ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2018 April 10; 9(2): 26-41

Published by Baishideng Publishing Group Inc

WJCO World Journal of Clinical Oncology

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ABOUT COVER

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AIM AND SCOPE

World Journal of Clinical Oncology (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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INDEXING/ABSTRACTING

World Journal of Clinical Oncology is now indexed in PubMed, PubMed Central, Scopus, and Emerging Sources Citation Index.

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Bimonthly

World Journal of Clinical Oncology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
April 10, 2018

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Clinical Oncology

Submit a Manuscript: http://www.f6publishing.com

World J Clin Oncol 2018 April 10; 9(2): 33-41

DOI: 10.5306/wjco.v9.i2.33

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Observational Study

Clinicopathological predictors of long-term benefit in breast cancer treated with neoadjuvant chemotherapy

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Author contributions: Galvez M, Castaneda CA and Rebaza LP contributed to the conception and design of the study , performed data analysis and interpretation; Galvez M, Castaneda CA, Sanchez J, Castillo M, Rebaza LP and Mejia O performed data acquisition, as well as provided administrative, technical and material support; all authors drafted the article and made critical revisions related to the intellectual content of the manuscript, and approved the final version of the article to be published.

Institutional review board statement: This study was reviewed and approved by the Instituto Nacional de Enfermedades Neoplasicas Institutional Review Board. Personal and filiation data including identity of every patient was protected with an added code in the Excel table. This is a retrospective case series that did not have any activity or contact with the patients.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All of the authors declare no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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Received: June 28, 2017
Peer-review started: July 3, 2017
First decision: December 7, 2017
Revised: December 19, 2017
Accepted: February 5, 2018
Article in press: February 5, 2018
Published online: April 10, 2018

Abstract

AIM

To investigate the survival impact of clinicopathological factors, including pathological complete response (pCR) and tumor-infiltrating lymphocytes (sTIL) levels according to subtypes, in breast cancer (BC) patients who received neo-adjuvant chemotherapy (NAC).

METHODS

We evaluated 435 BC patients who presented and received NAC at the Instituto Nacional de Enfermedades Neoplasicas from 2003 to 2014. sTIL was analyzed as the proportion of tumor stroma occupied by lymphocytes, and was prospectively evaluated on hematoxylin and eosin-stained sections of the preNAC core biopsy. pCR was considered in the absence of infiltrating cancer cells in primary tumor and axillary lymph nodes. Analysis of statistical association between clinical pathological features, sTIL, pCR and survival were carried out using SPSSvs19.

RESULTS

Median age was 49 years (range 24-84 years) and the most frequent clinical stage was ⅢB (58.3%). Luminal A, Luminal B, HER2-enriched and (triple-negative) TN phenotype was found in 24.6%, 37.9%, 17.7% and 19.8%, respectively. pCR was observed in 11% and median percentage of sTIL was 40% (2%-95%) in the whole population. pCR was associated to Ct1-2 (P = 0.045) and to high sTIL (P = 0.029) in the whole population. There was a slight trend towards significance for sTIL (P = 0.054) in Luminal A. sTIL was associated with grade Ⅲ (P < 0.001), no-Luminal A subtype (P < 0.001), RE-negative (P < 0.001), PgR-negative (P < 0.001), HER2-positive (P = 0.002) and pCR (P = 0.029) in the whole population. Longer disease-free survival was associated with grade Ⅰ-Ⅱ (P = 0.006), cN0 (P < 0.001), clinical stage Ⅱ (P = 0.004), ER-positive (P < 0.001), PgR-positive (P < 0.001), luminal A (P < 0.001) and pCR (P = 0.002). Longer disease-free survival was associated with grade Ⅰ-Ⅱ in Luminal A (P < 0.001), N0-1 in Luminal A (P = 0.045) and TNBC (P = 0.01), clinical stage Ⅱ in Luminal A (P = 0.003) and TNBC (P = 0.038), and pCR in TNBC (P < 0.001). Longer overall survival was associated with grade Ⅰ-Ⅱ (P < 0.001), ER-positive (P < 0.001), PgR-positive (P < 0.001), Luminal A (P < 0.001), cN0 (P = 0.002) and pCR (P = 0.002) in the whole population. Overall survival was associated with clinical stage Ⅱ (P = 0.017) in Luminal A, older age (P = 0.042) in Luminal B, and pCR in TNBC (P = 0.005).

CONCLUSION

Predictive and prognostic values of clinicopathological features, like pCR and sTIL, differ depending on the evaluated molecular subtype.

Key words: Breast cancer; Subtype; Tumor-infiltrating lymphocytes; Neoadjuvant therapy; Pathological complete response; Survival

Core tip: The authors evaluated a series of 435 breast cancer (BC) patients who received neoadjuvant chemotherapy. They evaluated the association between stromal tumor-infiltrating lymphocytes levels and pCR in preneoadjuvant chemotherapy samples according to molecular subtypes. The results confirm differences in the predictive and prognostic role of stromal tumor-infiltrating lymphocytes and pathological complete response depending on the tumor subtype. Additionally, the authors evaluate the value of traditional prognostic features in every BC subset. The results increase the understanding of biomarkers in the heterogeneous scenario of BC.

Galvez M, Castaneda CA, Sanchez J, Castillo M, Rebaza LP, Calderon G, De La Cruz M, Cotrina JM, Abugattas J, Dunstan J, Guerra H, Mejia O, Gomez HL. Clinicopathological predictors of long-term benefit in breast cancer treated with neoadjuvant chemotherapy. *World J Clin Oncol* 2018; 9(2): 33-41 Available from: URL: http://www.wjgnet.com/2218-4333/full/v9/i2/33.htm DOI: http://dx.doi.org/10.5306/wjco.v9.i2.33

INTRODUCTION

Breast cancer (BC) is the second most common cancer in the world and the most frequent cancer among women, with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers), and is the fifth cause of death from cancer overall (522000 deaths)[1]. Neoadjuvant chemotherapy (NAC) is the standard therapy for locally advanced BC and could improve both surgical options and long-term outcome[2]. Response to NAC is considered an *in vivo* test of tumor sensitivity to NAC, and the achievement of a pathological complete response (pCR) is associated with longer disease-free survival (DFS) and greater overall survival (OS)[3-7]. Tumor-infiltrating lymphocytes (TILs) serve to evaluate the host immune system response against a tumor and also constitutes a valuable predictive biomarker of NAC response and survival[8-11].

BC is a heterogeneous disease, and intrinsically different subtypes of BC have been identified in the past years based on gene expression profiles and on the combined immunohistochemical status of hormone and HER2 receptors. Responsiveness to preoperative therapies and outcome after surgery can be predicted by BC subtypes[12-14].

In this study, we investigated the survival impact of different clinicopathological factors, including pCR and TIL levels, according to the subtypes in BC patients who received NAC. The predictive role of different clinicopathological features for having high density TIL and obtaining pCR according to subtypes was also

determined.

MATERIALS AND METHODS

We found 435 patients diagnosed with BC at clinical stage ⅡB to ⅢC at the Medical Department of the Instituto Nacional de Enfermedades Neoplasicas from 2003 to 2014. Eligibility criteria for this retrospective study were a histological diagnosis based on a core needle biopsy, having received NAC regimen and having undergone surgery after NAC. Patient characteristics such as age, clinical stage, histological subtype and grade, presence of estrogen receptors (ERs), progesterone receptors (PgRs) and HER2, and molecular subtype was obtained from the pathology report of preNAC core biopsy. pCR was defined as absence of invasive cancer in the breast and axillary nodes, irrespective of carcinoma *in situ* (ypT0/is ypN0), as previously described[4,15]. Phenotype classification was prospectively concluded through the evaluation of ER, PgR, HER2 and Ki67 as well as histological grade (in cases without Ki67 information): Luminal A (ER ⩾ 10%, PgR ⩾ 20%, HER2-negative and Ki67 < 15% or HG-Ⅰ-Ⅱ), Luminal B (ER ≥ 10% and any PgR < 20%, HER2-positive, Ki67 < 15% or HG-Ⅲ), HER2-enriched (ER < 10%, PgR < 10% and HER2-positive) and triple-negative (TN) (ER < 10%, PgR < 10% and HER2-negative). Stromal (s)TIL was prospectively evaluated in preNAC core biopsy and was defined as percentage of stromal area covered by lymphocytes[16].

Follow-up and recurrence information (date and location) were obtained from patient files. Time-from-last-chemotherapy-to-surgery was considered as the number of months from the date of the last NAC administration to surgery of the primary tumor. OS was calculated from surgery date of the primary breast tumor to death or last follow-up date, and DFS was calculated from surgery date of the primary breast tumor to recurrence or last follow-up date.

Statistical analysis

Categorical comparisons and association analysis between clinical pathological features and pCR were carried out using the chi-square statistic or Fisher's exact test. Survival analysis, regarding OS and DFS, was performed using the Kaplan-Meier method, and differences between curves were estimated by log-rank test. In all cases, the level of alpha was set at 0.05 *a priori*. Statistical analysis was performed using SPSS v19 (IBM Corp., Armonk, NY, United States).

RESULTS

Clinicopathological description

There were 435 patients included in this study, with median age at diagnosis of 49 years (range: 24-84 years), median tumor size of 6.5 cm (range: 1.0-24.0 cm), T3 in 27.8% and T4 in 63.9%. Inflammatory disease was found in 29.2%. The most frequent clinical stages were ⅢB (60.5%) and ⅢA (18.6%). Ductal histology was found in 93.3%, high grade in 52.2%, ER+ status in 62.8%, PgR+ status in 51% and HER2+++ in 32.4%. Luminal A, Luminal B, HER2-enriched and TN phenotype was found in 24.6%, 37.9%, 17.7% and 19.8%, respectively. The most frequent NACs were doxorubicin-cyclophosphamide for 4 cycles followed by 12 weekly paclitaxel (67.18%), doxorubicin-cyclophosphamide for 4 cycles followed by every 3 wk paclitaxel in 4 cycles (18.85%) and doxorubicin-cyclophosphamide for 4 cycles alone (7.32%). The median time from the last chemotherapy to surgery was 63 d (maximum: 982 d). pCR was observed in 48 (11%) patients. Median percentage of sTILs was 40% (2%-95%) in the entire population and 70% (60%-95%) in patients with pCR. Recurrence was found in 35.7%. Median DFS was 7.54 and median OS was 5.16 years (95%CI: 4.16-6.15 years) (Table 1).

Clinicopathological factors associated to pCR according to BC subtypes

Association analysis found that pCR was associated with T1-2 (P = 0.045) and to high sTIL level (P = 0.029) in the entire population (Table 1). Higher sTIL level had a slight trend towards association with pCR (P = 0.054) in Luminal A, and smaller tumor size had a trend towards association with pCR (P = 0.098) in Luminal A. Clinical involvement of axillary lymph nodes was not associated to variation of pCR (Table 2). An additional analysis by level of axillary involvement found that N2-3 had lower rates of pCR than N0-1 only in TNBC (P = 0.018).

Clinicopathological factors associated with sTIL according to BC subtypes

Association analysis found that sTIL level was associated with grade Ⅲ (P < 0.001), no-Luminal A subtype (P < 0.001), ER-negative (P < 0.001), PgR-negative (P < 0.001), HER2-positive (P = 0.002) and pCR (P = 0.029) in the entire population (Table 1). Within each BC subtype, sTIL level remained associated with grade Ⅲ in Luminal B (P = 0.011) and TN (P = 0.006) subtypes, as well as cN+ in Luminal B (P = 0.02) (Table 3).

Prognostic clinicopathological factors according to BC subtypes

Survival analysis found longer DFS was associated with grade Ⅰ-Ⅱ (P = 0.006), cN0 (P < 0.001), clinical stage Ⅱ (P = 0.004), ER-positive (P < 0.001), PgR-positive (P < 0.001), Luminal A (P < 0.001) and pCR (P = 0.002). Longer DFS was associated with grade Ⅰ-Ⅱ in Luminal A (P = 0.033), N0-1 in Luminal A (P = 0.045) and TNBC (P = 0.01), clinical stage Ⅱ in Luminal A (P = 0.003) and TNBC (P = 0.038), and pCR in TNBC (P = 0.001) (Table 1).

Table 1 Clinical-pathological features *n* (%)

	Cases	sTIL ⩾ 50%	*P* value	pCR	*P* value	Overall Survival at 5 yr (OS = 50.1%)	*P* value	Progression free survival at 5 yr (DFS = 57.8%)	*P* value
	435	181		48					
Age (yr), median (range)	49 (24-84)	49 (24-84)	0.923	47 (28-80)	0.472		0.512		0.833
< 50	231 (53.1)	96 (35.2)		28 (12.1)		48.8%		59.7%	
⩾ 50	204 (46.9)	85 (36.7)		20 (9.8)		51.7%		55.9%	
Histological subtypes			0.928		0.234		0.512		0.497
Ductal	406 (93.3)	169 (43.6)		43 (10.6)		49.0%		57.5%	
Lobular	21 (4.8)	7 (36.8)		2 (9.5)		61.0%		55.2%	
Others	8 (1.8)	5 (62.5)		3 (37.5)		-		-	
Histological grade			< 0.001		0.170		0.001		0.006
G1-G2	200 (46.0)	59 (32.6)		17 (8.5)		57.1%		64.6%	
G3	227 (52.2)	119 (65.7)		29 (12.8)		42.8%		52.2%	
NR	8 (1.8)	3 (1.7)		2 (25)		83.3%		45.7%	
ER			< 0.001		0.098		< 0.001		0.000
No	162 (37.2)	89 (57.8)		23 (14.2)		36.1%		47.1%	
Yes	273 (62.8)	92 (35.2)		25 (9.2)		58.2%		64.3%	
PgR			0.003		0.246		< 0.001		0.000
No	213 (49)	104 (51.0)		27 (12.7)		41.0%		50.0%	
Yes	222 (51)	77 (36.5)		21 (9.5)		58.4%		64.8%	
HER2			0.002		0.135		0.334		0.135
No	294 (67.6)	106 (38.3)		28 (9.5)		53.7%		60.4%	
Yes	141 (32.4)	75 (54.3)		20 (14.2)		40.8%		52.3%	
Molecular subtypes			< 0.001		0.233		< 0.001		< 0.001
Luminal A	107 (24.6)	30 (29.7)		13 (12)		72.0%		76.1%	
Luminal B	165 (37.9)	61 (38.4)		12 (7)		50.6%		57.7%	
HER2-enriched	77 (17.7)	50 (66.7)		10 (13)		41.5%		54.9%	
Triple-Negative	86 (19.8)	40 (50.0)		13 (15)		32.5%		40.3%	
Tumor size (cm)			0.183		0.019		0.490		0.250
Median (range)	6.5 (1-24)	6.5 (1-16)		6.0 (2-15)					
cT									
cT1-cT2	36 (8.3)	19 (54.3)		8 (22.2)		55.0%		69.2%	
cT3-cT4	399 (91.7)	162 (42.6)		40 (10)		49.6%		56.8%	
cN			0.084		0.743		0.007		0.001
cN0	83 (19.1)	28 (35.0)		10 (12)		65.8%		77.0%	
cN1-cN2-cN3	352 (80.9)	153 (45.7)		38 (10.8)		47.2%		54.2%	
Clinical stage			0.192		0.088		0.155		0.004
Ⅱ	72 (16.6)	26 (36.6)		12 (16.7)		62.1%		74.3%	
Ⅲ	363 (83.4)	155 (45.1)		36 (9.9)		48.1%		55.4%	
sTIL%					0.002		0.598		0.747
Median (range)	40 (2-95)	70 (60-95)		65 (5-95)					
< 50%	266 (61.1)	0 (0)		20 (7.5)		49.6%		55.7%	
⩾ 50%	149 (34.3)	181 (100)		26 (17.4)		53.9%		63.1%	
Missing data	20 (4.6)	20 (0)		2 (10)		-		-	
TLCS (d)			0.411		0.633		0.317		0.156
Median (range)	63 (5-982)	58 (8-982)		65 (8-281)					
Shorter than median	207 (47.6)	91 (45.5)		22 (10.6)		48.5%		55.0%	
Longer than median	211 (48.5)	82 (41.4)		26 (12.3)		56.7%		61.2%	
Missing data	17 (3.9)	8 (47.1)		0 (0)		17.6%		46.3%	
pCR			0.029				0.002		0.002
No	387 (89)	154 (41.7)		0 (0)		47.4%		55.1%	
Yes	48 (11)	27 (58.7)		48 (100)		85.1%		84.9%	
Relapse			0.895		< 0.001		< 0.001		
No	284 (65.3)	118 (43.4)		42 (14.8)		81.6%		-	
Yes	151 (34.7)	63 (44.1)		6 (4)		8.58%		-	

TIL: Tumor-infiltrating lymphocytes; pCR: Pathological complete response; OS: Overall survival; DFS: Disease free survival; PgR: Progesterone; TLCS: Time-From-Last-Chemotherapy-To-Surgery.

Longer OS was associated with grade Ⅰ-Ⅱ (P < 0.001), ER-positive (P < 0.001), PgR-positive (P < 0.001), Luminal A (P < 0.001), cN0 (P = 0.007) and pCR (P = 0.002) in the entire population. It was also associated with older age in Luminal B (P = 0.042), to clinical stage Ⅱ in Luminal A (P = 0.017), and to cN0 (P = 0.045) and pCR in TNBC (P = 0.005) (Figure 1). Differences in TILs did not affect survival in the entire nor molecular subtype populations (Table 1 and Figure 2).

DISCUSSION

The biological heterogeneity of BC has been extensively described, and differences between intrinsic subtypes have been confirmed in the recent decade. We explored differences in the survival impact

Table 2 Association between response and Clinical-pathological features regarding molecular subtype *n* (%)

	Lum A			Lum B			HER2			TN		
	Total 107	pCR 13	*P* value	Total 165	pCR 12	*P* value	Total 77	pCR 10	*P* value	Total 86	pCR 13	*P* value
Age (yr)			1.000			0.315			0.507			0.157
median (range)	47 (28-75)	46 (28-62)		51 (25-84)	52 (39-69)		51 (28-80)	46 (29-80)		49 (26-73)	45 (28-68)	
< 50	72 (67)	9 (13)		78 (48)	4 (5)		37 (48)	6 (16.2)		44 (48)	9 (20)	
⩾ 50	35 (33)	4 (11)		87 (52)	8 (9)		40 (52)	4 (10)		42 (52)	4 (10)	
Histological subtypes			0.349			1.000			0.434			0.392
Ductal	97 (91)	11 (11)		153 (93)	11 (7)		73 (95)	9 (12.3)		83 (97)	12 (14)	
Lobular and others	10 (9)	2 (20)		12 (7)	1 (8)		4 (5)	1 (25)		3 (3)	1 (33)	
Histological grade			-			0.213			0.266			1.000
G1-G2	103 (97)	12 (12)		61 (39)	2 (3)		23 (30)	1 (4.3)		13 (15)	2 (15)	
G3	-	-		102 (61)	10 (10)		53 (69)	9 (17)		72 (85)	10 (14)	
NR	4 (3)	1 (25)		2 (1)	0 (0)		1 (1)	0 (0)		1 (0)	1 (100)	
Tumor size (cm)			0.102			0.213			0.511			0.620
Median (range)	6 (2-15)	5 (2-9)		7 (2-20)	6 (2-12)		7 (2.5-14)	6 (4-12)		7 (1-24)	8 (3-15)	
cT1-cT2	10 (7)	3 (30)		12 (7)	2 (17)		5 (6)	1 (20)		9 (10)	2 (22)	
cT3-cT4	97 (93)	10 (10)		153 (93)	10 (7)		72 (94)	9 (12.5)		77 (90)	11 (14)	
cN			0.306			0.222			0.270			0.021
cN0	27 (23)	5 (19)		28 (18)	0 (0)		53 (69)	5 (9.4)		14 (14)	4 (29)	
cN1-cN2–cN3	80 (77)	8 (10)		137 (82)	12 (9)		24 (31)	5 (20.8)		72 (86)	9 (13)	
Clinical stage			0.471			0.652			1.000			0.122
EC II	23 (20)	4 (17)		21 (12)	2 (10)		11 (14)	1 (9.1)		17 (16)	5 (29)	
EC III	84 (80)	9 (11)		144 (88)	10 (7)		66 (86)	9 (13.6)		69 (84)	8 (12)	
sTIL%			0.054			0.750			0.150			1.000
Median (range)	30 (2-90)	50 (10-90)		40 (5-90)	30 (8-90)		60 (5-95)	80 (30-95)		45 (2-90)	50 (5-80)	
< 50	71 (69)	6 (8)		98 (60)	6 (6)		25 (32)	1 (4)		40 (47)	6 (15)	
⩾ 50	30 (24)	7 (23)		61 (37)	5 (8)		50 (66)	9 (18)		40 (47)	6 (15)	
Missing data	6 (6)	0 (0)		6 (3)	1 (17)		2 (3)	0 (0)		6 (7)	1 (17)	
TLCS (d)			0.233			0.238			0.744			0.500
Median (range)	67 (14-458)	80 (16-281)		61 (5-412)	54 (8-140)		60 (11-240)	66 (37-106)		64 (8-982)	66 (14-122)	
Shorter than median	49 (48)	4 (8)		77 (45)	8 (10)		41 (53)	5 (12.2)		40 (48)	5 (13)	
Longer than median	57 (51)	9 (16)		76 (47)	4 (5)		33 (43)	5 (15.2)		45 (51)	8 (18)	
Missing data	1 (1)	0 (0)		12 (8)	0 (0)		3 (4)	0 (0)		1 (1)	0 (0)	
Relapse			0.121			0.753			0.300			< 0.001
No	87 (79)	13 (15)		109 (65)	9 (8)		46 (60)	8 (17.4)		42 (41)	12 (29)	
Yes	20 (21)	0 (0)		56 (35)	3 (5)		31 (40)	2 (6.5)		44 (59)	1 (2)	

TIL: Tumor-infiltrating lymphocytes; TLCS: Time-From-Last-Chemotherapy-To-Surgery.

of tumor features, including pCR and TIL levels in each of the four molecular subtypes. Rates of pCR are lower in Luminal-A (9.2%), HER2-enriched (13%) and TNBC (15.3%) subtypes. pCR is also associated with longer survival in the entire population as well as in TNBC (pCR = 92.3% *vs* not pCR = 26.5% 5-year OS, $P = 0.005$; and trend in Luminal A, Luminal B and HER2-enriched phenotypic subsets of our series). It is widely assumed that patients who achieve pCR have significantly better DFS and OS rates in all molecular subtypes[12-14,17-19]. von Minckwitz *et al*[6] found pCR was not associated with prognosis only in Luminal A tumors in a series of 6377 patients with anthracycline-taxane-based NAC from 7 randomized trials; some authors claim it is related to the observed continuous tumor shrinkage occurring in their ER-positive tumor group during extended NAC, different than early and short-period tumor shrinkage observed in the ER-negative group[6,18-24].

pCR was more frequent in small tumors for both the entire population and the Luminal A subtype in our series. This finding is concordant with the previously mentioned idea that the effect of chemotherapy in Luminal A is slower than in other subtypes. Besides, Baron *et al*[18] found a similar lower rate of pCR in tumor size larger than 5 cm ($P = 0.022$) in their entire series ($n = 608$), but no association in the Luminal setting ($P = 0.411$). Higher grade of axillary involvement (cN2-3) was associated with lower rates of pCR only in the TNBC subset of our series. This lower response in bulky metastases could explain the previously described TNBC paradox phenomena of higher pCR rates but also higher distant relapse[21].

pCR was associated with higher percentage of

Table 3 Association between percentage of tumor-infiltrating lymphocytes and clinical-pathological features regarding molecular subtype *n* (%)

	Lum A			Lum B			HER2			TN		
	< 50%	⩾ 50%	*P* value	< 50%	⩾ 50%	*P* value	< 50%	⩾ 50%	*P* value	< 50%	⩾ 50%	*P* value
	71	30		98	61		25	50		40	40	
Age (yr)			0.181			0.783			0.624			0.074
Median (range)	47 (28-75)	47 (36-74)		52 (28-73)	50 (25-84)		52 (28-66)	49 (29-80)		51 (26-73)	45 (27-73)	
< 50	50 (70)	17 (57)		46 (47)	30 (49)		11 (44)	25 (50)		16 (40)	24 (60)	
⩾ 50	21 (30)	13 (43)		52 (53)	31 (51)		14 (56)	25 (50)		24 (60)	16 (40)	
Histological subtypes			0.445			1.000			0.597			1.000
Ductal	66 (93)	26 (87)		91 (93)	57 (93)		23 (92)	48 (96)		39 (98)	38 (95)	
Lobular and others	5 (7)	4 (13)		7 (7)	4 (7)		2 (8)	2 (4)		1 (3)	2 (5)	
Histological grade			-			0.011			0.514			0.006
G1-G2	69 (97)	28 (93)		43 (44)	15 (25)		9 (36)	14 (28)		11 (28)	2 (5)	
G3	0 (0)	0 (0)		53 (54)	46 (75)		16 (64)	35 (71)		29 (73)	38 (95)	
NR	2 (3)	2 (7)		2 (2)	0 (0)		0 (0)	1 (2)		0 (0)	0 (0)	
Tumor size (cm)												
Median (range)	6 (3-13)	6 (2-15)		6 (3-20)	7 (2-15)		7 (3-14)	7 (3-14)		7 (4-24)	7 (1-16)	
cT			1.000			0.538			0.659			0.263
cT1-cT2	7 (10)	3 (10)		6 (6)	6 (10)		1 (4)	4 (8)		2 (5)	6 (15)	
cT3-cT4	64 (90)	27 (90)		92 (94)	55 (90)		24 (96)	46 (92)		38 (95)	34 (85)	
cN			0.890			0.020			0.631			0.762
cN0	18 (25)	8 (27)		22 (22)	5 (8)		6 (24)	8 (16)		6 (15)	7 (18)	
cN1-cN2-cN3	53 (75)	22 (73)		76 (78)	56 (92)		11 (44)	27 (54)		34 (85)	33 (83)	
Clinical Stage			0.666			0.141			0.742			0.576
EC II	17 (24)	6 (20)		16 (16)	5 (8)		3 (12)	8 (16)		9 (23)	7 (18)	
EC III	54 (76)	24 (80)		82 (84)	56 (92)		22 (88)	42 (84)		31 (78)	33 (83)	
TLCS (d)			0.631			0.882			0.502			0.141
Median (range)	64 (14-449)	70 (19-458)		61 (5-412)	58 (8-285)		68 (16-234)	56 (11-240)		74 (24-230)	51 (14-982)	
Shorter than median	34 (48)	13 (43)		48 (49)	28 (46)		12 (48)	28 (56)		15 (38)	22 (55)	
Longer than median	36 (51)	17 (57)		44 (45)	27 (44)		12 (48)	20 (40)		24 (60)	18 (45)	
Missing data	1 (1)	0 (0)		6 (6)	6 (10)		1 (4)	2 (4)		1 (3)	0 (0)	
pCR			0.054			0.750			0.150			1.000
No	65 (92)	23 (77)		92 (94)	56 (92)		24 (96)	41 (82)		34 (85)	34 (85)	
Yes	6 (8)	7 (23)		6 (6)	5 (8)		1 (4)	9 (18)		6 (15)	6 (15)	
Relapse			0.450			0.201			0.737			0.502
No	59 (83)	23 (77)		61 (62)	44 (72)		16 (64)	30 (60)		18 (45)	21 (53)	
Yes	12 (17)	7 (23)		37 (38)	17 (28)		9 (36)	20 (40)		22 (55)	19 (48)	

%sTIL was performed over 415 cases. There 20 missed values. TIL: Tumor-infiltrating lymphocytes; TLCS: Time-From-Last-Chemotherapy-To-Surgery.

sTILs in the entire population and also within the HER2-enriched subtype (P = 0.02). A trend towards association was found in Luminal A, Luminal B and TNBC. Different studies have found that high TIL levels in preNAC samples are associated to higher pCR rates in the entire BC population[25-27]. Wang *et al*[28] performed a meta-analysis with 23 studies including 13100 BC patients, and similarly found that high TIL level was associated with improved pCR rate in the entire population, and in HER2 and TNBC. A high TIL level significantly predicted longer OS in the entire population (P < 0.001) and in patients with HER2-positive (P = 0.005) BC and in TNBC patients (P < 0.001).

TIL showed association with grade Ⅲ tumors in the entire population and in Luminal B and TNBC subsets in our series. Similarly, Pruneri *et al*[29] describes that higher TIL levels have a trend towards association with HG3 (P = 0.052) and was associated to Ki67 ⩾ 50% (P < 0.0001) in a series of 897 TNBC cases, and could reflect the appearance of a larger amount of neoantigens that elicit an immunomediated response. Involvement of axillary lymph nodes was associated to higher TIL levels only in the Luminal B subset. High density of TILs has previously been described as associated to absence of lymph node involvement in the entire population of BC, and our results indicate that this association could differ by some subtypes[30]. Higher level of sTILs was not associated to longer survival in the entire population nor in any subtype in our series. This finding could be explained by the small size of our series and because the highest impact of TILs is over pCR instead of survival.

Our study has some limitations. First, because of the retrospective design of the study, different chemotherapy schemas were used depending on the oncologist decision and surgical election depending

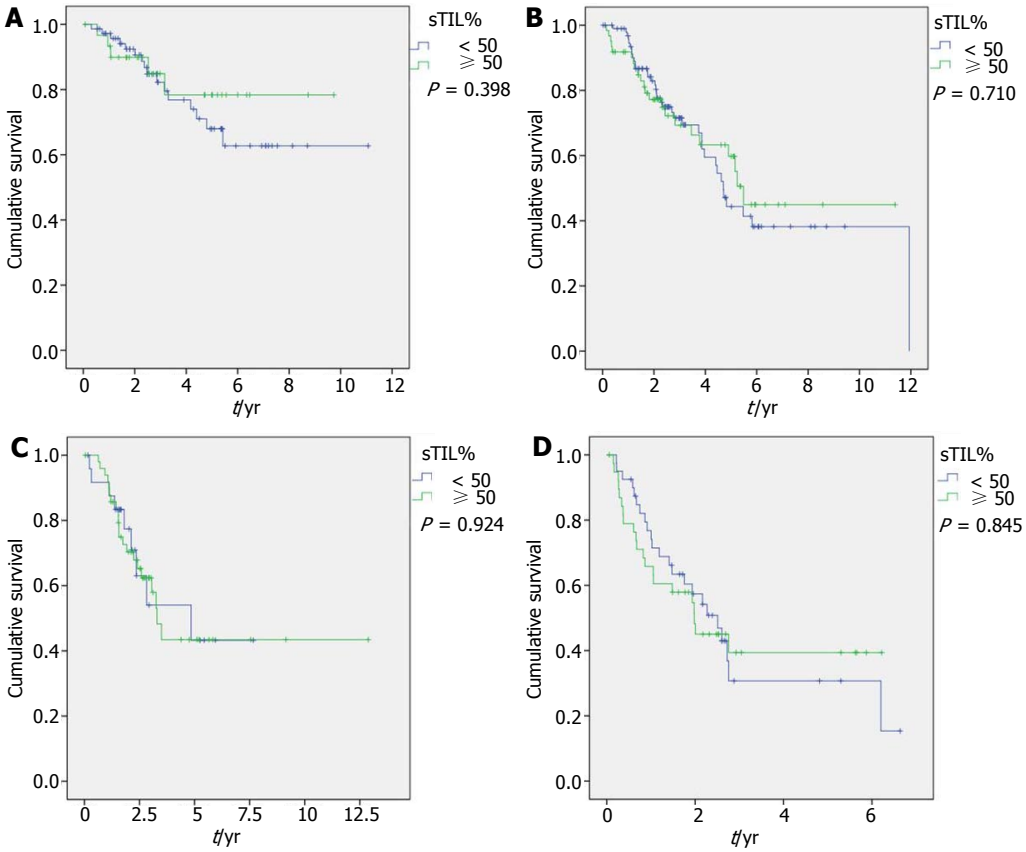

Figure 1 Overall survival regarding tumor-infiltrating lymphocytes (cut-off: 50%) for Luminal A (A), Luminal B (B), HER2-enriched (C) and Triple Negative group (D).

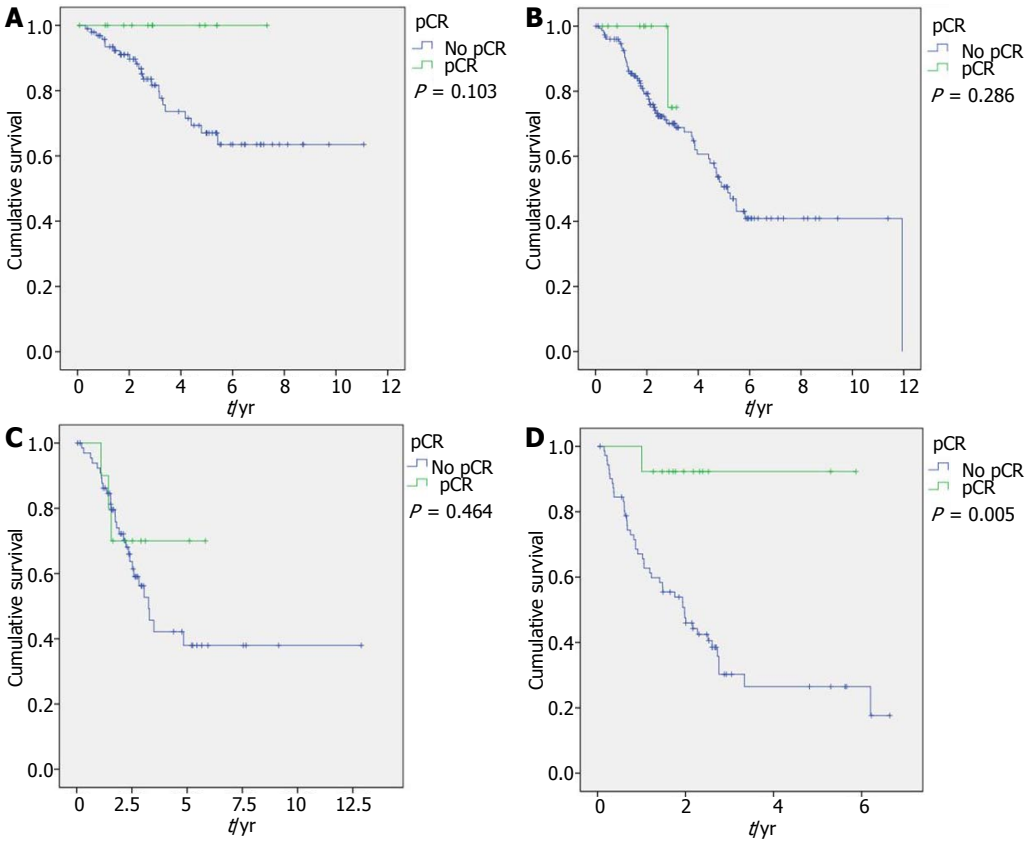

Figure 2 Overall survival regarding pathological complete response for Luminal A (A), Luminal B (B), HER2-enriched (C) and triple negative group (D).

on surgeon. Second, the sample sizes of each BC subgroup are rather small, so the prognostic impact of every clinicopathological feature in each BC subtype should be investigated in a larger population in subsequent studies. Despite these limitations, this is the first comprehensive report of the NAC effect over breast molecular subtypes in a Latin-American population.

ARTICLE HIGHLIGHTS

Research background

Breast cancer can be classified into Luminal A, Luminal B, HER2-enriched and triple-negative. Clinicopathological features can identify breast cancer prognosis and include pathological complete response (tumor sensibility to chemotherapy) and tumor-infiltrating lymphocytes (TILs; host activity against the tumor).

Research motivation

Discussion and new information about molecular breast cancer subtypes have been included in the most relevant cancer-related meeting, and more than 30,000 articles have been published in the last 2 years. Two biomarkers, pathological complete response (pCR) and TILs, have been re-defined and gained pathologist acceptance in the last 3 years.

Research objectives

The main objective is to evaluate the survival impact of different clinicopathological factors, including pCR and TIL levels, according to the subtypes in breast cancer patients who received neoadjuvant chemotherapy.

Research methods

Evaluation of TIL levels was prospectively performed following international guidelines. Breast cancer cases were classified according to 2017 St Gallen Breast Cancer Meeting guidelines.

Research results

pCR was associated with cT1-2 (P = 0.045) and high stromal (s)TILs (P = 0.029) in the entire population. However, this relationship was not found for every molecular subtype, probably because of the small sample size. pCR was associated with longer disease-free survival in the entire population (P = 0.002) and in TNBC (P < 0.001), as well as to longer overall survival in the entire population (P = 0.002) and in TNBC (P = 0.005).

Research conclusions

Predictive and prognostic value of clinicopathological features like pCR and sTIL level differ depending on the molecular subtype being evaluated. Identification of pCR and TIL roles in every molecular subtype will allow for identification of those patients who need more intense chemotherapy and those who will benefit from an immune-modulator treatment.

Research perspectives

No information about the relevance of pCR and TILs in South-American women with breast cancer have been published in. An increase in the knowledge about prognosis impact of pCR and TIL in every molecular breast cancer subtype will allow for obtaining more effective personalized therapies. Furthermore, similar analysis needs to be done with more precise methods to evaluate response to chemotherapy and host immune activity, such as tumor residual burden and CD3/CD8 ratio, respectively.

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P- Reviewer: Cihan YB, Dirier A, Houvenaeghel G, Shao R, Vinh-Hung V **S- Editor**: Cui LJ **L- Editor**: Filipodia
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