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Original Research Article

Neoadjuvant chemotherapy for luminal a breast cancer: Factors predictive of histopathologic response and oncologic outcome

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ABSTRACT

Background: The benefit of chemotherapy (NAC) for patients with ER/PR positive, HER2 negative breast cancer is unclear. Our aim was to determine factors associated with histopathologic response and oncologic outcome following NAC in this group.
Methods: Consecutive female patients undergoing neoadjuvant therapy and surgery for locally advanced Luminal A breast cancer between 2010 and 2015 were studied. Multivariable linear, logistic, and Cox regression analysis was undertaken.
Results: 114 patients were studied. Pathological complete response (pCR) was achieved in 7.9% of patients, ypN0 in 25.5%, and downstaging in 33.6%. However, 43.9% exhibited a Sataloff C-D response. Tumor grade independently predicted pCR ($P = 0.039$), while PR score predicted ypN0 ($P = 0.017$) and downstaging (P=0.029). 5-year invasive disease-free (iDFS) and overall survival (OS) were 68.5 ± 4.7% and 77.7 ± 4.3%, respectively.
Conclusion: After NAC for Luminal A breast cancer, pCR rates are low. Patients with high grade tumors with weak PR expression exhibit the most promising response rates.
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Introduction

Immunohistochemical subtyping has progressively moved breast cancer management towards tailored, patient-specific, tumor-specific treatment regimens. Increased use of chemotherapy in the neoadjuvant setting followed publication of NSABP-B18, and aligns with the drive towards breast- and axilla-conserving surgeries.[1]

Successful neoadjuvant treatment, measured by pathological complete response (pCR) is defined as absence of residual invasive cancer following completion of neoadjuvant systemic therapy (ypT0N0 or ypTisN0; AJCC 8th edition).[2,3] pCR is associated with a survival benefit, of most prognostic value in aggressive tumor subtypes (HER2 positive, triple negative).[4] While the specific role for NAC in HER2 positive and triple negative disease is clear, with a high pCR rate, and where pCR confers survival benefit, its role in treating luminal A disease is less concrete.[4] Luminal A encompasses 50–60% of all breast cancer, and in these slower-growing tumors, pCR rates as low as 8% are seen if NAC is used.[5] Current guidelines suggest that patients presenting with luminal A tumors >5 cm with more than 4 positive nodes, or borderline breast or axilla-conservable should be offered NAC, despite the low response rate compared to other tumor types.[6] For patients with Luminal A disease, the requirement for adjuvant treatment is typically dictated by Oncotype Dx®, and most recently, TAILORx has shown the safe omission of chemotherapy for many more patients with hormone-sensitive disease.[7] However, in the neoadjuvant setting, the locally advanced luminal A subgroup is not subjected to any further stratification before a decision regarding neoadjuvant therapy is made, despite the available clinical and histopathological information.

In this subgroup of locally advanced but molecularly low risk tumors, better predictors of response to NAC are urgently needed to discern who will benefit from systemic therapy, To date, measuring the additive benefit of NAC in this subgroup is difficult because of

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the overall low rate of recurrence and mortality, and the high sensitivity of these tumors to adjuvant hormonal therapy.[8]

The aim of the present study was to examine rates of chemotherapy response and assess oncologic outcome following neoadjuvant chemotherapy for luminal A tumors in our institution. Furthermore, we sought to identify patient and tumor factors associated with response and outcome, to better define which patient subgroup benefits most from NAC.

Methods

Patient selection and study design

The Breast Cancer Center at Galway University Hospital is a high-volume national center, and a detailed clinicopathologic database is prospectively maintained for all patients with breast cancer. Records for consecutive patients with locally advanced hormone positive, HER2 negative (Luminal A) breast cancer who underwent neoadjuvant chemotherapy with curative intent over a six-year period between 2010 and 2015 were assessed for inclusion. Patients treated with neoadjuvant endocrine therapy only were excluded.

Treatment protocol

During this period, patients with locally advanced Luminal A breast cancer received adriamycin (doxorubicin) and cyclophosphamide followed by paclitaxel (AC-T regimen, dose dense) where possible.[9] Indications for neoadjuvant therapy were as follows: clinically node positive, pathologically confirmed nodal metastases on sentinel lymph node biopsy, and primary tumor size $\geq$5 cm or borderline conservable,[6] with all patients discussed at a Multidisciplinary Tumor Board. Patients underwent resection approximately 6-weeks after completion of chemotherapy. Breast-conserving surgery (BCS) was undertaken as appropriate.

All patients received adjuvant endocrine therapy for at least five years postoperatively, as tolerated.[10] Indications for adjuvant radiotherapy were: BCS, axillary nodal involvement of $\geq$4 nodes, primary tumor size $\geq$5 cm, ypT4 disease and positive surgical margins.[11,12] Most patients received the standard regimen of 50 Gy (Gy) in 25 fractions as reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer trials, or the slightly higher dose of 50.4 Gy in 28 fractions.[13] Seven patients received the hypofractionated regimen of 40Gy in 15 fractions described in the UK START trials, as dictated by their histopathological characteristics.[14]

Variable definitions

Luminal A breast cancer was defined as ER/PR positive, HER2 negative disease, indicating an Allred score >2 determined by immunohistochemistry as per ASCO guidelines.[15,16] HER2 receptor status was identified by Herceptest as part of the initial histopathological work-up, with a score of 3+ considered positive.[17] Inconclusive HER2 results (2+) were subjected to fluorescence *in situ* hybridization testing for further characterization.[18] The American Joint Committee on Cancer (AJCC) 8th edition classification system was used throughout.

For patients who underwent pre-treatment sentinel lymph node biopsy, the final pathological nodal status was determined according to the summative surgically sampled nodal burden, including pre-treatment sampling. Neoadjuvant chemotherapy response was assessed according to the Sataloff tumor (T) and Sataloff nodal (N) classification as follows: T-A – total or near total therapeutic effect, T-B - >50% effect, T-C - <50% effect, T-D – no therapeutic effect; N-A – node negative with evidence of therapeutic effect, N–B – node negative without evidence of effect, N–C – node positive with evidence of effect, N-D – node positive with no evidence of therapeutic effect[19].

Pathologic complete response was defined as the absence of viable tumor cells at the primary site or within the nodal basin (ypT0N0, ypTisN0).[3] Downstaging was defined as a reduction in either the primary tumor (T stage) or nodal (N) stage (TNM classification), without progression at either site. The primary tumor size was considered to be stable if less than a 10% change was observed following neoadjuvant treatment.

Postoperative complications were coded using the Clavien-Dindo classification and comprehensive complications index (CCI).[20,21] Local recurrence was defined as recurrence of disease in the ipsilateral chest wall, while regional recurrence was defined as recurrence of disease in axillary, supraclavicular, or internal mammary lymph nodes, at first relapse. Distant recurrence was defined as disease recurrence occurring at any other site. Invasive disease-free survival was defined as freedom from invasive disease recurrence, second primary cancer, or death.

Statistical analysis

Data were analyzed using GraphPad Prism (v.6.0) for Windows, GraphPad software (San Diego, CA, USA) and SPSS® (v.23.0) software (SPSS, Chicago, IL, USA). Univariable comparisons were performed using linear regression, Student's t or Mann-Whitney U tests for continuous or $\chi 2$ or Fischer exact test for categorical variables. For the multivariable analyses, clinically relevant variables were inputted into linear, logistic or Cox proportional hazards regression models using a forward stepwise selection procedure. Data are reported as mean ± standard deviation (SD) unless otherwise specified, with the threshold of significance set at $P < 0.05$.

Results

Patient characteristics

Clinical characteristics

One hundred and fourteen (114) patients were included (Table 1). The majority of patients were overweight or obese at diagnosis (40 [61.5%]) and almost half were pre-menopausal (53 [46.5%]). Invasive ductal carcinoma was the most common subtype, occurring in 90 (78.9%), while 74 (64.9%) had background ductal carcinoma *in situ*. Most patients had Grade 2 (71 [62.8%]) or Grade 3 (38 [33.6%]) disease. Almost all were estrogen receptor (ER) positive (111 [97.4%]), while 91 (79.8%) were progesterone receptor (PR) positive, with median (interquartile range [IQR]) Allred scores of 8 (7-8)and 6 (3-8) respectively. The predominant clinical tumor stage was cT2 in 70 patients (63.6%), while 83 (74.8%) were clinically node positive at presentation.

Treatment characteristics

Treatment characteristics are demonstrated in Table 2. Most patients received doxorubicin, cyclophosphamide and paclitaxel (AC-T), after which almost half of patients were suitable for breast-conserving surgery (50 [43.9%]), while the majority underwent axillary clearance (89 [78.1%]) upon completion of neoadjuvant therapy. After mastectomy, some 34 (56.7%) underwent reconstruction; the majority being autologous (24 [70.6%]).

Postoperative complications occurred in 18 patients (16.1%) with a mean comprehensive complications index of 3.5 ± 9.6 (median 0 [0 - 0]). The most common postoperative morbidity encountered was seroma, occurring in 10 patients (8.9%), with 6

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Table 1
Clinicopathologic characteristics of study population.

Clinical characteristics	
Age at diagnosis, mean (SD)	50.0 (11.1)
Body weight, kg, median (IQR)	69.0 (63.0–80.0)
BMI, median (IQR)	25.9 (24.3–30.0)
BMI category, N (%)	
Normal weight	25 (38.5)
Overweight	24 (36.9)
Obese	16 (24.6)
Menopausal status, N (%)	
Premenopausal	53 (46.5)
Perimenopausal	20 (17.5)
Postmenopausal	41 (36.0)
Screen detected, N (%)	9 (7.9)
Genetic risk, N (%)	
BRCA 1	3 (2.6)
BRCA 2	0 (0.0)
Pathologic characteristics	
Affected breast N (%)	
Right	58 (50.9)
Left	56 (49.1)
Histologic type, N (%)	
Ductal	90 (78.9)
Lobular	16 (14.0)
Other	8 (7.0)
Background DCIS, N (%)	74 (64.9)
Grade, N (%)	
Grade 1	4 (3.5)
Grade 2	71 (62.8)
Grade 3	38 (33.6)
Receptor status	
ER positive, N (%)	111 (97.4)
ER Allred score, median (IQR)	8 (7-8)
PR positive, N (%)	91 (79.8)
PR Allred score, median (IQR)	6 (3-8)
Multifocal disease, N (%)	13 (11.4)
Clinical Stage, N (%)	
T0	1 (0.9)
T1	13 (11.8)
T2	70 (63.6)
T3	21 (19.1)
T4	5 (4.5)
N0	28 (25.2)
N1-3	83 (74.8)
Pathologic stage, N (%)	
T0	9 (8.0)
T1	21 (18.6)
T2	49 (43.4)
T3	32 (28.3)
T4	2 (1.8)
N0	17 (14.9)
$N0_{ITC}$	4 (3.5)
N1	47 (41.2)
N2	30 (26.3)
N3	16 (14.0)
Number of positive nodes, median (IQR)	2 (1-6)
Nodal yield, median (IQR)	15.5 (9-20)
Nottingham prognostic index, N (%)	
1	2 (1.8)
2	5 (4.5)
3	52 (46.8)
4	52 (46.8)
R0 resection[a], N (%)	111 (97.4)

BMI, body mass index; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; PR, progesterone receptor.
[a] Final histologic margin status (incorporates re-excision, if needed).

patients (5.3%) requiring reoperation for postoperative complications. The median (IQR) inpatient length of stay was 5 (3 - 7)days. The 30-day readmission rate was 2.7%. All patients received adjuvant endocrine therapy, with 91.9% of patients receiving postoperative radiation therapy.

Pathologic response to neoadjuvant chemotherapy

Pathologic complete response (pCR) to neoadjuvant therapy was observed in 9 (7.9%) patients, with a favorable Sataloff tumor response (grade A or B) in 60 (56.0%, Table 3). Seven patients (6.5%) exhibited a Sataloff tumor grade D response to treatment, indicating no evidence of therapeutic effect. 21 patients (18.4%) were pathologically node negative, of whom 6 (5.7%) demonstrated evidence of therapeutic effect (Sataloff nodal grade A). Of the 93 (81.6%) patients who were pathologically node positive after neoadjuvant therapy, some 29 (27.4%) demonstrated no evidence of treatment effect (Sataloff nodal grade D).

Following completion of neoadjuvant therapy, downstaging was observed in 37 patients (33.6%), with a reduction in tumor size observed in 48 (44.9%). Pathologic tumor size was greater than preoperatively predicted in 35 patients (32.7%). Pathologic response evaluation is summarized in Table 3.

Oncologic outcome

The median ±standard error follow-up time was 71.8 ± 3.0 months. The median invasive disease-free survival (iDFS) was 71.7 ± 3.2 months, with 3- and 5-year iDFS rates of 84.7 ± 3.4% and 68.5 ± 4.7%. 3- and 5-year locoregional recurrence-free, and systemic recurrence-free survival rates were 96.1 ± 1.9% and 96.1 ± 1.9%, and 89.8 ± 2.9% and 76.9 ± 4.4%, respectively. Locoregional recurrence was evident in 6 patients (5.3%), with systemic in 25 (21.9%). The most common site for systemic treatment failure was bone (14 [12.3%]).

Median disease-specific and overall survival were 71.3 ± 3.6 months and 71.8 ± 3.0 months, respectively. 3- and 5-year disease-specific and overall survival rates were 92.7 ± 2.5% and 80.2 ± 4.1%, 91.8 ± 2.6% and 77.7 ± 4.3%, respectively (Fig. S2).

Factors predictive of neoadjuvant chemotherapy response

Univariable analysis of factors predictive of neoadjuvant chemotherapy response is presented in Table 4, as well as Figs. 1 and 2.

No patient demographic factors significantly predicted pCR to neoadjuvant therapy, however patients with less advanced cT stage ($P = 0.006$), smaller clinical tumor size ($P = 0.011$) and higher grade ($P = 0.029$) were more likely to achieve pCR. There was a trend towards increased pCR rates among patients with a known BRCA1 mutation ($P = 0.098$). No patients with invasive lobular carcinoma achieved a pCR, compared with 7 (8.1%) patients with invasive ductal carcinoma. On multivariable analysis, tumor grade was independently predictive of pCR ($P = 0.039$, OR 6.00 [95% CI 1.09–33.01]).

No demographic or baseline pathologic variable predicted favorable Sataloff tumor response (grade A-B), however patients receiving AC-T exhibited increased response rates compared to non-ACT regimens (53 [64.6%] versus 2 [20%], $P = 0.007$). On multivariable analysis, reduced cN stage ($P = 0.036$, OR 0.24 [0.06–0.91]) and administration of AC-T ($P = 0.006$, OR 0.08 [0.01–0.48]) independently predicted favorable Sataloff tumor response (Table 5).

There was a trend towards increased downstaging among patients with lower body weight ($P = 0.082$), while higher cT stage was significantly associated with downstaging on univariable analysis ($P = 0.047$). On multivariable analysis, lower PR score was independently predictive of downstaging following neoadjuvant chemotherapy ($P = 0.029$, OR 0.83 [0.70–0.98]). PR positivity also independently predicted increased risk of pathological nodal involvement on multivariable analysis ($P = 0.017$, OR 8.83

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Table 2
Treatment characteristics and short-term outcomes.

Treatment characteristics	
Chemotherapy regimen, N (%)	
Doxorubicin, cyclophosphamide and paclitaxel	88 (89.8)
Other	10 (10.2)
Breast procedure[a], N (%)	
Wide local excision	50 (43.9)
Mastectomy	64 (56.1)
Axillary procedure[a], N (%)	
Sentinel node biopsy	25 (21.9)
Axillary clearance	89 (78.1)
Reconstruction, N (%)	34 (56.7)
Implant	10 (29.4)
Autologous	24 (70.6)
Adjuvant radiotherapy, N (%)	102 (91.9)
Adjuvant endocrine therapy	114 (100)
Postoperative outcomes	
Any complication, N (%)	18 (16.1)
Comprehensive complications index, median (IQR)	0 (0–0)
Clavien-Dindo ≥3b, N (%)	6 (5.3)
Clavien-Dindo Grade, N (%)	
No complication	94 (83.9)
Grade I	7 (6.3)
Grade II	5 (4.5)
Grade III	
Grade IIIa	0 (0.0)
Grade IIIb	6 (5.3)
Grade IV	0 (0.0)
Wound infection, N (%)	8 (7.1)
Hematoma, N (%)	3 (2.7)
Seroma, N (%)	10 (8.9)
Delayed wound healing, N (%)	2 (1.8)
Reoperation, N (%)	6 (5.3)
Inpatient LOS, median (range; IQR)	5 (0–18; 3–7)
30-day readmission, N (%)	3 (2.7)
In-hospital mortality, N (%)	0 (0.0)

LOS, length of stay; IQR, interquartile range.
[a] Final procedure.

[1.47–52.93]).

Examining the relative change in tumor size following neoadjuvant therapy, younger patients ($P = 0.008$) and those with higher grade tumors ($P = 0.004$) exhibited greater reductions in size. Patients receiving AC-T tended to exhibit greater reduction in tumor size ($P = 0.060$), while patients with invasive ductal carcinoma exhibited greater reductions in tumor size as compared with other histology ($P = 0.016$). On multivariable analysis, younger age ($P = 0.016$), higher tumor grade ($P = 0.002$) and ductal subtype ($P = 0.002$) independently predicted greater reduction in tumor size following neoadjuvant chemotherapy. Multivariable analysis results are summarized in Table 5.

Table 3
Pathologic response evaluation.

pCR, N (%)	9 (7.9)
Sataloff grade – primary Tumor, N (%)	
A	10 (9.3)
B	50 (46.7)
C	40 (37.4)
D	7 (6.5)
Sataloff grade – nodal, N (%)	
A	6 (5.7)
B	25 (23.6)
C	46 (43.4)
D	29 (27.4)
ypN0, N (%)	21 (18.4)
Downstaged, N (%)	37 (33.6)
Baseline Tumor size, mm, median (IQR)	39 (27–50)
Post neoadjuvant Tumor size, mm, median (IQR)	35 (21–60)
Change in size, mm, median (IQR)	−2 (-16 - 10)
Relative change in size, median % (IQR)	−6.3 (−45.2 – 26.3)
Change in size, N (%)	
Reduced	48 (44.9)
Stable	24 (22.4)
Increased	35 (32.7)

pCR, pathologic complete response.

Factors predictive of oncologic outcome

On multivariable analysis, tumor grade ($P < 0.001$, HR 9.66 [3.73–25.00]), cN stage ($P = 0.033$, HR 3.65 [1.11–12.00]), ER score ($P < 0.001$, HR 0.67 [0.55–0.82]), adjuvant radiation ($P = 0.003$, HR 0.13 [0.03–0.50]) and pathologic tumor size ($P = 0.027$, HR 1.02 [1.00–1.04]) were independently predictive of iDFS (Table 6). Similarly, tumor grade ($P = 0.002$, HR 5.25 [1.83–15.07]), cN stage ($P = 0.018$, HR 6.93 [1.40–34.28]), ER score ($P = 0.001$, HR 0.71 [0.58–0.86]) and pathologic tumor size ($P < 0.001$, HR 1.03 [1.01–1.04]) independently predicted OS, while tumor grade ($P = 0.013$, HR 3.89 [1.33–11.31]) and ER status ($P = 0.027$, HR 0.16 [0.03–0.81]), in addition to number of involved nodes ($P < 0.001$, HR 1.13 [1.06–1.21]) independently predicted DSS on multivariable analysis (Table 6). Univariable analyses of histopathological response and iDFS are shown in Fig. 3.

Discussion

Our findings suggest that certain clinicopathological traits may predict response within the locally advanced luminal A cohort. On multivariable analysis, older patients with grade 1 or 2 tumors that have strong PR (and ER) expression are least likely to respond to neoadjuvant chemotherapy. Patients with invasive lobular carcinoma (ILC), or rarer subtypes also respond poorly.

Younger patients with high grade, weakly PR-expressing ductal tumors derive the best response from neoadjuvant chemotherapy. Patients who receive the AC-T regimen also achieve a better response.

Clinical nodal status, smaller clinical tumor size, higher ER score, lower grade, and adjuvant radiotherapy predict improved survival. Notably, although lower PR scores and younger age predict response, neither predicts survival. Similarly, higher grade predicts response but lower grade at presentation predicts survival. In fact, none of the characteristics that predicted response were associated with improved survival. In this cohort, less aggressive baseline tumor characteristics were more positively prognostic than good chemotherapy response, where almost half (43.9%) of patients only achieved a Sataloff C or D response to NAC. Although previous studies showed pCR to be associated with improved survival, no such association for this cohort was found in our analysis. Furthermore, the overall low rate of pCR (7.9%) in this group makes it a relatively insensitive measure of chemotherapy effect.

Of the 26 patients (23.6%) who had T3 or T4 tumors at presentation, only 5 (19.2%) were suitable for breast-conserving surgery following NAC. Eighty-three patients (74.8%) were clinically N1-3 at presentation. Five of these (6.0%) were suitable for axilla-conserving surgery after NAC. NAC therefore facilitated breast- or axilla-conservation in only a minority of patients. 55.1% of patients either had no significant change in tumor size, or it increased in size, despite systemic therapy. Without a reciprocal control group of patients receiving immediate surgery, it is difficult to ascertain if NAC granted our cohort an improved oncologic outcome. Based on this study, the treatment interventions associated with improved iDFS were receipt of adjuvant radiotherapy, and ER score, which is likely a surrogate marker of adjuvant hormonal therapy effectiveness.[22]

Although many studies have investigated prediction of response

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Table 4
Univariable analyses of factors associated with response to chemotherapy for Luminal A breast cancer.

Clinical characteristics		pCR	No pCR	*P*-value	Sataloff T A + B	Sataloff T C + D	*P*-value	ypN0	ypN+	*P*-value	Downstaged	No downstage	*P*-value
Age at diagnosis, mean (SD)	50 (11.1)	49.81 (11.06)	52.22 (11.67)	0.533	48.68 (12.34)	51.62 (9.76)	0.185	54.76 (13.79)	48.92 (10.15)	0.079	49.03 (11.79)	50.16 (10.58)	0.609
Body weight, kg, mean (SD)	74.3 (17.7)	71.02 (14.41)	74.64 (18.06)	0.636	72.12 (13.93)	71.03 (13.20)	0.759	71.27 (15.87)	74.72 (18.02)	0.608	68.90 (13.68)	77.03 (19.31)	0.082
BMI, mean (SD)	28.0 (6.6)	28.04 (4.11)	28.00 (6.80)	0.988	26.97 (4.87)	27.42 (5.74)	0.752	27.42 (5.40)	28.06 (6.77)	0.809	26.07 (4.96)	28.98 (7.20)	0.101
BMI category, N (%)													
Normal weight	25 (38.5)	1 (4.0)	24 (96.0)	0.602	14 (56.0)	11 (44.0)	0.426	4 (16.0)	21 (84.0)	0.396	11 (44.0)	14 (56.0)	0.311
Overweight	24 (36.9)	2 (8.3)	22 (91.7)		17 (70.8)	6 (25.0)		1 (4.2)	23 (95.8)		6 (25.0)	17 (70.8)	
Obese	16 (24.6)	2 (12.5)	14 (87.5)		8 (50.0)	4 (25.0)		2 (12.5)	14 (87.5)		4 (25.0)	12 (75.0)	
Menopausal status, N (%)													
Premenopausal	53 (46.5)	3 (5.7)	50 (94.3)	0.711	30 (60.0)	20 (40.0)	0.746	6 (11.3)	47 (88.7)	0.154	19 (37.2)	32 (62.7)	0.616
Perimenopausal	20 (17.5)	2 (10.0)	18 (90.0)		10 (52.6)	9 (47.4)		4 (20.0)	16 (80.0)		5 (25.0)	15 (75.0)	
Postmenopausal	41 (36.0)	4 (9.8)	37 (90.2)		20 (52.6)	18 (47.3)		11 (26.8)	30 (73.2)		13 (33.3)	26 (66.7)	
Screen detected, N (%)	9 (7.9)	2 (22.2)	7 (77.8)	0.097	2 (22.2)	7 (77.8)	0.032	2 (22.2)	7 (77.8)	0.759	4 (44.4)	5 (55.6)	0.474
Genetic risk, N (%)													
BRCA 1	3 (2.6)	1 (33.3)	2 (66.7)	0.098	3 (100.0)	0 (0.0)	0.120	2 (66.7)	1 (33.3)	0.029	1 (33.3)	2 (66.7)	0.991
BRCA 2	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Pathologic characteristics													
Affected breast N (%)													
Right	58 (50.9)	5 (8.6)	53 (91.4)	0.770	29 (54.7)	24 (45.3)	0.779	14 (24.1)	44 (75.9)	0.109	18 (31.6)	39 (68.4)	0.636
Left	56 (49.1)	4 (7.1)	52 (92.9)		31 (57.4)	23 (42.6)		7 (12.5)	49 (87.5)		19 (25.8)	34 (74.2)	
Histologic type, N (%)													
Ductal	90 (78.9)	7 (7.8)	83 (92.2)	0.101	48 (55.2)	39 (44.8)	0.359	14 (15.6)	76 (84.4)	0.290	32 (36.0)	57 (64.0)	0.541
Lobular	16 (14.0)	0 (0.0)	16 (100)		7 (50.0)	7 (50.0)		5 (31.2)	11 (68.8)		3 (21.4)	11 (78.6)	
Other	8 (7.0)	2 (25.0)	6 (75.0)		5 (83.3)	1 (16.7)		2 (25.0)	6 (75.0)		2 (28.6)	5 (71.4)	
Background DCIS, N (%)	74 (64.9)	4 (5.4)	70 (94.6)	0.180	39 (56.5)	30 (43.5)	0.900	10 (13.5)	64 (86.5)	0.066	23 (31.5)	50 (68.5)	0.507
Grade, N (%)													
Grade 1	4 (3.5)	1 (25.0)	3 (75.0)	0.026	1 (50.0)	1 (50.0)	0.792	1 (25.0)	3 (75.0)	0.945	1 (25.0)	3 (75.0)	0.200
Grade 2	71 (62.8)	2 (2.8)	69 (97.2)		37 (54.4)	31 (45.6)		13 (18.3)	58 (81.7)		19 (27.9)	49 (72.1)	
Grade 3	38 (33.6)	6 (15.8)	32 (84.2)		22 (61.1)	14 (38.9)		7 (18.4)	31 (81.6)		17 (44.7)	21 (55.3)	
Receptor status													
ER positive, N (%)	111 (97.4)	9 (8.1)	102 (91.9)	0.607	59 (56.7)	45 (43.3)	0.421	20 (18.0)	91 (72.0)	0.500	37 (34.6)	70 (65.4)	0.211
ER Allred score, mean (SD)	7.1 (1.8)	6.33 (2.18)	7.12 (1.74)	0.208	7.10 (1.66)	6.91 (2.03)	0.603	6.33 (2.31)	7.22 (1.61)	0.109	6.95 (1.73)	7.07 (1.86)	0.737
PR positive, N (%)	91 (79.8)	6 (6.6)	85 (93.4)	0.305	47 (55.3)	38 (44.7)	0.749	12 (13.2)	79 (86.8)	0.004	28 (31.1)	62 (68.9)	0.234
PR Allred score, mean (SD)	5.0 (2.8)	3.78 (2.68)	5.07 (2.71)	0.188	4.88 (2.78)	4.89 (2.93)	0.985	3.71 (3.02)	5.25 (2.70)	0.023	4.49 (2.79)	5.34 (2.77)	0.129
Multifocal disease, N (%)	13 (11.4)	1 (7.7)	12 (92.3)	0.977	6 (54.5)	5 (45.5)	0.914	2 (15.4)	11 (84.6)	0.764	3 (23.1)	10 (76.9)	0.391
Clinical Stage, N (%)													
T0-T1	14 (12.7)	4 (28.6)	10 (71.4)	0.006	5 (45.5)	6 (54.5)	0.659	5 (35.7)	9 (64.3)	0.090	4 (30.8)	9 (69.2)	0.047
T2	70 (63.6)	5 (7.1)	65 (92.9)		37 (55.2)	30 (44.8)		13 (18.6)	57 (81.4)		19 (27.1)	51 (72.9)	
T3-T4	26 (23.6)	0 (0.0)	26 (100.0)		16 (61.5)	10 (38.5)		2 (7.7)	24 (92.3)		14 (53.8)	12 (46.2)	
N0	28 (25.2)	2 (7.1)	26 (92.9)	0.829	18 (69.2)	8 (30.8)	0.111	14 (50.0)	14 (50.0)	<0.001	8 (28.6)	20 (71.4)	0.511
N1-3	83 (74.8)	7 (8.4)	76 (91.6)		40 (51.3)	38 (48.7)		6 (7.2)	77 (92.8)		29 (35.4)	53 (64.6)	

BMI, body mass index; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; PR, progesterone receptor.

to neoadjuvant therapy overall, few have specifically addressed Luminal A tumors. Most studies focus on the highly responsive triple-negative or HER2+ cohorts.[23] In the Luminal A cohort, gene signatures such as Oncotype DX® and Mammaprint® are used in the adjuvant setting to give robust recommendation on chemotherapy versus endocrine therapy alone.[24] However, the use of these signatures has not transferred into the neoadjuvant setting.

Neoadjuvant endocrine therapy (NET) has been viewed as a potential alternative to NAC in post-menopausal patients. Although randomised trial data emerged over ten years ago citing similar rates of therapy response and breast conservation, NET has not been widely adopted in the interim.[25] A more recent US meta-analysis including 3490 patients concluded that neoadjuvant endocrine therapy in ER + patients was associated with similar response rates to NAC, but with significantly lower toxicity. Correct patient selection, ideally with biomarker support, and the optimum endocrine combination therapy require further investigation.[26]

Mechanisms explaining the associations between grade, PR expression, histologic subtype, and NAC response have been documented in the literature. Weak PR expression as a predictor of response has been investigated in large pooled analyses.[27] Lower PR expression predicts pCR, but ER positive, PR negative patients also have significantly worse disease-free and overall survival. Under normal circumstances, ER and PR expression is paired. It is likely that dyssynchronous ER/PR expression is a surrogate for tumor aggressiveness and cellular instability, as this heterogeneity betrays a developing abnormality in growth factor signaling in the tumor cells.[27,28]

Patients with invasive lobular carcinoma (ILC) typically respond poorly to NAC. Patients with ILC present at older ages, and are more likely to have higher T-stage, lower grade tumors with low p53 expression.[29] This predilection to large size and low grade means that although absolute size reduction in millimeters may be similar, there is a significant difference in percentage size reduction compared to IDC.

Age has previously not been shown to be associated with pCR in a large analysis of four alliance clinical trials.[30] However, younger women overall are at increased risk of biologically more aggressive

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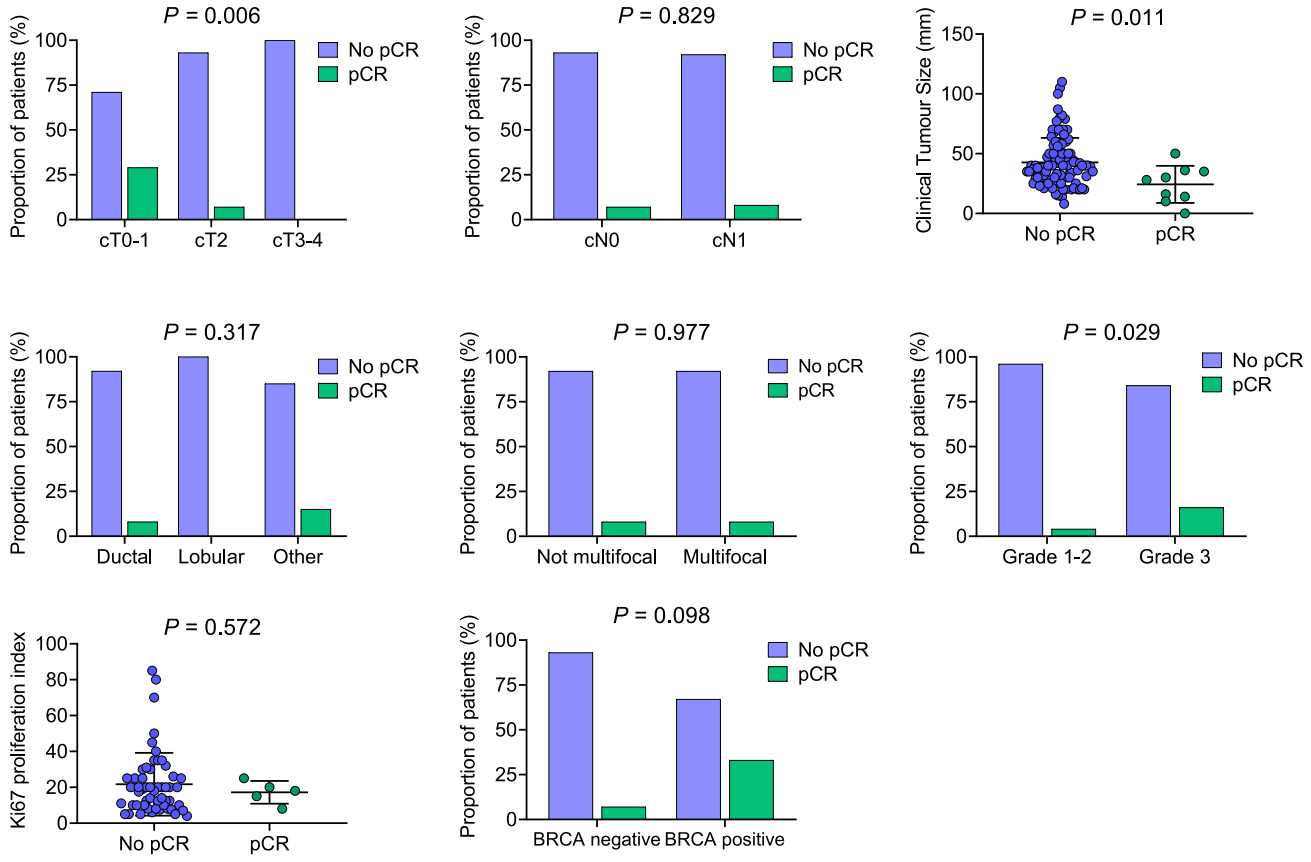

Fig. 1. Histopathologic characteristics and pathologic complete response.
Univariable analyses. Clinical T score ($P = 0.006$) and tumor grade ($P=0.029$) predict pCR.

breast cancer phenotypes. This may partly explain the association with greater percentage size reduction found in this study.[31] Tumor grade directly measures speed of cell growth and therefore is associated with improved response but poorer prognosis, although mitigated by improved prognosis if pCR is achieved. Low pCR rates mean that pCR did not predict improved survival on multivariable

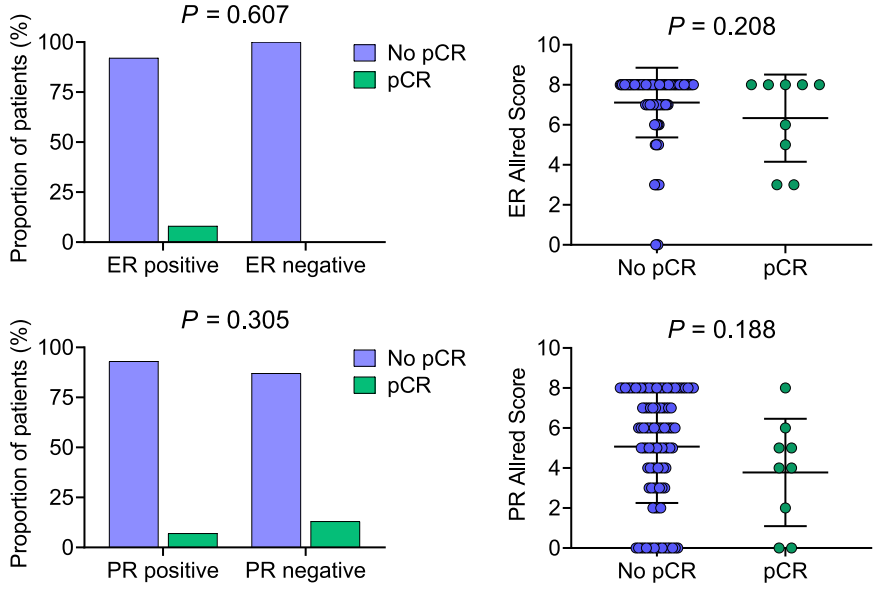

Fig. 2. Hormone receptor status and pathologic complete response.
Univariable analyses.

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Table 5
Multivariable analysis of factors associated with response to chemotherapy for Luminal A breast cancer.

	pCR		Downstaging		ypN+		Sataloff Tumor response[a]		Percentage size change		
	P-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	β (SE)	95% CI
Clinicopathological characteristics											
Age, years	0.251	–	0.611	–	0.218	–	0.110	–	0.016	0.231 (0.80)	0.38–3.55
Menopausal status	0.404	–	0.750	–	0.290	–	0.736	–	0.611	–	–
Tumor grade, G3 vs G1-2	0.039	6.00 (1.09–33.01)	0.063	–	0.297	–	0.621	–	0.002	−0.296 (15.45)	−79.59–−18.10
Histological subtype*	0.637	–	0.339	–	0.942	–	0.199	–	0.002	0.295 (16.13)	18.62–82.74
Clinical Tumor size	0.075	–	0.370	–	0.090	–	0.738	–	–	–	–
Clinical T stage, cT2-4 vs cT1	0.063	–	0.056	–	0.442	–	0.753	–	0.621	–	–
Clinical N stage, cN1-3 vs cN0	0.435	–	0.283	–	<0.001	23.31 (4.66–116.67)	0.036	0.24 (0.06–0.91)	0.986	–	–
ER status	0.513	–	0.218	–	0.396	–	0.469	–	0.756	–	–
ER Allred score	0.581	–	0.798	–	0.209	–	0.584	–	0.902	–	–
PR status	0.263	–	0.956	–	0.017	8.83 (1.47–52.93)	0.798	–	0.095	–	–
PR Allred score	0.164	–	0.029	0.83 (0.70–0.98)	0.606	–	0.829	–	0.199	–	–
Treatment characteristics											
Chemotherapy Regimen, other vs AC-T	0.392	–	0.283	–	0.162	–	0.006	0.08 (0.01–0.48)	0.550	–	–
Cycles completed	0.739	–	0.974	–	0.757	–	0.860	–	0.535	–	–

OR, odds ratio; CI, confidence interval; pCR, pathologic complete response; ER, estrogen receptor; PR, progesterone receptor.
*Analyzed as a categorical variable (ductal, lobular, other), category *P*-values and Odd Ratios not significant on logistic regression.
[a] Analyzed as Sataloff A-B vs C-D.

analysis. This weak association between pCR and prognosis for this cohort has been shown in the CTNeoBC pooled analysis.[4] This calls into question the utility of using pCR as a response measure in this cohort at all.

Chemotherapy improves survival outcomes in breast cancer and in the neoadjuvant setting has permitted breast conservation for

Table 6
Multivariable analysis of factors associated with oncologic outcome after neoadjuvant chemotherapy for luminal A breast cancer.

	iDFS		DSS		OS	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)
Clinicopathological characteristics						
Age, years	0.224	–	0.580	–	0.907	–
Menopausal status	0.604	–	0.337	–	0.187	–
Tumor grade, G3 vs G1-2	<0.001	9.66 (3.73–25.00)	0.013	3.89 (1.33–11.31)	0.002	5.25 (1.83–15.07)
Histological subtype[a]	0.648	–	0.603	–	0.498	–
Clinical Tumor size, mm	0.590	–	0.365	–	0.390	–
Clinical T stage[a]	0.377	–	0.449	–	0.769	–
Clinical N stage, cN1-3 vs cN0	0.033	3.65 (1.11–12.00)	0.074	–	0.018	6.93 (1.40–34.28)
ER status	0.736	–	0.027	0.16 (0.03–0.81)	0.439	–
ER Allred score	<0.001	0.67 (0.55–0.82)	0.195	–	0.001	0.71 (0.58–0.86)
PR status	0.879	–	0.513	–	0.501	–
PR Allred score	0.602	–	0.706	–	0.744	–
Treatment characteristics						
Neoadjuvant chemotherapy regimen	0.960	–	0.847	–	0.238	–
Cycles complete	0.117	–	0.502	–	0.612	–
Adjuvant chemotherapy	0.505	–	0.732	–	0.735	–
Adjuvant radiotherapy	0.003	0.13 (0.03–0.50)	0.120	–	0.037	–
Treatment response characteristics						
pCR	0.123	–	0.220	–	0.100	–
ypT stage[a]	0.195	–	0.533	–	0.418	–
Total positive node count	0.087	–	<0.001	1.13 (1.06–1.21)	0.335	–
R0 resection	0.854	–	0.853	–	0.347	–
Downstaging	0.986	–	0.686	–	0.616	–
Pathologic Tumor size, mm	0.027	1.02 (1.00–1.04)	0.092	–	<0.001	1.03 (1.01–1.04)
Size change (mm)	0.590	–	0.422	–	0.390	–
Size change %	0.431	–	0.218	–	0.738	–
Nottingham prognostic index	0.868	–	0.935	–	0.379	–

HR, hazard ratio; CI, confidence interval; pCR, pathologic complete response; ypN0, summative pathological node negativity post-neoadjuvant chemotherapy; ER, Estrogen receptor; PR, Progesterone receptor.
[a] Analyzed as a categorical variable, category P-values and Hazard Ratios not significant on Cox proportional hazards regression.

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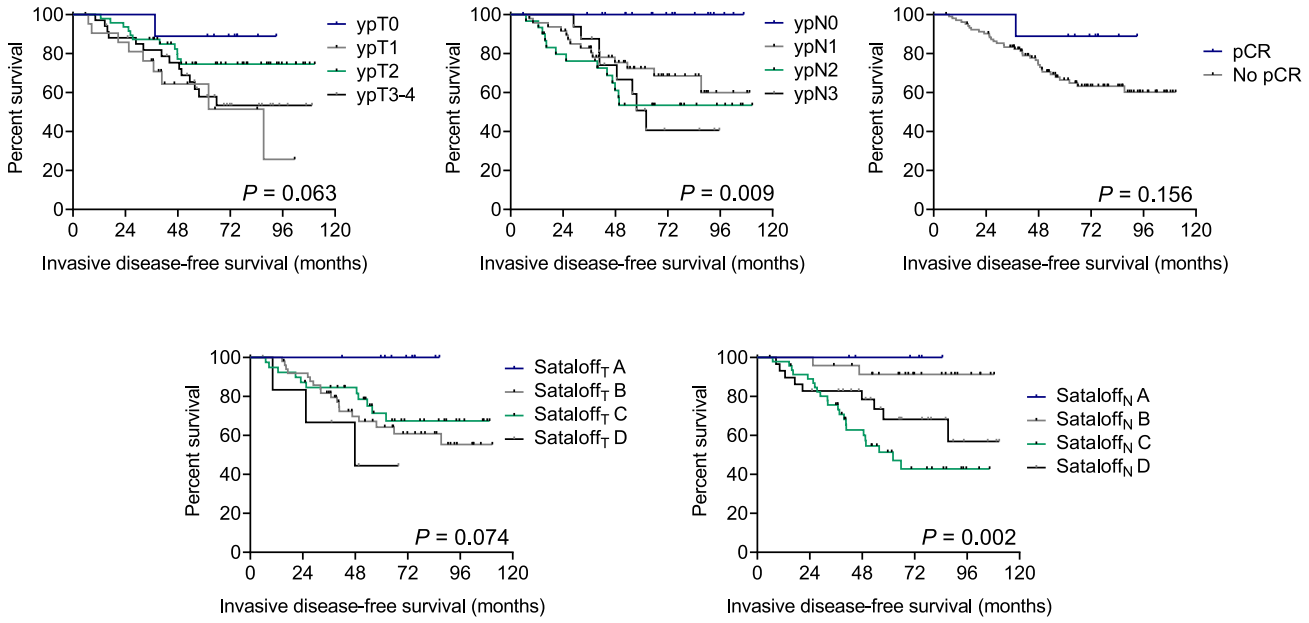

Fig. 3. Histopathologic response and invasive disease-free survival.
Kaplan Meier curves. ypN status (P = 0.009) and Sataloff nodal score (P = 0.002) associated with improved invasive disease-free survival.

patients in whom it would not otherwise be possible.[1,32] However, with increasing focus on personalized treatment regimens and patient quality of life, as well as survival outcomes, selecting the correct patients for neoadjuvant chemotherapy is important. Chemotherapy is not without risk, and patients who received the AC-T regimen in this study adopt a 7.3% chance of hospitalization due to toxicity within the first six months of treatment. Cardiac toxicity, secondary leukemia and neurotoxicity are known long-term potential side-effects.[33] Furthermore, the cost of treatment is substantial.[34]

Our study has several limitations. Measuring the response of breast cancer to neoadjuvant chemotherapy is difficult. Initial radiological evaluation can under-stage the size of the tumor, especially in a lobular cohort, thus making it less clear on pathological evaluation whether the tumor was initially undersized, or has progressed despite systemic treatment. Prospective comparison is required to evaluate if NAC grants this subset any improvement in oncologic outcome overall.

Luminal A breast cancers are less chemotherapy sensitive than their triple negative or HER2 positive counterparts, with poor response (Sataloff C or D) observed in almost half of patients. Younger patients with high grade tumors and weak PR expression exhibit the most promising response rates. By contrast, older patients with strongly ER/PR positive tumors that are grade 1 or 2 derive least benefit from chemotherapy. The traditional shotgun approach with emphasis on systemic therapy ensured that all patients with large tumors or nodal positivity received systemic therapy. This study underlines how few of them derived clinically measurable benefit and how a pCR, when it occurred was not associated with a survival benefit (possibly due to the underlying more aggressive nature of the tumor). It documents the underlying biological disparity between luminal A and other breast cancers and gives credence to a more molecularly stratified approach to management - perhaps a modern scoring system will augment the traditional Nottingham Prognostic Index in achieving an outcome-based systemic therapy plan.

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None.

Declaration of competing interest

The authors declare no conflict of interest in the production of this manuscript or in the research associated with it.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2020.11.053.

References

1. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol : official journal of the American Society of Clinical Oncology*. 1997 Jul;15(7):2483–2493. PubMed PMID: 9215816. Epub 1997/07/01. eng.
2. FaDA (FDA). Guidance for industry pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval. *Food and Drug Administration (FDA)*. 2014:5. Office of Communications DoDI.
3. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. *Ann Surg Oncol*. 2018;25(7):1783–1785, 2018/07/01.
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014 Jul 12;384(9938):164–172. PubMed PMID: 24529560. Epub 2014/02/18. eng.
5. Yersal O, Barutca S. Biological subtypes of breast cancer: prognostic and therapeutic implications. *World J Clin Oncol*. 2014 Aug 10;5(3):412–424. PubMed

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PMID: 25114856. Pubmed Central PMCID: PMC4127612. Epub 2014/08/13. eng.
6. NIfHaCE (Nice). *Early and Locally Advanced Breast Cancer: Diagnosis and Management*. National Institute for Health and Care Excellence (NICE); 2018 July 2018. Report No.: NICE guideline [NG101].
7. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018 Jul 12;379(2):111–121. PubMed PMID: 29860917. Pubmed Central PMCID: PMC6172658. Epub 2018/06/05.
8. Colleoni M, Viale G, Zahrieh D, et al. Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. *Clin Canc Res : an official journal of the American Association for Cancer Research*. 2004 Oct 1;10(19):6622–6628. PubMed PMID: 15475452. Epub 2004/10/12. eng.
9. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and Bowel Project protocols B-18 and B-27. *J Clin Oncol : official journal of the American Society of Clinical Oncology*. 2008 Feb 10;26(5):778–785. PubMed PMID: 18258986. Epub 2008/02/09. eng.
10. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. *J Clin Oncol : official journal of the American Society of Clinical Oncology*. 2014 Jul 20;32(21):2255–2269. PubMed PMID: 24868023. Pubmed Central PMCID: PMC4876310. Epub 2014/05/29. eng.
11. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011 Nov 12;378(9804), 1707-16. PubMed PMID: 22019144. Pubmed Central PMCID: PMC3254252. Epub 2011/10/25. eng.
12. Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: an American society of clinical oncology, American society for radiation oncology, and society of surgical oncology focused guideline update. *Practical radiation oncology*. 2016 Nov - Dec;6(6):e219–e234. PubMed PMID: 27659727. Epub 2016/09/24. eng.
13. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002 Oct 17;347(16):1233–1241. PubMed PMID: 12393820. Epub 2002/10/24. eng.
14. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol*. 2013 Oct;14(11):1086–1094. PubMed PMID: 24055415. Epub 2013/09/24. eng.
15. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol : an official journal of the United States and Canadian Academy of Pathology, Inc*. 1998 Feb;11(2):155–168. PubMed PMID: 9504686. Epub 1998/03/21. eng.
16. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of American pathologists clinical practice guideline focused update. *J Clin Oncol : official journal of the American Society of Clinical Oncology*. 2018 Jul 10;36(20):2105–2122. PubMed PMID: 29846122. Epub 2018/05/31.
17. Jacobs TW, Gown AM, Yaziji H, et al. Specificity of HercepTest in determining HER-2/neu status of breast cancers using the United States Food and Drug Administration-approved scoring system. *J Clin Oncol : official journal of the American Society of Clinical Oncology*. 1999 Jul;17(7):1983–1987. PubMed PMID: 10561248. Epub 1999/11/24. eng.
18. Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clin Breast Canc*. 2004 Apr;5(1):63–69. PubMed PMID: 15140287. Epub 2004/05/14. eng.
19. Sataloff DM, Mason BA, Prestipino AJ, et al. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: a determinant of outcome. *J Am Coll Surg*. 1995 Mar;180(3):297–306. PubMed PMID: 7874340. Epub 1995/03/01. eng.
20. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205–213. PubMed PMID: PMC1360123.
21. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013 Jul;258(1):1–7. PubMed PMID: 23728278. Epub 2013/06/04. eng.
22. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol : official journal of the American Society of Clinical Oncology*. 1999 May;17(5):1474–1481. PubMed PMID: 10334533. Epub 1999/05/20. eng.
23. Prat A, Fan C, Fernandez A, et al. Response and survival of breast cancer intrinsic subtypes following multi-agent neoadjuvant chemotherapy. *BMC Med*. 2015 Dec 18;13(1):303. PubMed PMID: 26684470. Pubmed Central PMCID: PMC4683815. Epub 2015/12/20.
24. Schmidt M, Thomssen C, Untch M. Intrinsic subtypes of primary breast cancer–gene expression analysis. *Oncol Res Treat*. 2016;39(3):102–110. PubMed PMID: 27031354. Epub 2016/04/01.
25. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer*. 2007 Jul 15;110(2):244–254. PubMed PMID: 17538978. Epub 2007/06/01. eng.
26. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. *JAMA oncology*. 2016 Nov 1;2(11):1477–1486. PubMed PMID: 27367583. Pubmed Central PMCID: PMC5738656. Epub 2016/07/02. eng.
27. van Mackelenbergh MT, Denkert C, Nekljudova V, et al. Outcome after neoadjuvant chemotherapy in estrogen receptor-positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials. *Breast Canc Res Treat*. 2018 Jan;167(1):59–71. PubMed PMID: 28875243. Epub 2017/09/07.
28. Arpino G, Weiss H, Lee AV, et al. Estrogen receptor-positive, progesterone receptor-negative breast cancer: association with growth factor receptor expression and tamoxifen resistance. *Journal of the National Cancer Institute*. 2005 Sep 7;97(17):1254–1261. PubMed PMID: 16145046. Epub 2005/09/08.
29. Lips EH, Mukhtar RA, Yau C, et al. Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. *Breast Canc Res Treat*. 2012 Nov;136(1):35–43. PubMed PMID: 22961065. Pubmed Central PMCID: PMC5702179. Epub 2012/09/11. eng.
30. Warner ET, Ballman KV, Buzdar A, et al. Age, race, BMI, and pathologic complete response following neoadjuvant chemotherapy: an analysis of four alliance clinical trials. *J Clin Oncol*. 2015;33(28_suppl):33, 2015/10/01.
31. Winchester DP, Osteen RT, Menck HR. The National Cancer Data Base report on breast carcinoma characteristics and outcome in relation to age. *Cancer*. 1996 Oct 15;78(8):1838–1843. PubMed PMID: 8859200. Epub 1996/10/15. eng.
32. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. *BMC Med*. 2015 Aug 17;13:195. PubMed PMID: 26278220. Pubmed Central PMCID: PMC4538915. Epub 2015/08/19. eng.
33. Azim Jr HA, de Azambuja E, Colozza M, et al. Long-term toxic effects of adjuvant chemotherapy in breast cancer. *Ann Oncol*. 2011 Sep;22(9):1939–1947. PubMed PMID: 21289366. Epub 2011/02/04.
34. Giordano SH, Niu J, Chavez-MacGregor M, et al. Estimating regimen-specific costs of chemotherapy for breast cancer: observational cohort study. *Cancer*. 2016 Nov 15;122(22):3447–3455. PubMed PMID: 27723214. Pubmed Central PMCID: PMC5479741. Epub 2016/10/11.

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