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BENEFITS OF ADJUVANT CHEMOTHERAPY ON PT1N0M0 TRIPLE-NEGATIVE BREAST CANCER SURVIVAL OUTCOMES

BENEFICIOS DE LA QUIMIOTERAPIA ADYUVANTE EN LOS RESULTADOS DE SUPERVIVENCIA EN CÁNCER DE MAMA TRIPLE NEGATIVO PT1N0M0

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ABSTRACT

Introduction: Triple-negative breast cancer (TNBC) is notably an aggressive breast cancer (BC) subtype, leading to early relapse and poor prognosis. Effects of adjuvant chemotherapy among early-stage TNBC (pT1N0M0) patients remain unclear in different populations. **Objectives:** Our study aimed to determine the impact of adjuvant chemotherapy on overall survival (OS) and progression-free survival (PFS) within the specific subset of Peruvian pT1N0M0 TNBC patients (pT1a/b vs. pT1c). **Methods:** We retrospectively analyzed 2007 TNBC cases diagnosed between 2000-2014 at the Instituto Nacional de Enfermedades Neoplásicas (Lima, Peru). We included only non-metastatic TNBC cases and classified them as pT1N0M0 after surgery. TNBC patients who underwent neoadjuvant chemotherapy were excluded. We describe our population according to the tumor size from the residue disease (pT1a/b vs. pT1c). We used the Kaplan-Meier method test to determine differences in survival curves for OS and PFS. A Univariate Cox proportional hazards model was used to identify risk factors for PFS. **Results:** Our study cohort included 124 TNBC patients. Around 65.3% (n=81) were undergoing adjuvant chemotherapy. Notably, among pT1c patients, this treatment was more prevalent compared to pT1a/b (72.1% vs. 50.0%). Survival analysis showed no significant OS benefit from chemotherapy (HR:2.46,95%CI:0.74-8.13,p=0.13). However, a marked improvement in PFS was noted exclusively in the pT1c subgroup, with patients not treated with chemotherapy offering a prognostic risk (HR:20.10,95% CI:5.54-73.10,p<0.0001). pT1a/b patients demonstrated no benefit from chemotherapy regarding progression (HR:3.07,95% CI:0.27-34.50,p=0.34). **Conclusion:** Our study highlights that adjuvant chemotherapy significantly improves PFS in pT1cN0M0 TNBC patients but shows no clear benefit for smaller tumors (pT1a/bN0M0). Future research should focus on personalized chemotherapy strategies in early-stage TNBC to identify predictive markers for survival.

Keywords: Adjuvant chemotherapy; Overall survival; Progression-free survival; Triple-negative breast cancer. (Source: MESH-NLM)

RESUMEN

Introducción: El cáncer de mama triple negativo (CMTN) es notablemente un subtipo agresivo de cáncer de mama, lo que conduce a recaídas tempranas y un mal pronóstico. Los efectos de la quimioterapia adyuvante en pacientes con CMTN en estadio temprano (pT1N0M0) siguen siendo inciertos en diferentes poblaciones. Objetivos: Nuestro estudio tuvo como objetivo determinar el impacto de la quimioterapia adyuvante sobre la supervivencia global (SG) y la supervivencia libre de progresión (SLP) en un subconjunto específico de pacientes peruanas con CMTN pT1N0M0 (pT1a/b vs. pT1c). **Métodos:** Analizamos retrospectivamente 2007 casos de CMTN diagnosticados entre 2000 y 2014 en el Instituto Nacional de Enfermedades Neoplásicas (Lima, Perú). Solo se incluyeron casos de CMTN no metastásico clasificados como pT1N0M0 tras la cirugía. Se excluyeron las pacientes que recibieron quimioterapia neoadyuvante. La población fue descrita según el tamaño tumoral de la enfermedad residual (pT1a/b vs. pT1c). Utilizamos el método de Kaplan-Meier para determinar las diferencias en las curvas de supervivencia para SG y SLP. Se empleó un modelo de riesgos proporcionales de Cox univariado para identificar factores de riesgo para la SLP. **Resultados:** Nuestra cohorte de estudio incluyó a 124 pacientes con CMTN. Alrededor del 65.3% (n=81) recibió quimioterapia adyuvante. Cabe destacar que este tratamiento fue más prevalente entre las pacientes pT1c en comparación con las pT1a/b (72.1% vs. 50.0%). El análisis de supervivencia no mostró un beneficio significativo en la SG con la quimioterapia (HR: 2.46, IC 95%: 0.74-8.13, p=0.13). Sin embargo, se observó una mejora notable en la SLP exclusivamente en el subgrupo pT1c, con un riesgo pronóstico para las pacientes no tratadas con quimioterapia (HR: 20.10, IC 95%: 5.54-73.10, p<0.0001). Las pacientes pT1a/b no mostraron beneficio de la quimioterapia en cuanto a la progresión (HR:3.07, IC 95%: 0.27-34.50, p=0.34). **Conclusión:** Nuestro estudio destaca que la quimioterapia adyuvante mejora significativamente la SLP en pacientes con CMTN pT1cN0M0, pero no muestra un beneficio claro para tumores más pequeños (pT1a/bN0M0). Las investigaciones futuras deben centrarse en estrategias personalizadas de quimioterapia en CMTN en estadio temprano para identificar marcadores predictivos de supervivencia.

Palabras clave: Quimioterapia adyuvante; Supervivencia global; Supervivencia libre de progresión; Cáncer de mama triple negativo. (Fuente: DeCS- BIREME)

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INTRODUCTION

Breast cancer (BC) is a public health problem and is the current leading cause of cancer-related death among women worldwide [1]. Triple-negative breast cancer (TNBC) is frequently associated with early relapse, which leads to an increased risk of developing distant metastases and death compared to other subtypes[2,3,4]. TNBC is defined by its lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2) and accounts for approximately 15%-20% of all BC cases [5]. However, Latin American studies usually report higher percentages of new TNBC cases. In Peru and Colombia, TNBC prevalence rates are 21.3% and 20.6%, respectively[6,7].

Despite pathologic tumor features (large tumor size, lymph node involvement, and advanced stages) having a clear association with worse survival outcomes [8,9], early detection of TNBC remains a challenge in developing countries. A Peruvian study stated that only 7.2% of TNBC cases diagnosed between 2000 and 2014 were classified as stage I [10].

Adjuvant chemotherapy is currently the only systemic treatment available for early-stage TNBC patients [11]. However, there is uncertainty around selecting TNBC T1N0M0 patients who would benefit from it to avoid overtreatment. Studies have shown contradictory results regarding this topic. For example, Yi Xing Ren et al. suggested that adjuvant chemotherapy improves recurrence-free survival (RFS) in T1cN0M0 TNBC patients but not in T1b[12]. On the other hand, a meta-analysis demonstrated the survival benefit of adjuvant chemotherapy for patients with pT1bN0 and pT1cN0 TNBC[13]. Therefore, there is a need to investigate the role of adjuvant chemotherapy in that population profile to provide clarity and improve the quality of life during treatment. Thus, this study aims to evaluate the effect of adjuvant chemotherapy on overall survival (OS) and progression-free survival (PFS) among pT1N0M0 TNBC subgroups (pT1a/b vs. pT1c).

METHODS

Design and study population

A retrospective study reported 2007 cases of TNBC diagnosed between January 2000 and December 2014 at the Instituto Nacional de Enfermedades Neoplásicas (INEN) in Lima, Peru. Immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) tests were used to identify these patients.

Antibodies Estrogen Anti-Receptor (Clone 1D5, Dako), Progesterone Anti-Receptor (Clone PGR636, Dako), and Anti-HER2/neu (A0485, Dako) were used for IHC analysis. ER/PR negative was defined when <1% of cells showed any level of nuclear staining. According to the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) guidelines[14], HER2-negative was reported when the IHC score was 0/1+ or 2+ but corroborated by FISH negative (not amplified). Previous literature has already reported the demographic characterization of the overall cohort design [10].

Eligibility criteria

We only included non-metastatic TNBC patients who underwent surgery as the first treatment, had residual disease classified as pT1N0M0 (tumor size ≤2 cm and negative axillary lymph nodes), and then received adjuvant chemotherapy. Exclusion criteria included male patients, cases with inflammatory breast tumors, and patients with missing data on tumor size, surgery type, chemotherapy, or surgery dates. Our study did not include TNBC patients who were reported to be treated with neoadjuvant chemotherapy.

Definition of variables

8th edition of the American Joint Committee on Cancer (AJCC) [15] was used to define clinicopathologic characteristics of the residual disease. pT1 classification was divided into three groups: T1a (>0.1cm and <0.5cm), T1b (>0.5cm), and T1c (>1cm). Overall survival (OS) and Progression-Free Survival (PFS) were calculated from surgery to death or first progression disease, respectively, or to the last contact.

Statistical analysis

Clinicopathologic characteristics between patients who received chemotherapy and those who did not by residual tumor size (pT1a/b vs pT1c) were described by

percentages and tested by Pearson's Chi-square test or Fisher's exact test as appropriate. We reported the age of TNBC patients through the median and range. A comparison of the use of adjuvant chemotherapy for quantitative variables was tested using the ANOVA test. 5-year survival rates were estimated using the Kaplan-Meier method, and the Log-rank test determined differences in survival curves. A Univariate Cox proportional hazards model was used for determining hazard ratios (HR) and 95% confidence intervals (CIs) to identify risk factors for PFS. Data were analyzed with R software version 4.0.3 using the packages "survival" (version 3.5-5) and "survminer" (version 0.4.9). P-values<0.05 were considered statistically significant.

Ethical Considerations

The Ethics Review Board of the Instituto Nacional de Enfermedades Neoplasicas (Lima, Peru) approved the study, and all relevant ethical guidelines conducted it.

RESULTS

Clinicopathologic characteristics

Our study included 124 patients diagnosed with T1N0 TNBC. According to Table 1, 30.6% (n=38) were reported as pT1a/b (pT1a = 13, pT1b = 25), while 69.4% (n=86) were pT1c. Overall median age was 51.0 (range: 43.8 – 61.0) years. Among pT1a/b patients, it was 52.5 (45.5 – 59.0) years and 49.5 (43.0 – 61.8) years within the pT1c patient group. Regarding menopausal status, 61.0% (n=75) were postmenopausal, and the rest were classified as premenopausal (39.0%, n=48). This trend was evident in both the pT1a/b and pT1c groups (Table 1).

Around 60.2% (n=74) underwent conversational surgery and 39.8% (n=49) underwent mastectomy. pT1c patients tend to have more conservative surgery cases than pT1a/b patients.

Moreover, the most common histological grade among the study population was G3 (69.4%, n=75). Similar proportions were evident between the pT1a/b (60.6%, n=20) and pT1c (73.3%, n=55) groups (Table 1).

The adjuvant treatments were chemotherapy and radiotherapy. 65.3% (n=81) of the population received adjuvant chemotherapy, and 55.6% (n=69) received radiotherapy. Adjuvant chemotherapy predominated in pT1c patients (72.1%, n=62, Table 1). It was also observed that 8.9% (n=11) died. Patients diagnosed with pT1a/b and pT1c reported five and six deaths, respectively. On the other hand, around 13.7% (n=17) developed progression, with 7.9% in pT1a/b and 16.3% in pT1c, as indicated in Table 1.

Profile of pT1a/b and pT1c TNBC patients according to the use of adjuvant chemotherapy

In Table 2, pT1a/b patients who did not receive chemotherapy had a median age of 57.0 years (49.0 – 59.5), while those who did 49.0 (39.5 – 57.5) years. On the other hand, for pT1c patients who were recommended chemotherapy, the median age was 48.5 (42.0 – 58.8). Among this group of patients, it was observed that those who did not receive treatment were significantly older (p=0.005, Table 2).

Most pT1a/b and pT1c patients who accessed chemotherapy complemented their treatment with radiotherapy. This proportion was significant for bothgroups (p=0.023, p=0.004). However, no significant differences were reported in menopausal status, type of surgery, histological grade, or overall survival in pT1a/b and pT1c patients according to the use of adjuvant chemotherapy.

Table 1. General characteristics.

Clinical characteristics	Total, N = 124[1]	pT1a/b, N = 38[1]	pTc, N = 86[1]
Age (years)	51.0 (43.8, 61.0)	52.5 (45.5, 59.0)	49.5 (43.0, 61.8)
Age group (years)			
0-35	12 (9.7%)	3 (7.9%)	9 (10.5%)
36-64	94 (75.8%)	31 (81.6%)	63 (73.3%)
65+	18 (14.5%)	4 (10.5%)	14 (16.3%)
Menopausal status			
Postmenopausal	75 (61.0%)	26 (68.4%)	49 (57.6%)
Premenopausal	48 (39.0%)	12 (31.6%)	36 (42.4%)
NR2	1	0	1
Type of surgery			
Conservative	74 (60.2%)	21 (55.3%)	53 (62.4%)
Mastectomy	49 (39.8%)	17 (44.7%)	32 (37.6%)
NR2	1	0	1
Histological grade			
G1	1 (0.9%)	0 (0.0%)	1 (1.3%)
G2	32 (29.6%)	13 (39.4%)	19 (25.3%)
G3	75 (69.4%)	20 (60.6%)	55 (73.3%)
NR3	17	5	12
Adjuvant chemotherapy			
No	43 (34.7%)	19 (50.0%)	24 (27.9%)
Yes	81 (65.3%)	19 (50.0%)	62 (72.1%)
Adjuvant radiotherapy			
No	55 (44.4%)	19 (50.0%)	36 (41.9%)
Yes	69 (55.6%)	19 (50.0%)	50 (58.1%)
Survival status			
Deceased	11 (8.9%)	5 (13.2%)	6 (7.0%)
Alive	113 (91.1%)	33 (86.8%)	80 (93.0%)
Progression status			
No	107 (86.3%)	35 (92.1%)	72 (83.7%)
Yes	17 (13.7%)	3 (7.9%)	14 (16.3%)

[1] Median (range); n (%)
[2] Not reported

Table 2. Characteristics of pT1a/b and pT1c patients according to the use of adjuvant chemotherapy.

Clinical characteristics	pT1a/b No, N = 19[1]	Yes, N = 19[1]	p-value[2]	pT1c No, N = 24[1]	Yes, N = 62[1]	p-value[2]
Age (years)	57.0 (49.0, 59.5)	49.0 (39.5, 57.5)	0.12	61.0 (46.5, 69.5)	48.5 (42.0, 58.8)	**0.005**
Age group (years)			0.7			**0.027**
0-35	1 (5.3%)	2 (10.5%)		1 (4.2%)	8 (12.9%)	
36-64	15 (78.9%)	16 (84.2%)		15 (62.5%)	48 (77.4%)	
65+	3 (15.8%)	1 (5.3%)		8 (33.3%)	6 (9.7%)	
Menopausal status			0.2			0.12
Postmenopausal	15 (78.9%)	11 (57.9%)		17 (70.8%)	32 (52.5%)	
Premenopausal	4 (21.1%)	8 (42.1%)		7 (29.2%)	29 (47.5%)	
NR[2]	-	-		-	1	
Type of surgery			0.10			0.14
Conservative	8 (42.1%)	13 (68.4%)		12 (50.0%)	41 (67.2%)	
Mastectomy	11 (57.9%)	6 (31.6%)		12 (50.0%)	20 (32.8%)	
NR[2]	-	-		-	1	
Histological grade			0.13			0.086
G1				1 (5.0%)	0 (0.0%)	
G2	8 (53.3%)	5 (27.8%)		7 (35.0%)	12 (21.8%)	
G3	7 (46.7%)	13 (72.2%)		12 (60.0%)	43 (78.2%)	
NR[3]	4	1		5	7	
Adjuvant radiotherapy			**0.023**			**0.004**
No	13 (68.4%)	6 (31.6%)		16 (66.7%)	20 (32.3%)	
Yes	6 (31.6%)	13 (68.4%)		8 (33.3%)	42 (67.7%)	
Survival status			>0.9			0.7
Deceased	3 (15.8%)	2 (10.5%)		2 (8.3%)	4 (6.5%)	
Alive	16 (84.2%)	17 (89.5%)		22 (91.7%)	58 (93.5%)	
Progression status			>0.9			**<0.001**
No	17 (89.5%)	18 (94.7%)		13 (54.2%)	59 (95.2%)	
Yes	2 (10.5%)	1 (5.3%)		11 (45.8%)	3 (4.8%)	

[1] Median (range); n (%)
[2] Anova test; Pearson's Chi-squared test
[3] No reported

Table 3. Cox univariate model for progression-free survival according to tumor size of residual disease.

Clinical characteristics	Total				pT1a/b				pT1c			
	N	HR[1]	95% IC[1]	p-value	N	HR[1]	95% IC[1]	p-value	N	HR[1]	95% IC[1]	p-value
Age (years)	124	1.02	0.98, 1.06	0.3	38	0.91	0.80, 1.05	.2			1.00, 1.08	0.068
Type of surgery	123			>0.9	38			.7				0.8
Conservative		—	—			—	—				—	
Mastectomy		1.04	0.40, 2.73			0.61	0.05, 6.76				0.41, 3.41	
Histological grade	108			0.2	33			0.9				0.2
G1		—	—			—	—				—	
G2		0.06	0.01, 0.57								0.01, 0.95	
G3		0.06	0.01, 0.51		29	1.08	0.10, 12.0				0.01, 0.71	21
Adjuvant chemotherapy	124			**<0.001**	38			.34				**<0.001**
Yes		—	—			—	—				—	
No		10.3	3.35, 31.8			3.07	0.27, 34.5				5.54, 73.1	

[1]HR = Hazard Ratio, CI = Confidence Interval

Survival analysis

According to the Kaplan – Meier survival analysis, it was determined no significant differences in 5-year OS rates when evaluating the use of adjuvant chemotherapy (p=0.13, Figure 1A). This same trend was evident between the pT1a/b patient groups (p=0.159, Figure 1B) and pT1c (p=0.320, Figure 1B). This landscape differed when PFS was analyzed, which at 5 years of follow-up showed a worse prognosis among patients who did not receive chemotherapy (p<0.0011, Figure 2A). However, the benefit of chemotherapy was only demonstrated as significant among pT1c patients (p<0.0001, Figure 2B). pT1a/b patients do not report improvement in relation to progression (p=0.340, Figure 2B). The Cox regression analysis concerning survival from progression reported that the absence of chemotherapy represents a risk factor (HR:10.3, 95% CI: 3.35 - 31.8, p<0.0001, Table 3). However, the statistical weight of this result lies in the fact that pT1c patients without chemotherapy have a 20.1 higher risk than those who did access treatment (95% CI: 5.54 - 73.1, p<0.0001, Table 3).

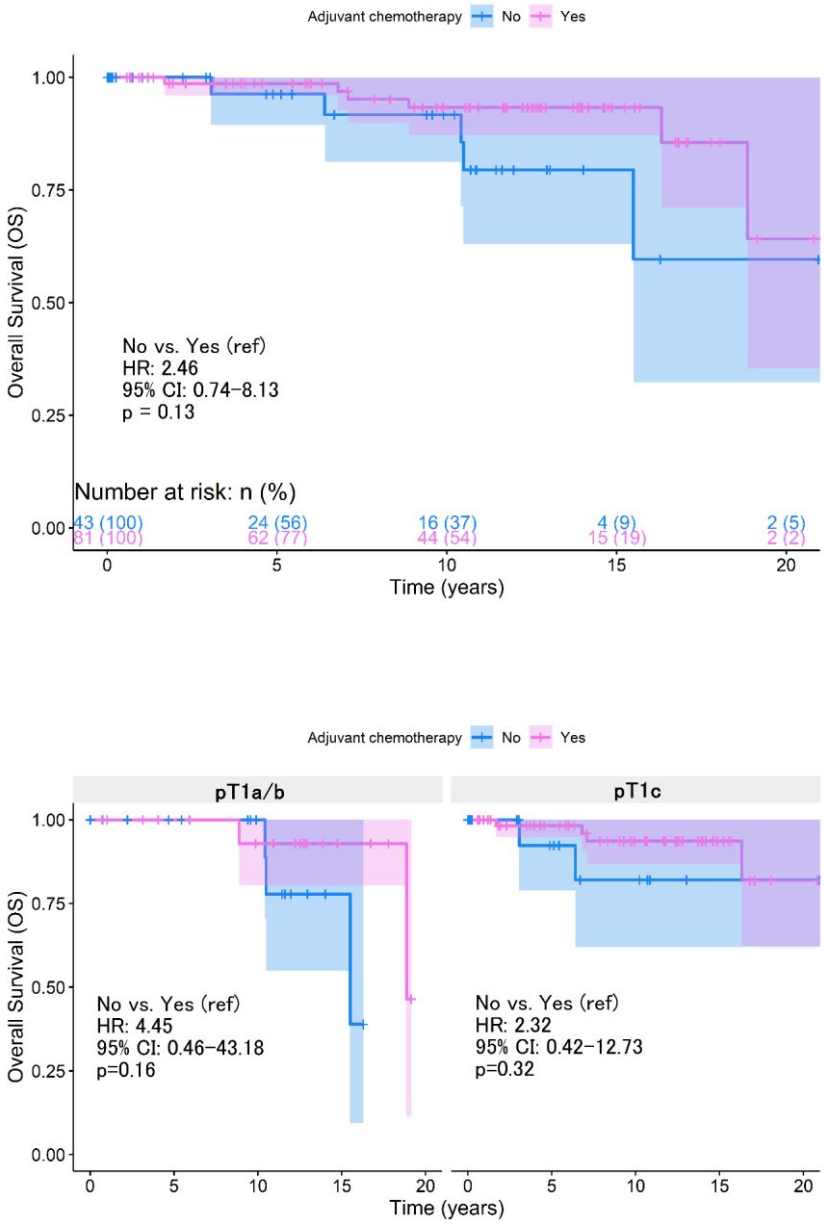

Figure 1. Overall survival analysis according to the use of adjuvant chemotherapy (A) Overall (B) Stratified by pT1a/b and pT1c.

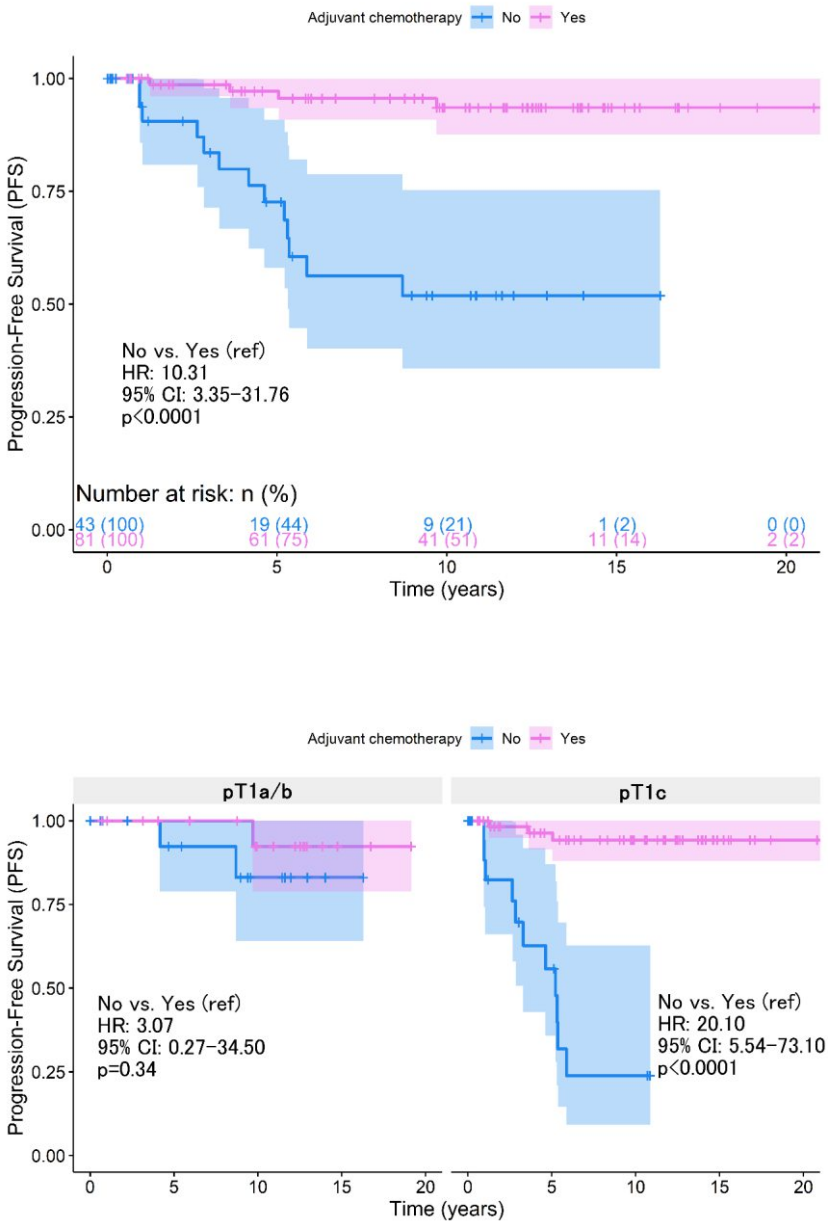

Figure 2. Progression- Free survival analysis according to the use of adjuvant chemotherapy (A) Overall (B) Stratified by pT1a/b and pT1c.

DISCUSSION

Our study aimed to determine the benefits of adjuvant chemotherapy among TNBC patients with early-stage tumors from residual disease (pT1N0M0). It is well-known adjuvant chemotherapy is the only approved treatment for early-stage TNBC patients and is recommended even for those with small and lymph node-negative tumors according to the 2023 European Society for Medical Oncology (ESMO) Clinical Practice Guideline (CPG) [16]. It explains why more than half of our population received chemotherapy as a systematic treatment. This trend is also evident among pT1N0M0 TNBC patients from China, reaching 88.0%[13]. However, evidence suggests an unclear benefit of adjuvant chemotherapy in T1N0M0 subgroups. Our analysis indicated an improvement in PFS because of treatment only among pT1cN0M0. pT1a/bN0M0 TNBC patients with adjuvant chemotherapy did not experience a better outcome, neither OS nor PFS, compared to those who did not were treated. Similarly, Yi Xing Ren et al. demonstrated a significant RFS benefit in T1cN0M0 TNBC patients receiving adjuvant chemotherapy

(HR: 0.24,95% CI:0.08-0.76, p=0.014). However, this effect was not observed in the T1b subgroup (HR=0.32, 95% CI: 0.03-3.18, p=0.330)[17]. Moreover, differences were not found between patients with T1mic/T1a TNBC tumors and patients with T1b tumors in the distant recurrence rate in the receipt of chemotherapy (95.9% vs 94.5%, respectively, p=0.63)[18].

On the contrary, the impact of chemotherapy on OS and breast cancer-specific survival (BCSS) was illustrated by Carbajal-Ochoa et al., who showed that adjuvant chemotherapy improved OS in T1b TNBC (HR:0.52, 95% CI:0.41-0.68, p<0.001) but did not significantly affect BCSS (HR:0.70, 95% CI: 0.45-1.07, p=0.10). In T1c, TNBC patients also reported an improvement in both OS (HR: 0.54, 95% CI: 0.47-0.62, p<0.001) and BCSS (HR: 0.79, 95% CI: 0.63-0.99, p=0.043)[19]. Despite these benefits, the application of chemotherapy in T1a tumors was questioned by Bravo-Solarte et al., who observed no improvement in OS or BCSS post-chemotherapy in this subgroup [20].

Our study is limited by its retrospective nature that led us to grouped T1a/b due to the few cases available. An et al., in their meta-analysis, demonstrated that adjuvant chemotherapy significantly reduced the rate of disease recurrence for patients with T1a/b disease as a group. Still, the population driving that was only patients with T1b disease, not those with T1a disease [13]. Another limitation was the lack of information on tumor-infiltrating lymphocytes (TILs) in clinical records of patients, which is the main reason this variable was not considered in our study. TILs have been identified as a prognostic biomarker in TNBC patients treated with adjuvant chemotherapy [21]. A retrospective study that included 182 systemically untreated TNBC patients found a subgroup of patients with ≥ 50% TILs had a decrease in invasive disease-free survival (iDFS) rates[22]. Park et al. also showed early TNBC patients with ≥ 30% TILs had excellent survival outcomes in the absence of adjuvant chemotherapy. Each 10% increment in TILs reduced the risk of iDFS, distant disease-free survival (D-DFS) and OS in 10% (95% CI, 0.82 to 0.97), 14% (95% CI, 0.77 to 0.95) and 12% (95% CI, 0.79 to 0.98), respectively[23]. In this sense, omitting TILs data could has limited our study since TILs play a promising role in predicting patient outcomes and guiding treatment decisions in early TNBC.

CONCLUSION

In conclusion, while adjuvant chemotherapy evidently improves outcomes in certain subgroups of TNBC patients, particularly those with T1cN0M0 disease, its application in smaller T1a/b tumors requires careful consideration. Current consensus guidelines recommend chemotherapy in T1b TNBC patients, reflecting a cautious approach towards a subgroup where the evidence of benefit is mixed. Effectiveness of chemotherapy across different tumor sizes within the T1N0M0 category highlights the need for personalized treatment strategies and the identification of biomarkers that could predict response to therapy. Future research should aim to refine these strategies, such as including TILs data, ensuring patients receive the most appropriate and effective care tailored to their risk profile.

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