Triple Negative Breast Cancer: a Retrospective Study of Hispanics Residing in Puerto Rico

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Objective: Triple-negative breast cancer (TNBC) demonstrates unique clinicopathological characteristics and survival outcomes. Several studies have documented important disparities in Hispanic women compared to other racial/ethnic groups; nevertheless, data on this entity in a population based Latin country are very limited. Our goal was to assess demographic and clinicopathological characteristics in essentially a pure population of Puerto Rican females with TNBC residing in Puerto Rico, as well as to determine their overall survival and progression-free survival in order to compare with published data.

Methods: By searching the electronic medical records data base, 54 patients were identified as TNBC. The median follow-up period was 25 months (range, 2-78). Univariate analysis of pretreatment risk factors was conducted.

Results: The median age at diagnosis was 55 years. Of 54 cases, 51 had stage I-III presentation. T1/T2 tumors were found in 88.9% and absence of nodal involvement in 68.5%. Prognostic factors for progression free survival (PFS) that were statistically significant were lymph node involvement (p=0.02), tumor size > 2 cm (p=0.037) and stage IV (p=0.00002). The 5-year overall survival and PFS were 81% and 80%, respectively.

Conclusion: Results are very similar to published data on females from North America and Europe. Differences in clinical outcome and stage at diagnosis in Hispanic women with TNBC are more likely explained by socioeconomic status and adequate access to care, rather than biological/genetic differences. The association of triple-negative breast cancer with poor prognosis deserves re-evaluation given that patients with negative node involvement and no metastasis appear to be highly curable. [*P R Health Sci J 2012;2:45-51*]

Key words: Triple Negative Breast Cancer, Hispanic, Demographic, Clinicopathologic, Survival

Breast cancer is currently the most common malignancy in women from both developed and developing countries with an estimated 1.38 million new cases diagnosed in 2008 (1). For most of the countries in the American continent, breast cancer is one of the top five causes of female mortality (2). Significant disparities among countries in the region are demonstrated by differences in incidence and mortality rates. Countries like Argentina, Chile, Uruguay and Southern Brazil have incidence rates as high as that in North America (3). During 2004-2006 the highest mortality rates were seen in Argentina, Paraguay, Uruguay, Trinidad and Tobago, Canada and the United States in contrast with El Salvador and Guatemala which exhibited the lowest rates (2). Breast cancer trends in Puerto Rico are similar to those in the American continent. In Puerto Rico it is the most common cancer in women. During 2000-2004 it comprised 31.9% of all female cancers and 17.8% of all female cancer deaths (4).

It is being increasingly recognized that breast cancer is not a single disease but rather a heterogeneous group of disorders

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The authors have no conflict of interest to disclose.

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composed of some rather distinct clinicopathologic entities (5, 6). As an illustration of breast cancer heterogeneity, the triple-negative subgroup displays several unique clinical, pathological and molecular characteristics (7, 8). Triple-negative breast cancer (TNBC) is a relatively new entity, mentioned for the first time in 2005 (9, 10). The immunophenotypic profile of TNBC is based on lack of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2) expression (8, 11). Unique features of triple-negative tumors include younger age at presentation (7, 9, 12, 13), higher prevalence in African American women (7, 11, 13), higher parity (7, 9, 14) and lack of breast feeding (7, 14). Furthermore, they have a more aggressive behavior, poorer survival, a higher histological grade and restricted therapeutic options in comparison to other breast cancer subtypes (8, 13, 14).

Several studies have documented important differences in TNBC presentation among racial/ethnic groups. Kurian et al described a lower lifetime risk of TNBC in Hispanic women compared to African American and Caucasian females (6). Nevertheless, poorer survival rates for breast cancer have been reported for Hispanics compared to non-Hispanic whites (15). In contrast to the Kurian study, a higher proportion of TNBC in Hispanic women in comparison to non-Hispanic white women has been documented (15, 16). Research concerning the burden of disease and implications of TNBC among Hispanic women is very scarce. Moreover, most studies in Hispanic women are based on tumor registries derived from residents in the USA (16). Hence, there is need for more research based population of TNBC in Latin American countries.

The major goal of this study was to assess the demographic and clinicopathological characteristics of TNBC at our institution and to compare our results with literature data from major USA and European centers as well as with available data on Hispanic females. The second aim was to evaluate the correlation of pretreatment prognostic factors such as lymph node involvement, clinical stage and Ki-67 expression with progression free survival (PFS) and overall survival (OS), as well as to compare these results with those previously described.

Methods

The Auxilio Mutuo Hospital is a private non-profit institution located in San Juan, the capital of Puerto Rico. It accepts patients from essentially all health insurance plans including Medicare, but it doesn't contract with "Reforma" health insurance, which is the local government's insurance plan for indigent patients. The patient mix is of a higher socioeconomic level than the average hospital in the island.

After obtaining IRB approval, we identified 860 patients with stage I-IV breast cancer seen at Auxilio Centro de Cáncer, which is part of Auxilio Mutuo Hospital, by searching the electronic medical records data base. Those with invasive triple negative breast cancer, defined as <1% ER, <1% PR expression and Her-2 negative, were then selected for further study.

A total of 89 cases with TNBC were identified of which 35 were not evaluable for the following reasons: 30 were seen only for a second opinion and were not treated at our center, in 5 the diagnosis could not be confirmed as invasive carcinoma or as TNBC. A total of 54 evaluable cases were included in this report. Of these 54 evaluable cases, 51 presented with stage I-III disease. Of these, 16 have been treated under a neoadjuvant chemotherapy protocol and another 9 were treated with neoadjuvant chemotherapy off protocol. Of the remaining 26 cases, 22 received adjuvant chemotherapy and 4 did not receive any chemotherapy because their tumor was deemed too small to require adjuvant chemotherapy.

The endpoints analyzed included progression free survival (PFS) and overall survival (OS). PFS was defined as the time elapsed between the diagnosis of breast cancer and the first evidence of relapse or progression. Three patients who died of causes unrelated to their cancer were not counted as failures for the purpose of calculation of PFS. Overall survival was defined as the time elapsed between the diagnosis of breast cancer and death. The three cases that died of unrelated causes were considered as dead for the purpose of OS calculations. Median follow-up time in months for patients who were alive was 25 months (range 2-78).

In view of the relatively small sample a multivariate prognostic factor analysis could not be performed but univariate analysis of the following pretreatment risk factors was carried out: age, lymph node status, Ki-67 and stage.

Axillary lymph node status was evaluated by means of mammography (n=32), ultrasound (n=31), MRI (n=30) and PET-CT scan (n=16). Of 51 cases with stage I-III, the axillary node(s) were positive in 16 cases. In the 6 cases not treated with neoadjuvant chemotherapy, metastatic disease to axillary node(s) was documented histologically in all 6 prior to starting adjuvant therapy. Metastatic disease to axillary node(s) was histologically documented by pre-treatment core needle biopsy in 8 of the 10 patients treated with neoadjuvant chemotherapy while in the remaining 2 cases it was documented clinically with PET scan which was considered highly suspicious.

Staging was expressed as clinical rather than pathological stage because 25 of the cases were treated with neoadjuvant chemotherapy which results in downstaging of many, thus making it impossible to compare the pathological stage of those cases with the pathological stage of those not treated with neoadjuvant chemotherapy.

Results

Demographic and clinicopathological characteristics of the 54 patients included in this study are presented in Table 1.

Figures 1a and 1b illustrate the OS and PFS, respectively, for the 51 patients with stage I-III presentation. The 1, 3, and 5 year estimates for OS were 95%, 81% and 81%, respectively. The 1, 3, and 5 year estimates for PFS were 95%, 91% and 80%, respectively. No relapses have been seen beyond 46 months.

Table 1. Demographic and clinicopathological characteristics (n=54)

Variable	N (%)
Median Age at diagnosis (range)	55 (28-77)
Median Follow-Up in months (range)	25 (2-78)
Menopausal Status	
Postmenopausal	30 (55.6)
Premenopausal	18 (33.3)
Not defined	6 (11.1)
Histological type	
Ductal	52 (96.3)
Lobular	2 (3.7)
T stage before chemotherapy	
1a	1 (1.8)
1b	3 (5.6)
1c	19 (35.2)
2	25 (46.3)
3	3 (5.6)
4b	2 (3.7)
Unknown	1 (1.8)
N stage before chemotherapy	
N0	37 (68.5)
N1	11 (20.4)
N2	3 (5.6)
N3	2 (3.7)
Unknown	1 (1.8)
M stage before chemotherapy	
M0	51 (94.4)
M1(stage IV)	3 (5.6)
Stage before chemotherapy	
I	24 (44%)
II	18 (33%)
III	6 (11%)
IV	3 (5.5%)
Unclear	3 (5.5%)
Histologic Grade	
I	0 (0.0)
II	5 (9. 3)
III	48 (88.9)
Unknown	1 (1.8)
Lymphovascular invasion	
Yes	11 (20.3)
No	37 (68.6)
Unknown	6 (11.1)
Median Ki-67 (range)*	52% (5-95)
Type of Chemotherapy Regimen†	
TEC, TAC or AC->T	38 (70.4)
AC or FEC	11 (20.4)
Other	1 (1.8)
None	4 (7.4)
Neoadjuvant Chemotherapy	25 (46.3)
Adjuvant Chemotherapy	24 (44.5)

*Ki-67 available in 29 patients; †TEC= Docetaxel, Epirubicin, Cyclophosphamide; TAC= Docetaxel, Doxorubicin, Cyclophosphamide; AC->T= Doxorubicin, Cyclophosphamide followed by Palitaxel; AC= Doxorubicin, Cyclophosphamide; FEC= 5-Fluorouracil, Epirubicin, Cyclophosphamide

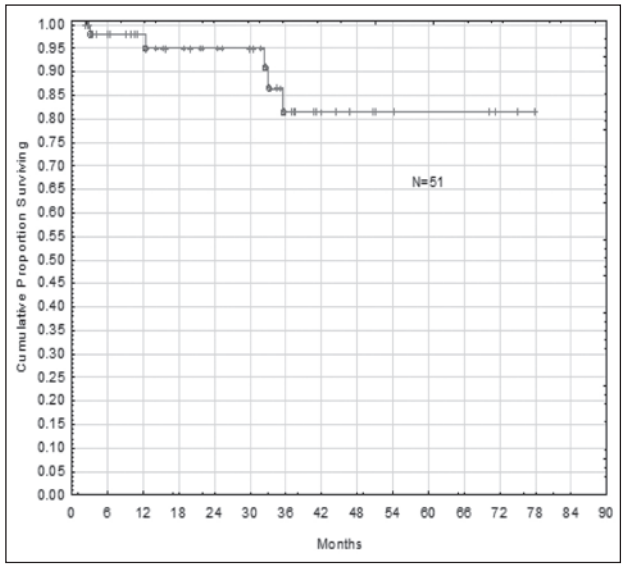

Figure 1a. Overall survival of stage I-III cases.

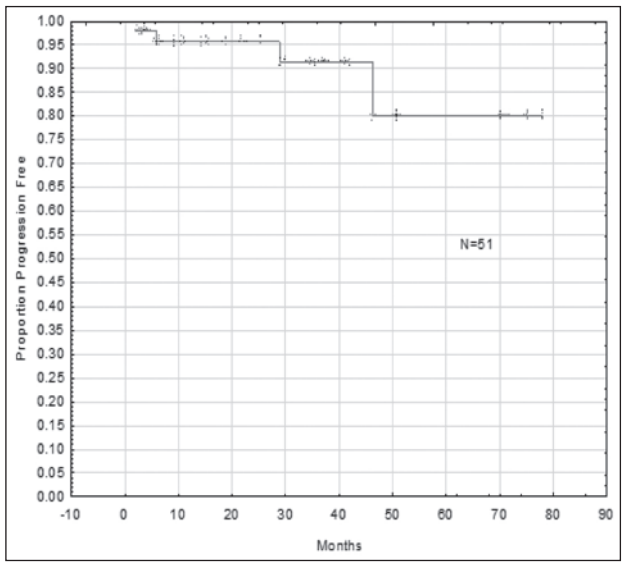

Figure 1b. Progression free survival of stages I-III cases.

Univariate analysis for PFS was carried out for the following factors: lymph node involvement, tumor size, stage, menopausal status and Ki-67. A statistically significant correlation with the Kaplan-Meier 5 year estimate of progression free survival was identified for lymph node involvement, tumor size > 2cm and stage IV (Table 2). Ki-67 >52% and menopausal status were not significantly associated with PFS (Table 2). Figure 2a depicts the PFS of patients with and without axillary node involvement. Similarly, figure 3 shows the OS of patients with stage IV compared with stage I-III.

In view of the relatively small sample size, a Cox multivariate prognostic factor analysis could not be effectively performed. However, tumor size and lymph node involvement appeared to

Table 2. Univariate analysis of 5-year progression free survival by Kaplan-Meier method according to prognostic factors

	Characteristic Present	Characteristic Absent	P value
	PFS	PFS	
Nodal involvement	67%	83%	.02
Tumor size >2 cm	55%	100%	.037
Stage IV	0%	81%	.00002
Histologic Grade 3	75%	100%	0.25
Ki-67 >52%	85%	93%	0.81
Menopause	83%	87%	0.12
Lymphovascular invasion	72%	73%	0.23
Age >55	86%	82%	0.14

PFS: progression free survival

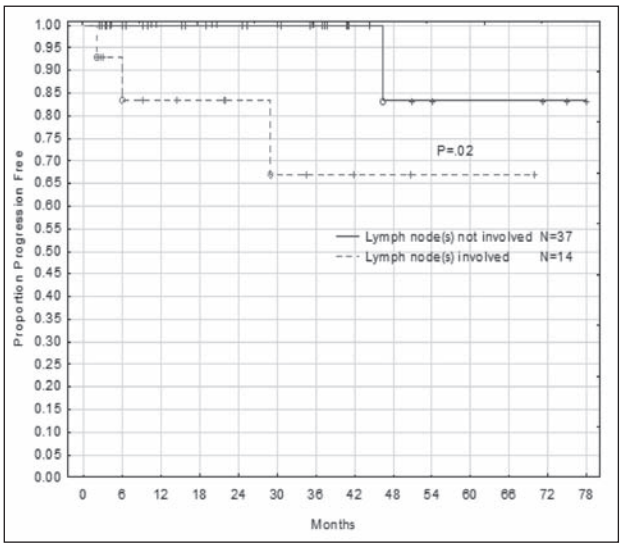

Figure 2a. Progression free survival according to lymph node involvement.

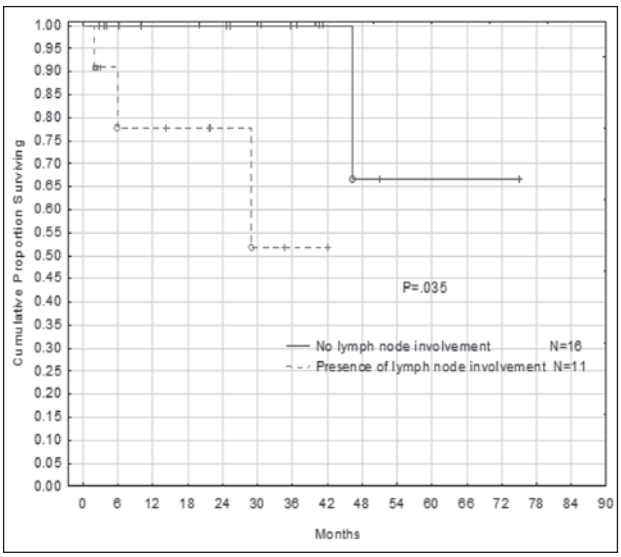

Figure 2b. Progression free survival according to lymph node involvement in patients with tumors > 2 cm.

be significantly correlated since most patients with small tumors didn't have node involvement in contrast with larger tumors (p= 0.029). Those patients with tumors larger than 2 cm with lymph node involvement (n= 11) had a 5 year PFS of 52% in contrast with those without node involvement (n=17) whose PFS was 67% (p=0.035) (Figure 2b). Only 3 out of 23 (13%) tumors smaller than 2 cm had lymph node involvement so this subgroup could not be adequately analyzed, but none of those 3 patients have progressed.

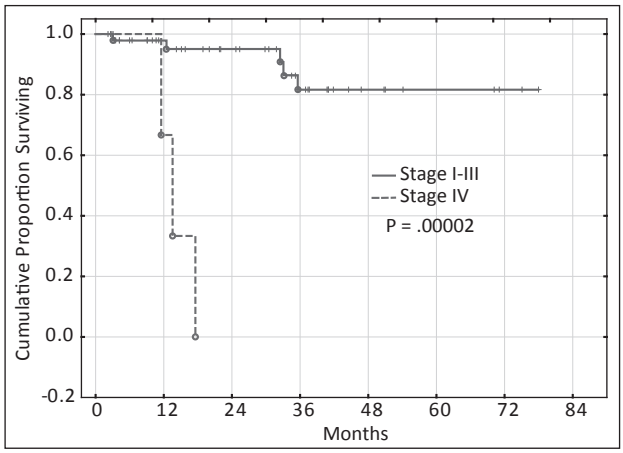

Figure 3. Overall survival stage I-III versus IV cases.

Discussion

Demographic features of TNBC characteristically include a median age in the fourth decade, as well as a highly proliferative tumor manifested by a high Ki-67, ductal rather than lobular cell type, and lastly a high histologic grade (9). Our patient population exhibited most of the features typical of this disorder with a median Ki-67 expression of 52% (Table 1) which contrasts with patients that display an ER(+) Her-2(-) phenotype whose Ki-67 is usually below 10%. Similarly, the histologic grade was high in most of our cases with close to 90% presenting with grade 3 and 96% had the ductal cell type (Table 1). Nevertheless, there was one important difference which needs to be discussed. The median age at diagnosis for our study population was 55 years, different from several other studies (17-20), which have reported median age at diagnosis between 46-49 years. However, other researchers (15, 21) have identified a median age closer to our finding.

Additional findings in our study were a higher proportion of T1/T2 tumors, and low frequency of axillary lymph node involvement. In contrast to our findings, Lara-Medina et al (19) reported in a Mexican population with TNBC, a higher proportion of stage III and IV presentations (52.7% and 12.2%, respectively); hence, a sole biologically-based explanation seems insufficient to account for such a difference between these two Hispanic studies. Access to adequate care is a relevant issue

which merits discussion. Although the definition of Hispanic is very ambiguous, our results in patients who essentially all can be considered Hispanic, show that if adequate access to care is available, the presenting features including less advanced stage, are similar to those which have been described for non-Hispanic Caucasians treated in major North American and European centers (20, 22-26). Additionally , the clinical outcome is also very similar. Several studies have shown a higher frequency of advanced stage at presentation among Hispanic women, even after adjustment for socio-economic status, suggesting a biological/genetic factor as main determinant (27, 28) but a population-based study from the California cancer registry (15) reported a higher proportion of early stage I and II (32.8% and 48.6%, respectively) comparable to our results. Our results suggest that differences regarding stage at diagnosis and clinical outcome are more likely due to the interplay of different factors, such as, access to health care and socioeconomic level rather than purely biologic in nature.

Table 3. Comparison of triple negative breast cancer overall survival

Study	Number of Patients	Overall Survival (%) 1-year	3-years	5-years
Liedtke et al.	235	90	74	64
Dent et al.	180	96*	85*	71*
Hernandez-Aya et al.	1,711	NR	NR	70
Dawood et al.	471	NR	71	NR
Bauer et al.	6,370	NR	NR	77
Ovcaricek et al.	269	97†	83†	74.5
Present series	51‡	95	81	81

NR: not reported; *assumed from fig 2; †assumed from fig 2; ‡includes stage I-III cases

Previous studies which report OS in TNBC are shown in table 3 together with the results of the present study. As can be seen, our results are very similar to those reported in these studies from major North American and European centers (15, 18, 20, 21, 25, 29). The OS in our study population for stages I-III was 95%, 81% and 81% at 1-year, 3-years and 5-years, respectively.

Similarly, the 5 year 80% PFS (Figure 1b) compares favorably with literature data. Finally, the PFS curve in our patient population shows that all relapses occurred within the first 46 months and none relapsed after 5 years of follow up. This early relapse pattern with a trend to develop a plateau in the curve at 5 years is characteristic of TNBC. Longer follow up of our patient population would be appropriate to make certain that no late relapses occur. It is a well established fact that after 5 years the mortality risk for TNBC drops substantially while the risk for ER(+) Her-2 (-), cases continues (30, 31).

The three most important prognostic factors in our TNBC population were lymph node status, tumor size and stage IV disease. The prognosis of patients with negative lymph node status and with tumor < 2 cm was more favorable (Figures 2a and 2b). This correlation between lymph node status and prognosis has also been shown in other studies and is considered by some as the most important risk factor (32-34). Stage IV disease has also been shown by other investigators to be particularly ominous in patients with TNBC (35, 36). Our study, in spite of the size limitation which doesn't allow us to perform an adequate multivariate analysis, suggests possibly an independent contribution of nodal involvement and tumor size to prognosis (Figure 2b). Tumor size and lymph node involvement were found by multivariate analysis to be independent factors in one study (37). In constrast, a large Korean study concluded that lymph node involvement, histologic grade, and lymphovascular invasion all were associated with prognosis but in the multivariate analysis only Ki-67 and histologic grade were relevant for prognosis (38). In our study, we also observed a trend for those with lower histologic grade and lower Ki-67 to have a better outcome (Table 2) but statistical significance was not reached perhaps because of the small number of patients with these favorable features. These points deserve further study.

We acknowledge the three major limitations of this study: first, the sample size is modest, second, the study is retrospective in nature and third, patients were staged in two different ways: those treated with neoadjuvant were clinically staged and those who received adjuvant therapy were pathologically staged. Nevertheless, the clinical staging performed was quite thorough as evidenced by the fact that in the 10 patients treated with neoadjuvant chemotherapy who were deemed to have axillary lymph node involvement, 8 of them were documented histologically and in the other 2 it was documented by PET scan. Although axillary node involvement might still have been seen in those with normal pre-treatment axillary nodes, those who were called N1-N3 were well documented. Despite these shortcomings, our study offers some more insight into TNBC among Hispanic women. It is one of the few studies performed within a population-based Latin American country.

This study enhances the perspective regarding important factors involved in survival outcomes for TNBC among Hispanic women. Our study provides further support in that disparities observed in Hispanic women due to TNBC are more likely associated with socio-economic status and access to care, rather than to biological factors. Future research is warranted for a better understanding of differences in TNBC among Hispanic women.

The belief that TNBC is a disorder with poor prognosis stems from the fact that compared with hormone receptor positive tumors the former behaves more aggressively and with short-term follow up they do worse than ER(+) Her-2 (-) cases. In addition, when TNBC patients presents with stage IV disease, their survival is extremely poor (Figure 3) in contrast with stage IV ER(+) Her-2 (-) cases who can survive for years in part due to the use of targeted hormonal therapy which is not

available for TNBC. However, with very long term follow up, patients with TNBC eventually do better than ER (+) Her-2 (-) cases because the former stop relapsing at 5 years while the latter continue to relapse with time.

Hence, the notion that TNBC is associated with poor prognosis should be reassessed in view of the fact that with prolonged follow up their prognosis turns out to be superior to ER(+) Her-2 (-) cases. Instead, we should regard TNBC with negative lymph nodes and no visceral metastasis as a highly curable disorder.

Resumen

Objetivo: El cáncer de seno triple negativo presenta características clínico-patológicas y sobrevivencia particulares. Varios estudios han documentado diferencias importantes en mujeres hispanas en comparación con otros grupos étnicos y raciales; sin embargo, estudios acerca de esta entidad, realizados en países latinoamericanos, son muy limitados. Nuestro objetivo fue evaluar las características demográficas y clínico-patológicas de una población femenina, netamente puertorriqueña con cáncer de seno triple negativo, así como determinar la sobrevivencia general y la sobrevivencia libre de enfermedad para comparar con estudios ya publicados. Métodos: A través de la búsqueda en la base de datos de los historiales médicos, se identificaron 54 pacientes con cáncer de seno triple negativo. El periodo promedio de seguimiento fue de 25 meses (rango, 2-78). Se realizó un análisis univariado de los factores de riesgo antes del tratamiento. Resultados: La edad promedio al momento del diagnostico fue de 55 años. De 54 casos, 51 se presentaron como estadios I-III. Se encontró 88.9% de tumores T1/T2, y 68.5% con nódulos linfáticos negativos. Los factores pronósticos que fueron estadísticamente significativos para sobrevivencia libre de enfermedad fueron nódulo linfático negativo (p=0.02), tumor > de 2 cm (p=0.037) y estadio IV (p=0.00002). La sobrevivencia general y sobrevivencia libre de enfermedad a 5 años fueron de 81% y 80%, respectivamente. Conclusión: Los resultados de nuestro estudio son muy similares a los publicados en Norteamérica y Europa. Las diferencias en sobrevivencia y estadio en mujeres hispanas con cáncer de seno triple negativo están probablemente más relacionados con el nivel socioeconómico y al acceso adecuado a los servicios de salud, más que a factores biológicos o genéticos. La asociación del cáncer de seno triple negativo con pronóstico negativo, merece ser reevaluada, dado que las pacientes con nódulos linfáticos negativos y sin metástasis pueden ser altamente curables.

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