0.005$).

DISCUSSION

Motivated by prior studies indicating that younger patients are more likely to achieve pCR following NAC, we assessed the influence of age on rates of breast and axillary downstaging. In this large cohort of women with stage I–III breast cancer undergoing NAC, rates of axillary downstaging among patients with cN1 disease were significantly higher among women aged ≤40 years compared with older women, allowing them to avoid ALND. While

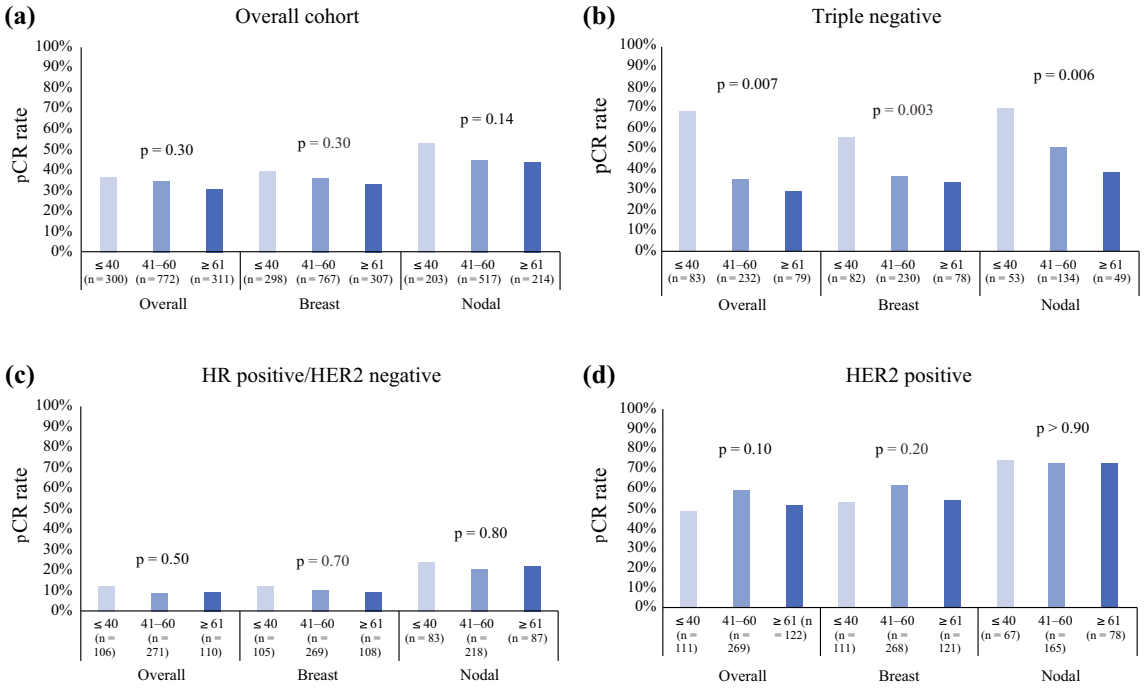

FIG. 1 pCR rates by age group. **a** Overall cohort; **b** triple-negative; **c** HR+/HER2−; and (**d**) HER2+. Top x-axis labels indicate age in years, and lower labels indicate response type/location. *pCR* pathologic complete response, *HR* hormone receptor, *HER2* human epidermal growth factor receptor

rates of pCR and downstaging to BCS-eligible did not differ by age in the overall cohort, younger women were less likely than older women to elect BCS when eligible.

Our findings emphasize the benefit of NAC for younger patients in achieving nodal pCR and de-escalating axillary surgery. The ability of NAC to support these outcomes in the general breast cancer population is well-established by prospective trials.[13–15] Among 630 cN1 patients in a recent study, 573 (91%) became cN0 and underwent SLNB, and 93% of these had successful mapping with identification of three or more SLNs; 41% of patients avoided ALND.[16] In our cohort, women aged ≤40 years who initially presented with cN1 disease were more likely than older women to have a clinically negative axilla after NAC and be eligible for SLNB. Among patients who became eligible for and underwent SLNB, younger women were most likely to have a nodal pCR and avoid ALND. This difference in axillary downstaging rates among age groups may relate to variations in NAC regimens, as younger women were more likely than older women to receive ACT (adriamycin and cyclophosphamide, followed by taxol)-based treatment. However, the type of NAC regimen was not significantly associated with overall pCR in our cohort. Among all patients with nodal disease on presentation (cN1–3), 47% achieved nodal pCR. Nodal pCR has been shown to be unrelated to nodal burden, but rather a function of tumor biology.[17] This raises the question of whether SLNB can be considered in patients with cN2–3 disease with a complete clinical response after NAC, potentially sparing them from the morbidity of an ALND. The safety of this approach is currently under investigation.

The present findings do not confirm prior studies suggesting that women diagnosed with breast cancer at a young age have higher rates of pCR after NAC. The German Breast Group reported a higher rate of pCR of 21% in women aged <40 years (compared with 18% in those aged 40–49 years and 14% in those aged ≥50 years; $p < 0.001$) treated in eight neoadjuvant trials.[6] These results were echoed in a single-institution retrospective study in which 316 women aged ≤40 years were more likely to achieve a pCR than women aged >40 years (37% vs. 26%; $p < 0.001$).[18] In the present study, achievement of pCR did not differ by age in the overall cohort, even after accounting for differences in tumor characteristics. This difference in the results may reflect differences between study populations, as older women in our cohort had more-aggressive tumor characteristics than those in prior studies, and may reflect methodological differences, such as cut-offs used to define age groups for comparison. Similarly, Loibl et al.[6] used a more restrictive definition of pCR, ypT0N0, and their patients were treated in the context of clinical trials, potentially including a selected patient population. In these prior studies,[6,18] the difference in the rates of pCR by age was confined to women with TN and HR+ subtypes. Consistent with these findings, younger women with TNBC in our cohort had significantly higher

TABLE 2 Univariate and multivariable analysis of factors associated with pCR (T0/is N0)

	Entire cohort [$n = 1383$]	No pCR [$n = 1017$]	pCR [$n = 366$]	Univariate	Multivariable		
				p Value	OR	95% CI	p Value
Age category, years				0.6			0.50
≤40	300 (22)	214 (21)	86 (23)		Ref		
41–60	772 (56)	571 (56)	201 (55)		0.97	0.64–1.50	
≥61	311 (22)	232 (23)	79 (22)		0.77	0.46–1.30	
Histology				<0.001			0.60
Ductal	1244 (92)	906 (90)	338 (96)		Ref		
Lobular/mixed	99 (7.3)	89 (8.8)	10 (2.8)		0.67	0.23–1.66	
Other	16 (1.2)	12 (1.2)	4 (1.1)		1.56	0.30–6.43	
Histologic grade				<0.001			<0.001
Poorly differentiated	964 (70)	638 (63)	326 (90)		Ref		
Moderately differentiated	391 (28)	354 (35)	37 (10)		0.31	0.18–0.50	
Well-differentiated	21 (1.5)	21 (2.1)	0 (0)		0.00		
Lymphovascular invasion	406 (39)	361 (43)	45 (21)	<0.001	0.46	0.31–0.68	<0.001
Clinical tumor stage				0.017			0.081
T0–T1	210 (15)	145 (14)	65 (18)		Ref		
T2	766 (55)	553 (54)	213 (58)		0.89	0.53–1.52	
T3	271 (20)	219 (22)	52 (14)		0.50	0.26–0.95	
T4	136 (9.8)	100 (9.8)	36 (9.8)		0.93	0.45–1.90	
Clinical nodal stage				0.001			0.40
N0	449 (32)	313 (31)	136 (37)		Ref		
N1	813 (59)	626 (62)	187 (51)		0.86	0.60–1.26	
N2–3	121 (8.7)	78 (7.7)	43 (12)		1.30	0.69–2.40	
Tumor subtype				<0.001			<0.001
TN	394 (28)	275 (27)	119 (33)		Ref		
HR+/HER2−	487 (35)	453 (45)	34 (9.3)		0.29	0.16–0.52	
HER2+	502 (36)	289 (28)	213 (58)		2.55	1.76–3.75	
NAC regimen[a]				0.093			–
ACT-based	1268 (92)	939 (93)	329 (91)		–	–	
CMF-based	9 (0.7)	9 (0.9)	0 (0)		–	–	
Other	5 (0.4)	3 (0.3)	2 (0.6)		–	–	
Taxane-based	95 (6.9)	64 (6.3)	31 (8.6)		–	–	
NAC included carboplatin[a]	172 (12)	116 (11)	56 (15)	0.057	–	–	–

Data are expressed as n (%)

[a]NAC regimen was not included in the multivariable model as it was not significant on univariate analysis

pCR pathologic complete response, *OR* odds ratio, *CI* confidence interval, *TN* triple-negative, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *NAC* neoadjuvant chemotherapy, *ACT* doxorubicin and cyclophosphamide followed by a taxane, *CMF* cyclophosphamide, methotrexate, 5-fluorouracil

rates of pCR (52%) compared with older age groups (35% in those aged 41–60 years and 29% in those aged ≥61 years). No difference in pCR by age was seen among other subtypes.

As shown in the present study and supported by the literature,[6,18] younger women with TNBC more often achieve pCR than their older counterparts. In multiple clinical trials,[7,19,20] women with HER2+ and TN tumors had the highest rates of pCR. We hypothesized that the higher pCR rates among TN patients reflect a higher proportion of BRCA mutation carriers and TIL-rich tumors among young women in this subgroup. Approximately 12% of breast cancer cases arising in women aged ≤40 years are related to pathogenic mutations in *BRCA1* or

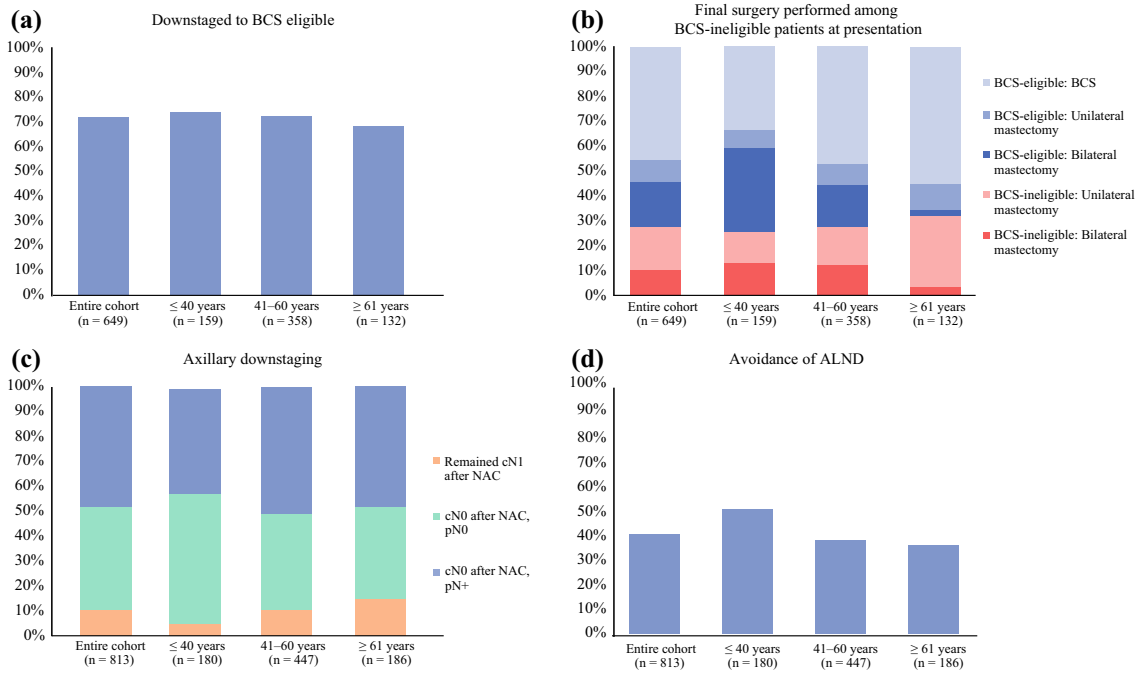

FIG. 2 Downstaging and surgery by age. **a** Rate of downstaging to BCS eligibility; **b** final surgery according to BCS eligibility; **c** rate of axillary downstaging; and **d** percentage of patients who avoided ALND. *BCS* breast-conserving surgery, *NAC* neoadjuvant chemotherapy, *ALND* axillary lymph node dissection

TABLE 3 Effect of stromal TILs on pCR (ypT0/Tis, N0) in the triple-negative subtype

Percentage of stromal TILs		Entire cohort	≤40 years	41–60 years	≥61 years	*p* Value
TILs ≤40%	*n* (% within age group)	286 (84)	56 (75)	163 (83)	67 (96)	0.037
	pCR (%)	101 (35)	28 (50)	53 (33)	20 (30)	
TILs >40%	*n* (% within age group)	55 (16)	19 (25)	33 (17)	3 (4)	0.541
	pCR (%)	31 (56)	12 (63)	18 (55)	1 (33)	

pCR pathologic complete response, *TILs* tumor-infiltrating lymphocytes

BRCA2 genes,[21,22] and these mutations are most common in TNBC.[23] In our cohort, 29% of young women with TNBC had a deleterious BRCA mutation, compared with 17% and 6.3% among women in the older age groups. Tumors in BRCA carriers are known to be particularly sensitive to chemotherapy, likely due to reduced capacity for DNA repair and higher tumor proliferation. Among TNBC patients specifically, BRCA carriers have a higher pCR rate than non-carriers.[24–26] Similarly, higher concentrations of stromal TILs in TN tumors are associated with an increased likelihood of pCR,[27–29] and stromal TIL concentrations are higher in younger patients.[29] Among women with TNBC in our study, 25% of women aged ≤40 years had TIL-rich tumors, compared with only 17% and 4.3% of older women, respectively. Together, these data suggest that among patient with TNBC, those aged ≤40 years may be more likely to have chemosensitive tumors and achieve a pCR after NAC.

Approximately 72% of women in this study who were ineligible for BCS at presentation downstaged to BCS-eligible, within the published range of 42–75%.[30–33] Variations in breast downstaging have been attributed to differences in cohort and study design, such as inclusion of T4 and multicentric disease, neoadjuvant systemic therapy regimen, tumor subtype distribution, and prospective versus retrospective assessment of eligibility.

Despite equivalent rates of downstaging in the breast across age groups, younger women were significantly less likely to choose and ultimately undergo BCS. Low acceptance of BCS after NAC has been previously described. In a prospective analysis of women with TNBC treated with NAC, Golshan et al. found that only 56% of BCS-eligible patients chose BCS.[32] In a cohort of women aged ≤40 years, 60% of 133 women eligible for BCS after neoadjuvant systemic therapy chose that approach.[34] Patients may elect mastectomy because of personal

preference, presence of a genetic mutation, family history, insurance coverage, and geographic variations.[32–35] In our study, BCS-eligible younger women had uniformly lower rates of BCS compared with older women regardless of BRCA status, suggesting that the higher proportion of BRCA carriers among younger patients does not account for this difference. In light of recent data suggesting improved survival outcomes among women electing BCS compared with mastectomy,[36] our study suggests that shared decision making between clinicians and young patients with breast cancer is essential, and that further studies to understand surgical decision making and long-term patient-reported outcomes are needed.

The strengths of our study include the large consecutive cohort of patients with prospective determination of BCS eligibility before and after NAC, homogeneity in NAC regimens, and standardized pathologic assessment. Limitations of our study include the subjective bias of physician assessment in determination of BCS eligibility and its conduct at a single large-volume institution with highly specialized providers, which may limit generalizability. Nonetheless, the characteristics of our patient population are similar to previously published data and are likely representative of women with breast cancer treated with NAC in the population at large. Furthermore, management decisions were concordant with national guidelines. Additionally, we were unable to evaluate for the successful completion of the recommended NAC regimen, which may be lower in older women who are more susceptible to toxicities. However, the similar rates of pCR across age groups suggest differential completion of NAC is unlikely to be a significant driver of differences in pCR in this cohort.

CONCLUSIONS

In a large cohort of women with stage I–III breast cancer treated with NAC, the rates of pCR were similar across age groups. Among women with TNBC, women aged $\leq$40 years most often achieved a pCR, likely owing to a higher proportion of BRCA carriers and TIL-rich tumors with enhanced chemosensitivity. Rates of axillary downstaging and avoidance of ALND were highest among young women compared with older age groups. Despite equivalent rates of downstaging to breast conservation, young women were less likely to elect BCS when eligible. This study supports the use of NAC in young women, particularly when node-positive, with the goal of de-escalating axillary surgery and avoiding mastectomy when desired. Further efforts to understand factors affecting surgical decision making and long-term patient-reported outcomes among young, BCS-eligible women are needed.

CONFLICT OF INTEREST Conflict of interest All authors declared no conflict of interest.

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