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ORIGINAL ARTICLE

Clinical characteristics and spatial analysis of breast cancer in Jalisco, Mexico

*Igor M. Ramos-Herrera[1], Miguel E. González-Castañeda[2], José L. Vázquez-Castellanos[1], Daniel Mora-Plascencia[1], Juan de Dios Robles-Pastrana[2], Samantha López-Águila[3], Rosa Ma. Valdez-López[1], Mario G. Carranza-Matus[4], Armando Morales-Fernández[1], Miguel Galarde-López[5], and Antonio Reyna-Sevilla[6]**

[1]Department of Public Health, University Center of Health Sciences, Universidad de Guadalajara, Guadalajara, Jal.; [2]Department of Geography and Territorial Order, Universidad de Guadalajara, Guadalajara, Jal.; [3]Cancer Institute of Jalisco, Health Services of Jalisco, Guadalajara, Jal.; [4]Health Services of Jalisco, Guadalajara, Jal.; [5]National Center for Disciplinary Research in Animal Health and Safety, National Institute of Forestry, Agricultural and Livestock Research, Mexico City; [6]Directorate of Medical Benefits, IMSS, Mexico City. Mexico

Abstract

Background: *A study that involved spatial analysis tools is presented to demonstrate their possible impact on secondary prevention actions of breast cancer (BC).* **Objective:** *To examine clinical characteristics of BC in women living in Jalisco, Mexico, and to analyze the spatial distribution of diagnoses.* **Methods:** *Ecological-exploratory study. Clinical records of women diagnosed with BC during 2013-2017 were reviewed to collect clinical and sociodemographic variables. Using descriptive, inferential, and spatial statistics, age groups were compared according to stage classification (early/late), and spatial density.* **Results:** *There were 1,245 diagnoses. Average age 52.9 years (± 12.3); 80.7% performed housework. According to mammography, 55.7% of women reported BI-RADS 4 and 5; 55.2% were diagnosed late, mainly in the ≥ 60 age group (odds ratio = 1.15, 95% confidence interval = 0.65-1.09). 87.5% of diagnoses were concentrated in municipalities with higher population density in the study area; a higher number of diagnoses per spatial unit (km²) were observed in the northeast area.* **Conclusions:** *BC detection and diagnosis are still performed in clinically advanced stages, so it´s suggested to focus secondary prevention actions territorially to increase their population impact.*

Keywords: *Breast neoplasms. Early detection of cancer. Biomarkers tumor. Spatial analysis. Geographic mapping.*

Características clínicas y análisis espacial del cáncer de mama en Jalisco, México

Resumen

Antecedentes: *Se presenta un estudio que involucró herramientas de análisis espacial para demostrar su posible impacto en acciones de prevención secundaria para cáncer de mama (CM).* **Objetivos:** *Examinar características clínicas del CM en mujeres residentes de Jalisco, México, y analizar la distribución espacial de los diagnósticos.* **Métodos:** *Estudio ecológico-exploratorio. Se revisaron expedientes clínicos de mujeres con diagnóstico de CM del periodo 2013-2017, se recolectaron variables clínicas y sociodemográficas. Mediante estadística descriptiva, inferencial y espacial se compararon grupos de edad según clasificación del estadio (temprano/tardío) y la densidad espacial.* **Resultados:** *Se hallaron 1,245 diagnósticos. Edad promedio 52.9 años (± 12.3). El 80.7% realizaba labores domésticas. Según mastografía, el 55.7% de las mujeres reportó BI-RADS 4 y 5; el 55.2% fueron diagnosticadas tardíamente, principalmente en el grupo de 60 o más años (OR: 1.15; IC 95%: 0.65-1.09). El 87.5% de los diagnósticos se concentró en municipios con mayor densidad poblacional en*

***Correspondence:**
Antonio Reyna-Sevilla
E-mail: gs.antonioreyna@gmail.com

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el área de estudio; se observó un mayor número de diagnósticos por unidad espacial (km²) en zona noreste. **Conclusión:** *La detección y diagnóstico de CM aún se realiza en etapas clínicamente avanzadas, por lo que se sugiere focalizar territorialmente acciones de prevención secundaria a fin de aumentar su impacto poblacional.*

Palabras clave: *Neoplasias de mama. Detección temprana de cáncer. Biomarcadores tumorales. Análisis espacial. Mapeo geográfico.*

Introduction

Worldwide, breast cancer (BC) not only represents one of the most common cancers but also the main cause of mortality for women[1,2]. Mortality rates have shown a sustained increase in the past two decades[3], mainly in low- and middle-income countries[4]. Similarly, in Mexico BC has posed a health issue for women, especially in the reproductive or advanced stage of life. In 2020, BC represented 15.3% of all malignant neoplasms among women in Mexico, with a mortality rate of 17.9/100 thousand women over 20 years of age[5,6].

In this sense, early clinical diagnosis has proven to be one of the most effective secondary prevention measures to timely address BC[7]. Moreover, it is considered one of the most important prognostic criteria for survival along with some biomarkers, such as estrogen receptors (ER), progesterone (PR), and human epidermal growth factor receptor 2. However, diagnoses are commonly done in advanced stages worldwide[1]. In Mexico, some studies have reported that 6 out of 10 BC diagnoses are made between stages IIB and IV[8,9]. Identifying the clinical stage, prognostic markers, and clinical characteristics plays a key role since they may indicate the biological behavior of BC, thus determining the clinical and therapeutic treatment and survival for patients.

Nevertheless, in Mexico, the clinical characteristics of BC have been little investigated compared to the analysis of the global burden of the disease[10,11], mortality trends[12], and use of preventive and diagnostic health services[13], which is partly explained by the lack of a population-based census. Therefore, this study aimed to assess the clinical characteristics of BC among women living in the Guadalajara Metropolitan Area (GMA), which is located in the state of Jalisco, Mexico, who were treated in a tertiary care hospital during 2013-2017, as well as to analyze the distribution, differences and spatial patterns of diagnoses.

Materials and methods

The design of this study was ecological-exploratory. It was conducted at the Jalisco Institute of Cancerology (IJC per its Spanish acronym), a third-level hospital for cancer patients, located in the municipality of Guadalajara, Jalisco, Mexico, dependent on the Ministry of Health of the State of Jalisco. Ethical approval to conduct this study was obtained from the Ethics and Research Committee of the IJC (Reference PRO-12/16), as well as by the Committee of the University Center for Health Sciences of the Universidad de Guadalajara (reference CI-03920). Due to the nature of the study, which involved an analysis of secondary epidemiological data, informed consent was not required from subjects. This manuscript has been written according to the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) statement guideline. Due to the nature of the study, which involved an analysis of secondary epidemiological data, study registration was not necessary.

Data collection and inclusion criteria

According to the criteria of the Mexican Standards NOM 041-SSA2-2011[14] and the National Comprehensive Cancer Network of the United States[15], clinical records of women who were diagnosed with BC at IJC between 2013 and 2017 were used as a secondary source. Therefore, no sample or power calculation was necessary. In addition, the population of the following municipalities comprising the GMA has included: Guadalajara, San Pedro Tlaquepaque, Tonalá, Tlajomulco de Zúñiga, Zapopan, El Salto, Juanacatlán, Ixtlahuacán de los Membrillos, Acatlán de Juárez, Zapotlanejo, and Villa Corona, which is justified by territorial proximity, several interventions, and government planning[16,17]. The GMA is the second largest metropolis in Mexico, outranked only by the Metropolitan Area of the Valley of Mexico. According to the National Institute of Statistics and Geography[5], the GMA has 5,179,874 inhabitants, with four municipalities containing 69.6% of the population (Guadalajara, San Pedro Tlaquepaque, Tonalá, and Zapopan).

The subject demographics and variables collected by the clinical records were: address, age, education (categorical), employment (categorical), BI-RADS

classification, genetic biomarkers, and clinical stage, the latter classified as early (stages 0, IA, IB, IIA) and late (IIB, IIIA, IIIB, IIIC, IV), according to the criteria contained in the NOM 041-SSA2-2011[14]. The exclusion criteria were women whose municipality of residence was different from those that integrated the GMA, a different diagnosis than BC, or without a clinical record to collect the variables of interest for this research.

Statistical and geospatial analysis

The sociodemographic and clinical variables were analyzed using descriptive statistics, so absolute and relative frequencies (95% confidence interval [CI]) were obtained. Furthermore, Pearson's chi-square test ($p < 0.05$) was used to compare age groups based on early or late clinical-stage classification. Data analysis was performed using IBM SPSS Statistics (version 22). Considering the residence address of the women diagnosed with BC, a geolocation process was conducted using the national geostatistical framework and Google My Maps platform, resulting in a spatial distribution map covering the diagnoses in the study area. Then, four algorithms were used in the QGIS software version 3.22.3 (Creative Commons Corporation, Mountain View, California, United States) to analyze the spatial density of the diagnoses and quantitatively identify areas with higher and lower concentrations. This analysis was conducted only in the four municipalities with the highest population density (Guadalajara, San Pedro Tlaquepaque, Tonalá, and Zapopan) to obtain precise and detailed territorial data. Thus, a vector layer was generated with a size similar to the surface of the GMA, comprised by square km grids. Subsequently, the frequency of BC diagnoses for each of these spatial units was estimated. On the other hand, the Kernel Density Estimation was used to identify the concentrated areas of diagnoses, which were compared with the population density of the GMA. In this analysis, the population parameters were carefully selected to ensure the sensitivity and reliability of the results[18]. Finally, the Kernel Density Estimation was complemented with isolines as support for delimitating the concentrated areas (concentric lines).

Results

2,385 women living in the State of Jalisco were treated at the IJC. Their BC diagnoses were made during the 5-year study period. However, only 1,245 women met the selection criteria. Table 1 shows their sociodemographic characteristics, in which the average age was 52.9 years (SD = 12.3), while the highest percentage for level of schooling was secondary school (24.6%), followed by elementary school (21.8%).

Table 1. Sociodemographic characteristics and municipality of residence of women diagnosed with breast cancer (BC) and treated at the Jalisco Institute of Cancerology (IJC), 2013-2017

Variable	n	%
Average age (years)	52.9	12.3 (SD)
Minimum age	19	
Maximum age	95	
Schooling (grade concluded)		
Elementary	272	21.8
Secondary	306	24.6
High School	172	13.8
Professional	194	15.6
No formal education	270	21.7
Unknown	31	2.5
Occupation		
Paid	212	17
Domestic work	1,006	80.8
Does not work	27	2.2
Municipality of residence		
Guadalajara	593	47.6
Zapopan	287	23.1
Tlaquepaque	125	10
Tonalá	84	6.7
Tlajomulco de Zuñiga	60	4.8
Zapotlanejo	31	2.5
El Salto	26	2.1
Ixtlahuacan de los Membrillos	10	0.8
Ixtlahuacan del Río	7	0.6
Villa Corona	7	0.6
Cuquio	5	0.4
Juanacatlan	3	0.2
Acatlan de Juarez	2	0.2
Unknown	5	0.4

Source: prepared by the authors based on clinical records provided by the Jalisco Institute of Cancerology (IJC), 2013-2017.

Table 2 shows the absolute and relative frequency for BI-RADS classification, clinical stage, and biomarkers. According to the screening mammography, most women reported BI-RADS 4 (31.3%) and 5 (24.4%), that is, suspicious and highly suggestive cases of malignancy, respectively. At the time the diagnostic was confirmed, 488 women (39.2%) were classified as early clinical stage (stages 0-IIA), while 687 women (55.2%) were diagnosed in late stages (stages IIB-IV). Concerning the biomarkers, the highest proportion was ER+

Table 2. Clinical characteristics of women diagnosed with breast cancer (BC) and treated at the Jalisco Institute of Cancerology (IJC), 2013-2017

BI-RADS	n	%
0	99	8
1	6	0.5
2	127	10.2
3	65	5.2
4	390	31.3
5	304	24.4
6	8	0.6
No data	246	19.8
Clinical stage		
0	95	7.6
IA	123	9.9
IB	16	1.3
IIA	254	20.4
IIB	195	15.7
IIIA	200	16.1
IIIB	152	12.2
IIIC	75	6
IV	65	5.2
No data	70	5.6
Biomarkers		
Estrogen receptor (ER+)	746	59.9
Progesterone receptor (PR+)	717	57.6
Human epidermal growth factor receptor 2 (HER2+)	438	35.2
Triple-Positive (ER+, PR+, HER2+)	292	23.5

Source: prepared by the authors based on clinical records provided by the Jalisco Institute of Cancerology (IJC), 2013-2017.

Table 3. Clinical diagnosis of breast cancer* (BC), according to age group of women treated at the Jalisco Institute of Cancerology (IJC), 2013-2017

Age (years)	Early diagnostic (n)	%	Late diagnostic (n)	%
15-19	1	0.1	0	0.0
20-29	11	0.9	12	1.0
30-39	38	3.2	74	6.3
40-49	161	13.7	191	16.3
50-59	148	12.6	205	17.4
60-69	95	8.1	122	10.4
70-79	27	2.3	62	5.3
80-89	6	0.5	18	1.5
≥ 90	1	0.1	3	0.3
Total	488	41.5	687	58.5

*70 cases were omitted because no histopathological study with a clinical stage report was found in the file.
Source: Prepared by the authors based on clinical records provided by the Jalisco Institute of Cancerology (IJC), 2013-2017.

(59.9%), but we also identified that 23.4% were positive for the three biomarkers considered in this study.

On the other hand, table 3 shows that, regardless of early or late diagnosis, most women were between 40-59 years old, with no statistically significant differences. Even when establishing two comparison groups, that is, women ≤ 60 years old and > 60 years old, a probability of late diagnosis of 57.3 and 61.4%, respectively, was observed. The odds ratio estimate was 1.15 (95% CI 0.65-1.09), with no statistical significance.

The distribution analysis of BC diagnoses showed that 87.5% (n = 1,089) were concentrated in the four municipalities characterized by the highest population density in the GMA: Guadalajara, Zapopan, Tlaquepaque and Tonalá (Fig. 1). Furthermore, the highest frequency of diagnoses was recorded in the northeastern area, up to 11 per spatial unit (square km), while in the southwestern area, with values ≤ 5, the contrary was observed.

The Kernel density estimation showed three areas with the highest concentration of diagnoses, which were delimited using isolines in Guadalajara northeast, Zapopan Northwest, and Tlaquepaque South (Fig. 2). On the other hand, color shading identified only one area of greater spatial density (red) in the GMA, located in Guadalajara northeast.

Discussion

The results showed a recent overview for the clinical characteristics of BC among women living in the GMA, located in the state of Jalisco, Mexico. Therefore, we identified that detecting and diagnosing BC are still being done in suspicious phases, that is, highly suggestive of malignancy or clinically advanced. Moreover, women were characterized by having a lower level of schooling, being housewives and residents of urban areas, with an average age of 53 years. On the other hand, the spatial analysis showed the concentration areas for BC diagnoses in the study area. Thus, it is appropriate to suggest that detection strategies should be implemented through breast self-examination, clinical examination, and screening mammography – secondary prevention – considering a territorial perspective,

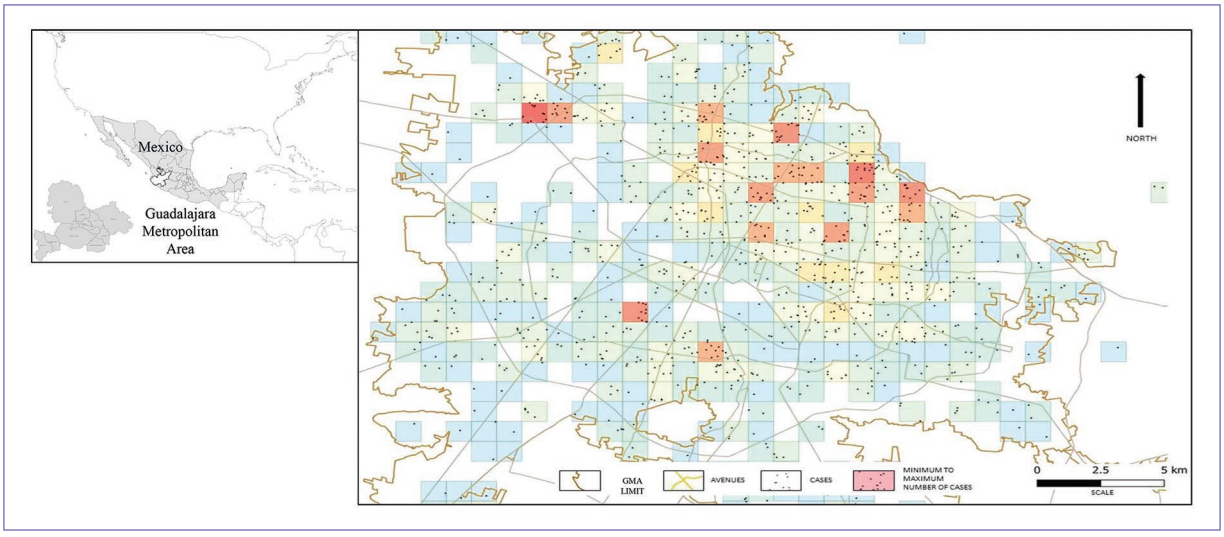

Figure 1. Distribution and frequency of breast cancer diagnoses (BC) per spatial unit (square km) in the Guadalajara Metropolitan Area (GMA), 2013-2017. *Source: prepared by the authors based on clinical records provided by the Jalisco Institute of Cancerology (IJC), 2013-2017.*

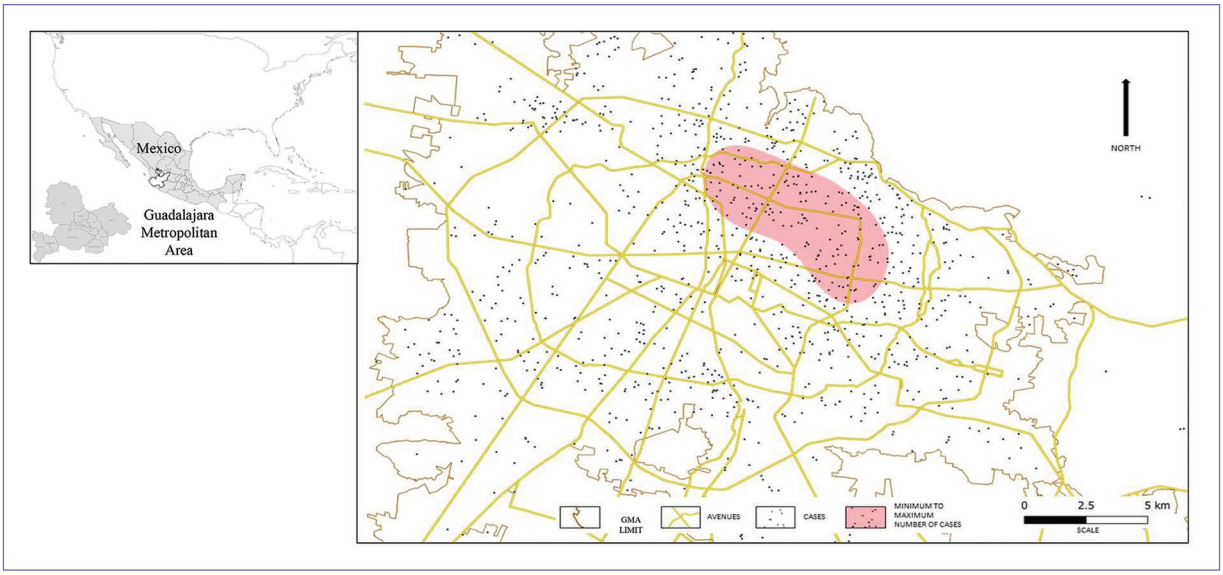

Figure 2. Spatial density for breast cancer diagnoses (BC) in the Guadalajara Metropolitan Area (GMA), 2013-2017. *Source: prepared by the authors based on clinical records provided by the Jalisco Institute of Cancerology (IJC), 2013-2017.*

that is, focusing on the places where the female population associated with risk factors for BC lives, which could certainly be complemented by the spatial analysis tools used in this study to increase the population impact of the secondary prevention strategies.

The strategy to control BC stands out for focusing on early detection of the disease to avoid the consequences attributable to late-stage BC diagnoses[19]. Therefore, BI-RADS 4, 5, or late-stage diagnoses suggest that screening programs are not effective[19]. In this sense, this situation is very likely to occur in several states of Mexico, since studies have reported late-stage BC diagnoses, particularly at 53 years of age[8,9]. Similarly, screening coverage for lower-income

countries is < 23%[20], as reported by a representative study on Mexican women[13], while the Breast Cancer Program implemented by the Mexican Ministry of Health has reported a figure of 15% and a diagnostic coverage of 16%[21]. These figures may explain the detection percentages for BI-RADS 4 and 5, as well as the proportion of diagnoses in advanced stages that were identified in women living in the GMA. Primarily because in Mexico the detection process through screening mammography is characterized by being opportunistic and not preventive, attributable to failures in information systems, management, and patient monitoring, among other important aspects[21].

Since 2013, when more than 14 million women were reported in Mexico, there was a warning about the disparity between the installed capacity in clinical services for screening and the number of women aged 40-69 years[13]. The most recent population census reported approximately 19 million, which shows the potential demand for health services (prevention, detection, diagnosis, treatment, rehabilitation) and coverage for the target group. Being diagnosed with BC can be a shocking experience that, unfortunately, many women undergo worldwide[22]. Therefore, it is essential to apply secondary prevention strategies to reduce the possibility for BC to occur in advanced stages, which is associated with low survival[1] and older age. Nevertheless, our results revealed no statistically significant differences concerning early or late diagnosis between different age groups, which is in line with other studies in which age does not have an impact on the possibility for early or late diagnosis. However, this could be because of a delay in seeking professional medical care, a delay in health systems when detecting or diagnosing, or the usual place of residence – urban or rural[23,24]. Thus, a low survival prognosis (≤ 5 years) is expected when more than 3 months have elapsed since the patient identified the first symptom and the initiation of medical treatment[25]. Women who regularly practice breast self-examination are more likely to be diagnosed in the early stages, so timely detection through effective screening programs has explained the decreased mortality observed in countries such as Australia, Canada, or the United States[1].

On the other hand, since we used the Kernel Density Estimation, our results allowed us to accurately identify the distribution and concentration patterns of BC diagnoses in the GMA, as reported by other metropolitan areas of Latin America, such as Mexico City[26], or Quito, Ecuador[27]. In this sense, facing unequal access to BC care services may occur. Furthermore, there are sociodemographic elements that can explain differences and spatial patterns associated with diagnoses, for example, the distance from care services[28], degree of urbanization[29], socio-economic status and level of schooling[1,26,] or the absence of social security[28] in metropolitan cities. It is in these areas where cultural and social factors, deficiencies in health services, and economic limitations exert influence on getting appropriate diagnosis and treatment for BC. Our results suggest that neither the place of residence nor age are factors associated with early or late diagnosis, but instead, they may be related to rural residence or comorbidities, delay in seeking health care, or in scheduling health services to meet the indicators established by the NOM 041-SSA2-2011[14]. Whether the diagnosis is made in the early or late stage, the geographical distribution of BC diagnoses may show how women access to health services regarding health promotion, prevention, clinical examination, screening mammography, clinical diagnosis, treatment, and possible rehabilitation procedures.

Considering our results, the following limitations should be noted. Since data from other health institutions, municipalities of Jalisco or federal entities of Mexico were not included or analyzed, it is not possible to generalize the results, although we found similarities with other studies. Furthermore, we did not analyze socioeconomic or clinical variables that could be associated with the possibility of detecting and diagnosing BC in clinically advanced phases. Taking into account that most developing countries do not have quality information on the profile of diagnosed cancers, unless there are population-based cancer registries, which has not yet been achieved in Mexico, we note that this study collected data directly from clinical records, that is, a reliable secondary source, since it is in accordance with criteria established by the Ministry of Health regarding content and organization. Moreover, clinical management and therapeutic decisions depend mainly on the information contained in the files. Finally, we note that in the spatial analysis, specific and non-aggregate data were used, which provided a territorial perspective with greater precision in terms of the results, so spurious results were not generated.

Conclusion

This study provided recent evidence on characteristics of detection and clinical diagnosis of BC among women living in the GMA, Mexico, and showed that these processes continue to occur in suspicious phases, highly suggestive of malignancy or clinically advanced.

Furthermore, there are areas in the city where actions aimed at detecting and diagnosing the disease early could be territorially focused, that is, on a local territorial scale to increase their population impact.

Approval

Ethical approval to conduct this study was obtained from the Ethics and Research Committee of the IJC (Reference PRO-12/16), as well as by the Committee of the University Center for Health Sciences of the Universidad de Guadalajara (reference CI-03920).

Authors contribution

I.M. Ramos-Herrera, M.E. González-Castañeda, J.L. Vázquez-Castellanos, D. Mora-Plascencia, and A. Reyna-Sevilla: study conception, result interpretation and discussion. I.M. Ramos-Herrera, M.E. González-Castañeda, A. Reyna-Sevilla, J.D. Robles-Pastrana, and M.G. Carranza-Matus: study design, analysis and data interpretation. I.M. Ramos-Herrera, A. Reyna-Sevilla, S. López-Águila, R.M. Valdez-López, A. Morales-Fernández, and M. Galarde-López: manuscript preparation.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Las estrategias de afrontamiento como factores asociados a la adherencia terapéutica en pacientes con cáncer de mama

Sarahi J. Hernández-Reyes[1], Iris Pineda-Mújica[2], Lilia S. Gallardo-Vidal[2], Adriana J. Rodríguez-Méndez[3], Ma. Fernanda Aguilar-Etchegaray[2] y Jacqueline Jiménez-Avila[2]*

[1]Unidad de Medicina Familiar 9, IMSS; [2]Unidad de Medicina Familiar 13, IMSS; [3]Facultad de Medicina, Universidad Autónoma de Querétaro. Santiago de Querétaro, Qro., México

Resumen

Antecedentes: *Los efectos secundarios del tratamiento del cáncer de mama reducen la adherencia terapéutica, dando como resultado un aumento de la recurrencia, la progresión y la mortalidad, y la forma en que el paciente lo afronta puede estar asociada a esta adherencia.* **Objetivo:** *Determinar la asociación entre estrategias de afrontamiento y la adherencia al tratamiento en pacientes con cáncer de mama.* **Método:** *Diseño de asociación en mujeres con cáncer de mama atendidas en el servicio de oncología con y sin adherencia terapéutica (n = 40 por grupo). Se aplicó el test de Morisky-Green para evaluar adherencia terapéutica y el Inventario de estrategias de afrontamiento (CSI). Los resultados se analizaron por medio de la prueba de chi-cuadrada, odds ratio (OR), análisis de regresión logística y análisis de probabilidad de riesgo para no adherencia terapéutica.* **Resultados:** *Las estrategias de afrontamiento adaptativas presentaron mayor fuerza de asociación para la adherencia terapéutica (p < 0.05). Estas se incorporaron a un análisis de regresión logística (p < 0.000) y se obtuvo un 97% de probabilidad de no adherencia terapéutica en aquellas pacientes que no afrontan la enfermedad de manera adaptativa.* **Conclusiones:** *Las estrategias de afrontamiento adaptativas favorecen la adherencia terapéutica al cáncer de mama.*

Palabras clave: *Estrategias de afrontamiento. Adherencia terapéutica. Cáncer de mama.*

Coping strategies as associated factors for therapeutic adherence in breast cancer patients

Abstract

Background: *The side effects of breast cancer treatment reduce therapeutic adherence, resulting in increased recurrence, progression and mortality, and the way the patient copes may be associated with this adherence.* **Objective:** *To determine the association between coping strategies and adherence to the treatment in patients with breast cancer.* **Method:** *Association design in women with breast cancer treated in the oncology service with and without therapeutic adherence (n = 40 per group).The Morisky-Green test was applied to evaluate therapeutic adherence and the Coping Strategies Inventory (CSI). The results were analyzed using the Chi-square test, odds ratio (OR), logistic regression analysis, and risk probability analysis for therapeutic non-adherence.* **Results:** *Adaptive coping strategies were those with the highest strength of association for therapeutic adherence (p < 0.05). These were incorporated into a logistic regression analysis (p < 0.000), and 97% probability of therapeutic non-adherence was obtained in those patients who do not face the disease in an adaptive way.* **Conclusions:** *Adaptive coping strategies promote therapeutic adherence to breast cancer.*

Keywords: *Coping strategies. Therapeutic adherence. Breast cancer.*

Correspondencia:
Lilia S. Gallardo-Vidal
E-mail: susi2947@gmail.com

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Introducción

El cáncer de mama es la segunda neoplasia más frecuente y la principal causa de muerte entre las mujeres. Representa el 25% de los casos de cáncer y el 16% de las muertes en mujeres[1,2]. En México es la primera causa de muerte por cáncer en el sexo femenino y se ha observado un incremento considerable tanto en la incidencia como en la mortalidad en estas últimas décadas. En la actualidad se ha colocado en el primer lugar de incidencias de neoplasias malignas en el sexo femenino y se estima un incremento anual de 1.7 millones de casos nuevos, así como un incremento en un 10.9% relativo en estos últimos años[3].

A pesar de los avances científicos en el diagnóstico y tratamiento de cáncer de mama, así como el aumento en la esperanza de vida de las mujeres afectadas, este diagnóstico sigue siendo altamente estigmatizado y en muchas de las ocasiones las pacientes abandonan el tratamiento, lo que da como consecuencia un riesgo relevante de muerte[4] o de progresión de la enfermedad[5,6].

La adherencia al tratamiento se define como un comportamiento influenciado por la conformidad[7] o motivación, decisión, libre albedrío e ideología de vida de cada paciente, llevando a la implementación, el compromiso y la responsabilidad de adoptar un enfoque terapéutico. Puede medirse de manera directa, es decir, por medio de biomarcadores, de manera indirecta contando pastillas o de forma subjetiva con reportes y diarios[8].

La falta de adherencia se presenta cuando un paciente omite dosis con frecuencia, de acuerdo con lo prescrito, y la falta de persistencia se presenta cuando se interrumpe el tratamiento de manera continua y prolongada[4,9].

En el caso de las pacientes diagnosticadas con cáncer de mama que se manejan con terapias endocrinas adyuvantes, el abandono en etapas tempranas de esta estrategia se da hasta en un 40 a 59%[5,10], en la mayoría de las veces por los efectos adversos asociados a los medicamentos, especialmente con el uso de tamoxifeno[6]. También se ha relacionado la falta de adherencia terapéutica a la percepción de no requerir tratamiento por su etapa clínica temprana, características del tumor, tipo de tratamiento, depresión, ansiedad[11,12], información inadecuada, falta de apoyo social, los elevados costos del tratamiento, la mala relación médico-paciente[10], y durante el tiempo de la pandemia de COVID-19, el miedo al contagio[13].

Cuando una mujer recibe el diagnóstico de cáncer de mama, se enfrenta a una situación de vulnerabilidad extrema[14], se presenta ante ella la incertidumbre del proceso que va a vivir, el tratamiento que va a recibir y sus efectos adversos, el pronóstico y la posibilidad de enfrentarse a la muerte; por lo que utiliza todos sus mecanismos internos para afrontar esta nueva situación[15]. Algunas afrontan la enfermedad adaptándose a esta nueva realidad y aceptan el reto de los efectos adversos del tratamiento a cambio de años de vida ganados, indagan más sobre la enfermedad, buscan ayuda familiar, social, psicológica y espiritual, y le dan un significado positivo al cáncer. Expresan libremente sus emociones, sus miedos y sus dudas; sin embargo, en algunos casos a las pacientes les cuesta trabajo adaptarse a esta nueva situación, se aíslan, se culpan por no haber tomado medidas preventivas, no aceptan su nueva realidad, minimizan los riesgos de la no adherencia terapéutica convencional[7,9,15], y en su lugar utilizan terapias alternativas, que en muchas de las ocasiones pueden favorecer la progresión del cáncer y la interacción farmacológica[16].

Por tal motivo, la forma en que la paciente con cáncer de mama afronta su padecimiento es fundamental, debido a que existen estrategias de afrontamiento adaptativas, como la reestructuración cognitiva, la resolución de problemas, la expresión emocional y el apoyo social, y no adaptativas, como el pensamiento desiderativo, la evitación de problemas, la retirada social y la autocrítica[7,8,15].

Existen estudios cualitativos que han permitido comprender las experiencias de las pacientes al recibir el diagnóstico y el tipo de tratamiento para el cáncer de mama; apenas concluyen con la primera etapa de mastectomía, quimioterapia y/o radioterapia y se están adaptando a los efectos de estos tratamientos cuando tienen que afrontar nuevos retos ante la terapia hormonal adyuvante[17]. Algunas de ellas afrontan de manera adaptativa, pero otras no y terminan abandonando el tratamiento convencional[7,10,18].

En la actualidad no existen estudios cuantitativos que demuestren el tipo de estrategia de afrontamiento y su asociación con la adherencia terapéutica en pacientes diagnosticadas con cáncer de mama, por consiguiente el propósito de esta investigación es demostrar la asociación entre las diferentes estrategias de afrontamiento al cáncer de mama y la adherencia terapéutica, ver la fuerza de asociación y estimar la probabilidad de no adherencia con las diferentes combinaciones de las estrategias de afrontamiento.

Método

Se llevó a cabo un estudio transversal comparativo de asociación. Se estudiaron mujeres diagnosticadas con cáncer de mama, con terapia endocrina adyuvante indistintamente del rango de edad que se presentaron al servicio de oncología de una institución pública en Querétaro, México, del año 2021 al 2022. Se calculó el tamaño de la muestra mediante la fórmula para dos proporciones con un nivel de confianza del 95% y un poder de la prueba del 80%, con un total de 40 pacientes por grupo; el muestreo fue por conveniencia. Se agregaron mujeres con reporte histopatológico de cáncer de mama, se excluyeron pacientes con comorbilidades como diabetes tipo 2, hipertensión arterial sistémica, otros tipos de cáncer, dislipidemias, enfermedades reumatológicas, déficit cognitivo, embarazadas, depresión, trastorno de ansiedad u otras enfermedades psiquiátricas diagnosticadas. Se eliminaron las pacientes con datos incompletos.

El protocolo fue sometido a evaluación y aceptación por el Comité de Ética e Investigación de la Institución, y cuando este fue aceptado y se obtuvo un número de registro (R-2021-2201-053), se procedió a invitar a las pacientes, a firmar un consentimiento informado y a contestar la hoja de recolección de datos y los instrumentos de adherencia terapéutica y de estrategias de afrontamiento.

Para medir la adherencia terapéutica, se utilizó el *Medication Adherence Questionnaire* (MAQ) de Morisky-Green. Este consta de ocho preguntas con respuestas dicotómicas (sí o no), las cuatro primeras evalúan actitudes ante la medicación y las cuatro adicionales hacen referencia al comportamiento relativo a la toma de medicación, especialmente a la infrautilización. A partir de este, se dividió la muestra en dos grupos: con adherencia al tratamiento y sin adherencia al tratamiento[19].

Para la evaluación de las estrategias de afrontamiento, se aplicó el Inventario de estrategias de afrontamiento (CSI) de Tobbin, Holroyd, Reynolds y Wigal (1989) adaptado al castellano por Cano et al. (2007) con un alfa de Cronbach > 0.7. La escala cuenta con ocho dimensiones y se divide en dos partes: la primera consiste en relatar la situación estresante vivida recientemente y la segunda está formada por 40 ítems, con respuestas tipo Likert de cinco puntos, que miden el grado de utilización de las ocho estrategias de afrontamiento en la situación relatada previamente. Se evalúa cada estrategia individualmente, en una escala que oscila entre 0 y 20 puntos, entre más alta la calificación indica el estilo utilizado de la paciente para afrontar la notificación de la patología. Las estrategias no son excluyentes entre sí. Las estrategias adaptativas son el resultado de ajustes positivos, tanto cognitivos como conductuales, mientras que las estrategias no adaptativas están asociadas con una desvinculación conductual de situaciones estresantes y sentimientos de pérdida de control[20].

Los resultados fueron analizados por medio de frecuencias y porcentajes, y para poder estimar la asociación entre la adherencia terapéutica y las estrategias de afrontamiento se utilizó la prueba de chi-cuadrada (χ^2), prueba exacta de Fisher, y *odds ratio* (OR) para medir la fuerza de asociación, y aquellas que consiguieron una significación estadística se sometieron a un análisis de regresión logística. Así mismo se realizó la estimación de probabilidad a la no adherencia terapéutica con las diferentes combinaciones de las estrategias con mayor asociación expresada en porcentajes; para este análisis se utilizó la fórmula 1/(1+e-y). Para garantizar la calidad metodológica del diseño, el presente estudio se apegó a las pautas STROBE (*STrengthening the Reporting of OBservational studies in Epidemiology*) para estudios observacionales[21].

Resultados

En un total de 80 pacientes (40 para cada grupo), predominó la edad de 60 años o más, el estado civil casado, nivel básico de escolaridad, ocupación ama de casa, religión católica (Tabla 1) y el tratamiento conservador (escisión completa del tumor primario con margen patológico negativo) ($p < 0.05$) (Fig. 1).

La resolución de problemas (92.5%) y el apoyo social (92.5%) fueron las estrategias de afrontamiento más utilizadas por el grupo con adherencia terapéutica, y el pensamiento desiderativo (67.5%) predominó en el grupo sin adherencia terapéutica. Las estrategias de afrontamiento adaptativas fueron las que mayor fuerza de asociación presentaron ($p < 0.05$); en el caso de las no adaptativas solamente la retirada social obtuvo una fuerza de asociación significativa ($p = 0.001$) (Tabla 2).

Las estrategias de afrontamiento con mayor fuerza de asociación que permitieron crear un modelo fueron las adaptativas (χ^2: 35.642; $p < 0.000$) (Tabla 3). En este modelo existe el 97.9% de probabilidad de la no adherencia terapéutica en las pacientes con cáncer de mama si la paciente no utiliza ninguna de las cuatro

Tabla 1. Características de las pacientes con cáncer de mama con y sin adherencia terapéutica

Características	Con adherencia al tratamiento (n = 40)	Sin adherencia al tratamiento (n = 40)	Total (n = 80)	p*
Edad (años)				0.440
30-39	5 (12.5%)	5 (12.5%)	10 (12.5%)	
40-49	6 (15%)	12 (30%)	18 (22.5%)	
50-59	11 (27.5%)	9 (22.5%)	20 (25%)	
≥ 60	18 (45%)	14 (35%)	32 (40%)	
Estado civil				0.286
Solteras	1 (2.5%)	5 (12.5%)	6 (7.5%)	
Casadas	27 (67.5%)	24 (60%)	51 (63%)	
Divorciadas	3 (7.5%)	2 (5.0%)	5 (6.5%)	
Unión libre	6 (15%)	3 (7.5%)	9 (11.5%)	
Viudas	3 (7.5%)	6 (15%)	9 (11.5%)	
Escolaridad				0.256
Sin estudios	0 (0)	1 (2.5%)	1 (1%)	
Nivel básico	29 (72.5%)	33 (82.5%)	62 (79%)	
Nivel superior	11 (27.5%)	6 (15%)	16 (20%)	
Ocupación				0.056
Ama de casa	22 (55%)	19 (47.5%)	41 (51%)	
Profesionista	11 (27.5%)	4 (10%)	15 (19%)	
Obrera	4 (10%)	6 (15%)	10 (13%)	
Empleada	2 (5%)	10 (25%)	12 (15%)	
Comerciante	1 (2.5%)	1 (2.5%)	2 (2%)	
Religión				0.125
Sin religión	1 (2.5%)	3 (7.5%)	4 (5%)	
Católica	35 (87.5%)	24 (60%)	59 (74%)	
Mormona	0 (0)	1 (2.5%)	1 (1%)	
Cristiana	4 (10%)	10 (25%)	14 (18%)	
Testigo de Jehová	0 (0)	1 (2.5%)	1 (1%)	
Otras	0 (0)	1 (2.5%)	1 (1%)	

*Pruebas de χ^2 y exacta de Fisher con un nivel de confianza del 95%.

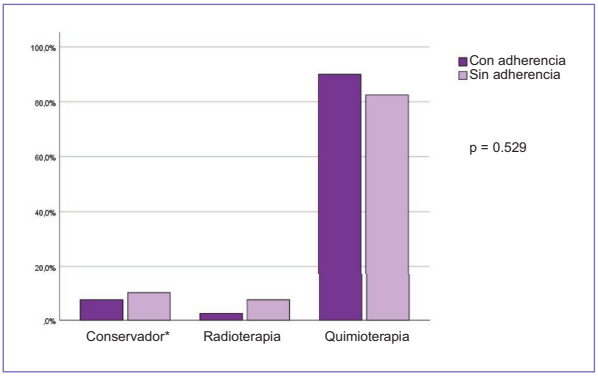

Figura 1. Tipo de tratamiento recibido en las pacientes con cáncer de mama. El análisis estadístico incluyó la prueba de χ^2 y la prueba exacta de Fisher. *El tratamiento conservador consistió en la escisión completa del tumor primario con margen patológico negativo.

estrategias de afrontamiento adaptativas, y el 20.9% de probabilidad de no adherirse al tratamiento si utiliza las cuatro estrategias (Tabla 4).

Discusión

El cáncer de mama es la segunda neoplasia más frecuente en la población femenina en México, con un impacto significativo en la mortalidad[22]. Padecer una enfermedad oncológica conlleva un deterioro físico y la interrupción de las actividades cotidianas debido al tratamiento, o a sus efectos secundarios[23], algunas mujeres rechazan los tratamientos convencionales y optan por terapias alternativas no aprobadas, que pueden resultar contraproducentes para su salud[24]. A pesar del gran potencial de nuevas terapias, como la endocrina adyuvante, para mejorar el pronóstico de las pacientes con cáncer de mama, la adherencia terapéutica sigue siendo subóptima debido a los efectos adversos asociados[4,6]. Estos efectos suelen ser minimizados por el personal de salud, por lo tanto no los comunican a las pacientes, y muchas no saben cómo manejarlos, ya que afectan a diversos aspectos de su vida, incluyendo el físico, laboral, social, familiar y de pareja[9].

Tabla 2. Estrategias de afrontamiento utilizadas en las pacientes con cáncer de mama

Estrategias de afrontamiento*	Con adherencia al tratamiento		Sin adherencia al tratamiento		OR	Intervalo de confianza 95%		p†
	f	%	f	%		Mínimo	Máximo	
Adaptativas								
Resolución de problemas	37	92.5	19	47.5	0.189	0.065	0.564	< 0.000
Apoyo social	37	92.5	19	47.5	0.189	0.065	0.564	< 0.000
Reestructuración cognitiva	34	85.0	20	50.0	0.367	0.176	0.761	0.001
Expresión emocional	33	82.5	19	47.5	0.394	0.201	0.773	0.001
No adaptativas								
Evitación de problemas	15	37.5	19	47.5	1.232	0.776	1.955	0.332
Retirada social	7	17.5	21	52.5	2.538	1.294	4.980	0.001
Pensamiento desiderativo	21	52.5	27	67.5	1.357	0.883	2.070	0.171
Autocrítica	7	17.5	14	35.0	1.768	0.880	3.201	0.075

*Obtenidas del Inventario de estrategias de afrontamiento (las estrategias no son excluyentes entre sí).
†Pruebas de χ^2 y exacta de Fisher.
OR: *odds ratio*.

Tabla 3. Modelo de regresión logística para explicar la adherencia terapéutica en las pacientes con cáncer de mama con las estrategias de afrontamiento adaptativas

χ		p	
35.642		< 0.000	
	Coeficiente	Estadístico	Significación
Constante	21.799		
Resolución de problemas	32.324	10.525	0.001
Apoyo social	29.481	7.682	0.006
Reestructuración cognitiva	22.860	1.061	0.857
Expresión emocional	21.831	0.032	0.303

El análisis estadístico incluyó la prueba de χ^2 y el cálculo del modelo de regresión logística múltiple, con un intervalo de confianza del 95%.

La actitud positiva frente al estrés generado por el diagnóstico de cáncer de mama juega un papel fundamental en la adherencia al tratamiento, a pesar de los efectos adversos, el beneficio de ganar años de vida motiva a muchas adherirse al régimen terapéutico[24,25].

Hasta la fecha no existen estudios cuantitativos que demuestren la relación entre la adherencia terapéutica y la atención integral a las pacientes con cáncer de mama, que sigue enfocándose únicamente en el ámbito biológico, sin considerar una atención holística[15].

En este estudio se identificó una fuerte asociación entre la adherencia terapéutica y el uso de estrategias de afrontamiento adaptativas. Entre estas, la resolución de problemas y el apoyo social fueron las más empleadas por las pacientes adherentes al tratamiento.

La «resolución de problemas» es una estrategia clave, ya que reduce el estrés al modificar o gestionar la situación que lo genera[14]. Cuando la paciente con cáncer de mama acepta los efectos adversos de la terapia y enfrenta la situación con determinación, enfocándose en la supervivencia, supera el miedo y se adhiere al tratamiento[7,26].

Diversos estudios cualitativos han destacado la relevancia del apoyo social en las pacientes diagnosticadas con cáncer de mama y tratadas con terapia hormonal adyuvante, especialmente en grupos de autoayuda. Estos grupos les brindan la oportunidad de compartir experiencias, lo que disminuye la ansiedad y la incertidumbre generada tanto por la enfermedad como por los efectos del tratamiento[7,9]. Los resultados de este estudio confirman estadísticamente que las mujeres que recibieron apoyo social mostraron una fuerte asociación con la adherencia terapéutica, mientras que aquellas sin apoyo social tendieron a experimentar mayor aislamiento. Este apoyo es crucial, ya que permite a las pacientes sentirse acompañadas, compartir sus vivencias[27] y reducir el estrés. Como se evidencia en la tabla 4, en los escenarios donde el apoyo social está ausente, la probabilidad de no adherirse al tratamiento aumenta significativamente.

La reestructuración cognitiva también juega un papel relevante, ya que modifica la interpretación del cáncer de mama y disminuye el estrés asociado, permitiendo

Tabla 4. Cálculo de probabilidad para explicar la falta de adherencia terapéutica por combinación de las estrategias de afrontamiento adaptativas

Probabilidad, %	Resolución de problemas	Apoyo social	Reestructuración cognitiva	Expresión emocional
97.9	No	No	No	No
97.6	No	No	No	Sí
95.6	No	No	Sí	No
95.0	No	No	Sí	Sí
85.4	No	Sí	No	No
83.9	Sí	No	No	No
81.9	Sí	No	No	Sí
73.1	No	Sí	Sí	No
70.8	Sí	No	Sí	No
70.3	No	Sí	Sí	Sí
67.8	Sí	No	Sí	Sí
39.4	Sí	Sí	No	No
36.2	Sí	Sí	No	Sí
23.3	Sí	Sí	Sí	No
20.9	Sí	Sí	Sí	Sí

El análisis estadístico incluyó el cálculo del modelo de regresión logística múltiple y, posteriormente, la estimación de la probabilidad de presentar la falta de adherencia terapéutica empleando la fórmula 1/(1 + e-y).

que las pacientes reconozcan los beneficios del tratamiento, y que estos superan los efectos adversos[6,9].

Cuando la paciente tiene creencias erróneas sobre el tratamiento, puede dudar de sus beneficios, lo que reduce su adherencia[10], tal y como se observa en la tabla 4.

La «expresión emocional» permite a las pacientes compartir sus sentimientos sin temor al juicio, lo cual ayuda a liberar el estrés[14]. A menudo, las personas no expresan sus emociones por miedo a mostrarse vulnerables, lo que puede generar un mayor estrés a largo plazo y aumentar el riesgo de descuidar su salud[28].

Los resultados de este estudio subrayan la importancia de incorporar, como protocolo en los sistemas de salud, grupos de autoayuda coordinados por un equipo multidisciplinario. Estos grupos deben incluir intervenciones psicoeducativas que, además de proporcionar información sobre la enfermedad, los tratamientos y sus efectos adversos, favorezcan estrategias de afrontamiento tanto para la enfermedad como para los efectos de los medicamentos.

Una limitación del estudio fue el tamaño de la muestra, lo cual probablemente influyó en la falta de resultados significativos en relación con las estrategias de afrontamiento no adaptativas. Además, no se valoraron otros factores que podrían estar relacionados con la falta de adherencia.

Conclusiones

Las estrategias de afrontamiento adaptativas están fuertemente asociadas con la adherencia terapéutica en pacientes con cáncer de mama que reciben terapia endocrina adyuvante.

Es fundamental implementar un modelo de atención que contenga acciones enfocadas al afrontamiento adaptativo en los programas de atención integral a las pacientes con cáncer de mama y en los centros oncológicos; así mismo que en ese modelo se incluyan grupos de autoayuda.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han seguido los protocolos de confidencialidad de su institución, han obtenido el consentimiento informado de los pacientes, y cuentan con la aprobación del Comité de Ética. Se han seguido las recomendaciones de las guías SAGER, según la naturaleza del estudio.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron algún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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ORIGINAL ARTICLE

Timeliness in cancer care: an analysis of delays in diagnosis and treatment initiation

Isnedys E. Ballesteros-Goes[1], Edgar F. Manrique-Hernández[2], Maricel Licht-Ardila[3], Leidy M. Rincón-Ramírez[1,4], Alejandra Mendoza-Monsalve[5], Alexandra Hurtado-Ortiz[6], Carmen J. Suarez Monsalve[7], and Anderson Bermon[8]*

[1]Quality Specialization, Corporación Universitaria Iberoamericana, Bogotá; [2]Public Health Department, Universidad Industrial de Santander, Bucaramanga; [3]Department of Epidemiology, Fundación Cardiovascular de Colombia, Piedecuesta, Santander; [4]IPS M and S SOLUTIONS S.A.S, San Gil, Santander; [5]Public Health Department, Fundación Universitaria del Área Andina, Bogotá; [6]Postgraduate Department in Infectious Disease, Universidad de Santander, Santander; [7]Value-Based Medicine Department, Fundación Cardiovascular de Colombia, Piedecuesta; [8]Epidemiology, Escuela de Graduados, Universidad CES, Medellin. Colombia

Abstract

Background: *Cancer care is a complex process involving timely diagnosis, initiation of treatment, and coordination across health system components. Delays in this continuum may arise due to limitations in healthcare infrastructure, socioeconomic disparities, and unequal access to specialized care.* **Objective:** *To assess delays in diagnosis and treatment initiation, and their association with the clinical characteristics of cancer patients affiliated with a health benefit management entity.* **Method:** *A cross-sectional study was conducted between January and July 2023, including cancer patients affiliated with a vertically integrated health insurer. Delays were categorized into four groups, and descriptive statistics were performed using STATA.* **Results:** *A total of 102 participants were included. Among them, 37.3% experienced delays in receiving diagnostic results, with the highest frequency observed in patients with hematologic cancers (63.6%). Delays in treatment initiation were also more prevalent in this subgroup (18.2%). While authorization delays were infrequent (observed in only 0.9% of patients), procedural delays were reported in 81.4% of the cases.* **Conclusion:** *This study identifies delays in diagnosis and treatment, highlighting that the quality of care is the primary barrier.*

Keywords: *Cancer diagnosis. Treatment delays. Healthcare quality. Early detection. Neoplasms.*

Prontitud en la atención del cáncer: un análisis de los retrasos en el diagnóstico y el inicio del tratamiento

Resumen

Antecedentes: *El cuidado del cáncer es un proceso que abarca diagnóstico, tratamiento e integración de sistemas de salud. Los retrasos pueden ser causados por factores como limitaciones en la infraestructura de salud, disparidades socioeconómicas y variaciones en el acceso a atención especializada.* **Objetivo:** *Evaluar los retrasos en el diagnóstico y el inicio del tratamiento, y su relación con las características clínicas de los pacientes con cáncer afiliados a una entidad que administra planes de beneficios en salud.* **Método:** *Se realizó un estudio transversal entre enero y julio de 2023, analizando pacientes con cáncer afiliados a un asegurador de salud con integración vertical. Los retrasos se clasificaron en cuatro categorías y se realizaron estadísticas descriptivas utilizando STATA.* **Resultados:** *Se incluyó un total de 102 participantes.*

***Correspondence:**
Edgar F. Manrique-Hernández
E-mail: fabianmh1993@gmail.com

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De ellos, el 37.3% experimentó retrasos en la recepción de los resultados diagnósticos, con la mayor frecuencia observada en pacientes con cánceres hematológicos (63.6%). Los retrasos en el inicio del tratamiento también fueron más prevalentes en este subgrupo (18.2%). Aunque los retrasos por autorizaciones fueron poco frecuentes (observados solo en el 0.9% de los pacientes), los retrasos en los procedimientos se reportaron en el 81.4% de los casos. **Conclusión:** *Este estudio identifica demoras en el diagnóstico y el tratamiento, destacando que la calidad de la atención constituye la principal barrera.*

Palabras clave: *Diagnóstico de cáncer. Retrasos en el tratamiento. Calidad de la atención sanitaria. Detección temprana. Neoplasias.*

Introduction

Cancer encompasses a heterogeneous group of diseases, defined by the type and location of the primary tumor[1]. The increasing global burden of cancer underscores the need for efficient clinical management strategies that ensure timely, accurate, and coordinated interventions. These strategies must be patient-centered and adhere to the highest technical and scientific standards across all stages of care, aiming to reduce cancer incidence, disability, mortality, and improve quality of life at both the population and individual levels[2-4].

Cancer care is inherently complex, involving not only diagnosis and treatment but also the integration of various components of the health system to provide continuous and comprehensive care[5]. Delays at any point along this care continuum-from initial symptom presentation to the initiation of definitive treatment-can significantly compromise clinical outcomes[6]. These delays may be driven by limitations in healthcare infrastructure, socioeconomic disparities, and unequal access to specialized services. Addressing these challenges requires a system-level approach that integrates advances in diagnostics, treatment modalities, and healthcare delivery models to ensure timely and equitable access for all patients[1].

The high complexity of oncologic therapies, combined with barriers in accessing healthcare services or logistical constraints within oncology departments, often contributes to delays in care. These factors have played a role in maintaining elevated cancer mortality rates in Latin America, leading the World Health Organization to emphasize the importance of early cancer diagnosis programs, particularly in low- and middle-income countries[7].

In Colombia, the general system of social security in health (SGSSS) provides universal coverage through a managed competition model involving public and private insurers (Entidades Promotoras de Salud), which contract services from healthcare providers (Instituciones Prestadoras de Salud). Although the system is designed to ensure access to healthcare, it is frequently challenged by bureaucratic inefficiencies, delays in authorization, prolonged waiting times for specialist consultations, and fragmented referral pathways. These structural deficiencies can result in significant delays across the cancer care continuum[8].

Several local studies have identified barriers to timely oncology care in Colombia, particularly concerning breast and cervical cancer[9,10]. However, these investigations often have limited scope, focusing on single institutions, specific regions, or particular cancer types. Moreover, there is a lack of research evaluating how administrative processes within the insurance-based healthcare model impact the timeliness of diagnosis and treatment initiation. This represents a substantial gap in the literature.

To address this gap, the present study evaluates delays in cancer diagnosis and treatment initiation among patients affiliated with a Health Benefit Plan Administrator (Entidad Administradora de Planes de Beneficios) and explores their association with patients' clinical characteristics. Given that timely access to oncologic care and effective coordination across services are fundamental for improving outcomes, this study aims to assess delays in diagnosis and treatment initiation, and their relationship with clinical characteristics of cancer patients affiliated with a health benefit management entity.

Materials and methods

A cross-sectional analytical study was conducted between January and July 2023, involving patients with a confirmed pathological diagnosis of cancer. Inclusion criteria required affiliation with the healthcare insurer under study, which operates under a vertical integration model, allowing for comprehensive traceability and consolidation of clinical information. Patients with a prior cancer diagnosis were excluded, as the focus was exclusively on the management of their present condition. All participants were residents of the northeastern region of Colombia.

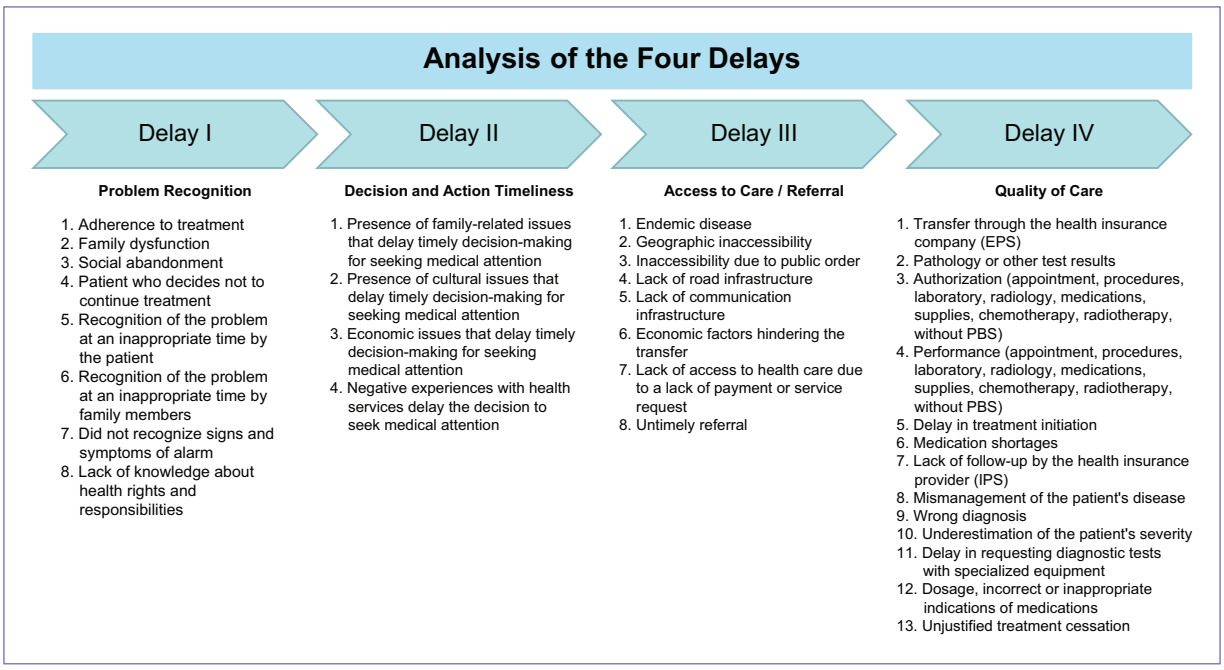

Figure 1. Definition of the four-delay analysis. *Source: based on the general methodology of the unit of analysis for special cases related to public health events of interest.*

No formal sample size calculation was performed; instead, a census approach was used, including all consecutive patients who met the eligibility criteria during the study period. This 6-month timeframe was selected to analyze delays in diagnosis and treatment within a defined temporal window. Patients were identified through electronic medical records using ICD-10 codes corresponding to malignant neoplasms.

The variables analyzed included age at diagnosis, cancer type, social security scheme, sex, clinical stage of the disease, municipality of residence, patient type (prevalent or incident), and the four delays[11]. The four-delay methodology was adopted to define delays*:* Type I lack of problem recognition refers to the patient's failure to recognize the seriousness of symptoms or the need to seek medical attention, often due to limited awareness or knowledge. Type II: lack of timely decision-making and action involves sociocultural, geographical, or economic barriers that hinder timely access to health services. Type III: lack of access to care and referral logistics refers to logistical barriers and limitations in accessing a healthcare institution equipped to provide necessary services. Type IV: failure in the quality of care from primary to tertiary levels. This includes delays in receiving appropriate and timely treatment, related to the quality of care provided at lower levels of the health system (Figure 1).

To determine whether a patient experienced a delay, we used reference indicators for timely diagnosis and treatment initiation as defined by the Colombian Ministry of Health and Social Protection in Resolution 3339 of 2019, specifically for prioritized cancers[12] (Table 1).

Data collection was managed using the Research Electronic Data Capture, ensuring secure and efficient data handling. Each patient's medical record was reviewed by trained personnel to ensure data accuracy and consistency. Delay classification was also conducted by trained reviewers. In cases where classification was uncertain, the final categorization was determined by consensus among the authors. Discrepancies were resolved promptly through collaborative review. For missing data, efforts were made to recover information through additional medical records or by contacting healthcare professionals involved in the patients' care. Records with irretrievably missing data were excluded from the analysis to preserve the integrity of the results.

Descriptive statistics were applied to characterize the study population. Categorical variables, including delay types, were presented as absolute frequencies and

Table 1. Timelines established by the Ministry of Health and Social Protection of Colombia-high-cost account for prioritized cancers according to resolution 3339 of 2019

Location	Timelines for timely intervention	Compliance range		
Breast/cervix	Diagnostic opportunity in cancer	≤ 30 days	≤ 45 and > 30 days	> 45 days
	Opportunity for treatment initiation	≤ 15 days	≤ 30 and > 15 days	> 30 days
Prostate/colon and rectum/ stomach/lung	Opportunity for diagnosis	≤ 30 days	≥ 30 - < 60 days	≥ 60 days
	Opportunity for treatment	≤ 30 days	≥ 30 -< 60 days	≥ 60 days
Melanoma	Opportunity for diagnosis	≤ 30 days	31-44 days	≥ 45 days
	Opportunity for treatment	≤ 30 days	31-44 days	≥ 45 days
Non-Hodgkin lymphoma	Opportunity for diagnosis	≤ 15 days	≥ 15 - < 30 days	≥ 30 days
	Opportunity for treatment	≤ 30 days	≥ 30 - < 60 days	≥ 60 days
Hodgkin lymphoma	Opportunity for diagnosis	≤ 15 days	≥ 15 - < 30 days	≥ 30 days
	Opportunity for treatment	≤ 30 days	≥ 30 - < 60 days	≥ 60 days
Acute myeloid leukemia	Opportunity from diagnosis to treatment, CNR	≤ 5 days	-	> 5 days
	Opportunity for transplantation, CNR	To be defined		
Acute lymphoid leukemia	Opportunity from diagnosis to treatment, CNR	≤ 5 days	-	> 5 days
	Opportunity for transplantation, CNR	To be defined		

Source: dictionary of indicators consensus and risk-HIGIA-CAC.

percentages. For continuous variables, normality was assessed using the Shapiro-Wilk test. Variables with a normal distribution were reported as means and standard deviations, while non-normally distributed variables were described using medians and interquartile ranges. Bivariate analyses were performed using the χ^2 test or Fisher's exact test, as appropriate. Statistical analyses were performed using STATA software, version 16.

Ethical statement

This study complied with international ethical standards and was based on secondary data from routine clinical care, without altering medical management or exposing patients to additional risks. The study protocol was reviewed and approved by the Institutional Scientific and Research Ethics Committees, ensuring adherence to ethical research principles.

Results

A total of 102 patients were included in the analysis. The median age was 61 years, and the majority were female (66.7%). Most participants (70.6%) were affiliated with the contributory health insurance regime. Incident cases accounted for 83.3% of the sample, and 88.2% of patients presented with solid tumors. The most common cancer types were skin cancer (18.6%), breast cancer (12.8%), and prostate cancer (10.8%). Among solid tumors, stage III was the most frequently observed (17.8%), followed by stage I (16.7%) (Table 2).

In this study, 83.3% were incident cases. Of the total population, 37.3% experienced delays in receiving pathology results or other diagnostic tests. These delays were significantly more frequent in incident cases (43.5%) than in prevalent cases (5.9%) ($p \leq 0.001$). Although most patients did not report delays in the authorization of procedures (99.0%) or the initiation of treatment (97.1%), delays in the execution of procedures were common, affecting 81.4% of patients. These delays were more frequent among incident cases (83.5%) compared to prevalent cases (70.6%), although the difference was not statistically significant ($p = 0.18$).

Delays related to problem recognition by patients or their families were relatively infrequent. Only 9.8% of participants reported a delay in recognizing the need for medical attention, with a slightly higher frequency in incident cases (11.8%) than in prevalent cases, though the difference was not statistically significant

Table 2. Participant characteristics

Category	No. (%)
Age (median IQR)	61 (46-72)
Sex	
Female	68 (66.7)
Male	34 (33.3)
Regimen	
Contributory	72 (70.6)
Subsidized	30 (29.4)
Diagnosis	
Incident	85 (83.3)
Prevalent	17 (16.7)
Pathology classification	
Hematological	12 (11.8)
Solid tumors	90 (88.2)
Staging (solid)	
In situ	7 (7.8)
I	15 (16.7)
II	12 (13.3)
III	16 (17.8)
IV	10 (11.1)
No date	14 (15.6)
Diagnostic group	
Skin	19 (18.6)
Breast	13 (12.8)
Prostate	11 (10.8)
Thyroid gland and other glands	9 (8.8)
Female genital organs	9 (8.8)
Colon and rectum	8 (7.8)
Cervix	8 (7.8)
Non-Hodgkin lymphoma	6 (5.9)
Digestive organs	4 (3.9)
Stomach	3 (2.9)
Urinary tract	3 (2.9)
Chronic myeloid leukemia	2 (1.9)
Trachea, bronchi, and lungs	2 (1.9)
Acute lymphoid leukemia	1 (0.9)
Acute myeloid leukemia	1 (0.9)
Multiple myeloma and malignant plasma cell tumors	1 (0.9)
Eye, brain, and other parts of the central nervous system	1 (0.9)
Other classification	1 (0.9)

IQR: Interquartile range.

(p = 0.147). Other reported factors included lack of follow-up by healthcare institutions (9.8%), transfers to other insurers (3.9%), and referral or counter-referral delays (1.0%), none of which showed significant differences between groups (Table 3).

An analysis of delays related to quality of care (Delay Type IV), comparing solid versus hematologic cancers, revealed statistically significant differences in treatment initiation. Patients with hematologic malignancies had a higher frequency of delays in treatment initiation (16.7%; n = 2), compared to those with solid tumors (1.1%; n = 1) (p = 0.04). Conversely, delays in the execution of procedures were more prevalent in patients with solid tumors (84.6%) than in those with hematologic cancers (58.3%) (p = 0.04). Delays in receiving pathology or test results were also more frequent in hematologic cancer patients (58.3%) compared to those with solid tumors (34.1%), although this difference did not reach statistical significance (p = 0.10). Family-related issues affecting timely decision-making were reported exclusively in hematologic cancer patients (8.3%), with a trend toward significance (p = 0.12) (Table 4).

Concerning the distribution of treatment delays by cancer type and stage, skin, breast, and prostate cancers showed the highest number of delays in stage IV, with 17, 11, and 11 cases, respectively. Overall, 87 delays (85.3%) occurred in stage IV, compared to 12 (11.8%) in stage I, 2 (2.0%) in stage III, and 1 (1.0%) in stage II. Supplementary table 1 highlights these findings, with red indicating the highest frequency of delays, green and yellow indicating low frequency or absence of delays, and no data recorded denoting missing data for certain groups.

Discussion

Cancer diagnosis at advanced stages remains a significant challenge for healthcare systems worldwide, leading to worse patient outcomes[1]. Early detection is crucial, as patients diagnosed in earlier stages typically experience better prognosis[13]. However, barriers at various levels, ranging from patient delays in seeking care to systemic issues in healthcare delivery, contribute to diagnostic delays, particularly in low- and middle-income countries[14]. Understanding the context surrounding delayed cancer diagnosis and treatment initiation is critical for improving patient outcomes and optimizing healthcare resources[15].

The study included a majority of incident cancer cases, emphasizing the high prevalence of new cancer diagnoses within the study population and the urgent need for timely interventions[1]. The majority of participants were women, and although the age at diagnosis did not differ between incident cases and prevalent cases, the presence of advanced-stage cancer remains a relevant finding. A considerable proportion of cases were classified in advanced stages, with stage III being particularly prevalent[16]. This underscores the persistent barriers to early detection and timely diagnosis, which remain critical challenges in cancer care[1].

Table 3. Analysis of delays by incident and prevalent patients

Type of delay	Total n = 102 (%)	Incident (n = 85)	Prevalent (n = 17)	p
Delay one: recognition of the problem				
Adherence to treatment	2 (2.0)	1 (1.6)	1 (5.9)	0.31
Social abandonment	1 (1.0)	1 (1.2)	-	0.83
Patient decides not to continue treatment	2 (1.8)	1 (1.6)	1 (5.9)	0.31
Late recognition of the problem by the patient	10 (9.8)	10 (11.8)	-	0.15
Late recognition of the problem by the family	2 (2.0)	2 (2.4)	-	0.69
Delay two: timeliness of decision and action				
Presence of family issues affecting timely decision to seek medical care	1 (1.0)	-	1 (5.9)	0.17
Delay three: access to care				
Referral and counter-referral (delays by personnel or family)	1 (1.0)	1 (1.6)	1 (5.9)	0.31
Delay four: quality of care				
Transfer to EPS	4 (3.9)	2 (2.35)	2 (11.8)	0.13
Results of pathology or other exams	38 (37.3)	37 (43.53)	1 (5.9)	< 0.001
Authorization*	1 (1.0)	1 (1.2)	0 (0.0)	0.83
Execution*	88 (81.4)	71 (83.4)	12 (70.6)	0.18
Delay in treatment initiation	3 (2.9)	3 (3.6)	0 (0.0)	0.58
Lack of follow-up from IPS	10 (9.8)	8 (9.4)	2 (11.8)	0.52

*Appointments, procedures, labs, radiology, medications, supplies, chemotherapy, radiotherapy, non-PBS services. IPS: Instituciones Prestadoras de Salud.

Table 4. Analysis of delays and cancer type

Type of delay	Hematologic (n = 12)	Solid tumor (n = 91)	p
Delay one: recognition of the problem			
Adherence to treatment	-	2 (2.2)	0.78
Social abandonment	-	1 (1.1)	0.83
Patient decides not to continue treatment	-	2 (2.2)	0.78
Late recognition of the problem by the patient	2 (16.7)	8 (9.8)	0.33
Late recognition of the problem by the family	-	2 (2.2)	0.78
Delay two: timeliness of decision and action			
Presence of family issues affecting timely decision to seek medical care	1 (8.3)	-	0.12
Delay three: access to care			
Referral and counter-referral (delays by personnel or family)	-	2 (2.2)	0.78
Delay four: quality of care			
Transfer to insurance provider	-	4 (4.4)	0.61
Results of pathology or other exams	7 (58.3)	31 (34.1)	0.10
Authorization*	-	1 (1.1)	0.83
Execution*	7 (58.3)	77 (84.6)	0.04
Delay in treatment initiation	2 (16.7)	1 (1.1)	0.04
Lack of follow-up from IPS	1 (8.3)	9 (9.9)	0.67

*Appointments, procedures, labs, radiology, medications, supplies, chemotherapy, radiotherapy, non-PBS services.

Regarding the four types of delays, the most common and impactful for patients was delay type four: quality of care, accounting for 85.3% of the total delays. This was followed by delay type one: recognition of the problem, in third place was delay type three: access to care/referral, and finally, delay type two: timeliness of decision and action. This suggests that the most frequent delays affecting patients were those directly related to patient-driven issues and delays caused by healthcare providers within the care process[17].

Significant differences were observed in delay type four, particularly in the subcategories related to pathology results. When analyzing the type of cancer, statistically significant differences were found in the initiation

of treatment, with more delays in hematological cancers. The delays observed in hematological cancers ($p = 0.04$) are likely related to various factors, such as diagnostic complexity, treatment logistics, and, additionally, inefficiencies within the healthcare system. However, a more in-depth study is required to precisely determine the causes of these delays and their impact on patient outcomes. Minimizing delays in diagnosis and the initiation of treatment, as such delays can substantially impact patient survival and outcomes[18].

These results are consistent with those reported in the systematic review association of treatment delays with survival for patients with head and neck cancer. This review found that the primary causes of delays were attributed to patient factors (e.g., failure to recognize symptoms as cancer-related) and professional factors (e.g., scheduling additional imaging or tests)[19]. Issues related to prolonged time to initiation of treatment appear to be more pronounced in academic medical centers, where patients are often diagnosed before referral and experience delays during the transition of care to the academic center[20].

Comparing these findings with studies conducted in Colombia, a study in Bogotá identified similar delays, particularly in the recognition of symptoms and referral process, affecting the timely initiation of treatment in patients with breast and prostate cancer[21]. In addition, a study in Medellín found that diagnostic delays were associated with being enrolled in a state-subsidized regime and being older than 40 years for breast cancer[22]. These findings highlight the commonality of treatment delays within Colombia, where barriers at various levels-patient, healthcare provider, and system-affect cancer care delivery.

These findings are consistent with those reported in the systematic review and meta-analysis on cancer treatment delay and mortality. Delays in cancer treatment are a global issue across healthcare systems[23]. Even a 4-week delay in cancer treatment has been associated with increased mortality for surgical, systemic, and radiotherapy interventions across seven types of cancer[24]. The evidence also suggests a strong relationship between delays in pathology results or other diagnostic tests and a patient's ability to receive timely diagnosis and treatment. This is likely due to the high volume of diagnostic requests, which often exceeds the capacity of the healthcare system. In addition, delays appear to originate from the primary care level, where physicians may face challenges in recognizing or suspecting cancer, leading to delays in referrals to secondary or tertiary care.

The structure of the Colombian healthcare system plays a significant role in the delays observed in cancer diagnosis and treatment. The system is a mixed model, consisting of both public and private sectors, with two primary regimes: the contributory regime for formal-sector workers and the subsidized regime for individuals with fewer resources. Despite efforts to ensure universal health coverage through the SGSSS, various challenges, including infrastructure limitations, regional disparities, and inefficiencies in service delivery, contribute to delays. These factors create barriers to timely diagnosis and treatment, as patients may face difficulties in accessing specialized care, particularly in rural or underserved areas. The fragmentation of the system, alongside its complex regulatory and referral processes, exacerbates these delays, further hindering prompt cancer care.

The findings from this study highlight several areas where policy changes could help mitigate delays in cancer diagnosis and treatment. One key policy recommendation is improving the infrastructure and resources in rural and underserved areas to ensure more timely access to specialized care. In addition, enhancing the efficiency of referral systems and diagnostic processes through digital health integration and better communication across healthcare levels could significantly reduce delays. It is also crucial to address systemic inefficiencies within the healthcare system by streamlining authorization processes and ensuring quicker turnaround times for pathology results. Public health policies should prioritize cancer awareness and early detection campaigns to reduce delays in problem recognition by patients. Furthermore, there should be continued investment in healthcare staff training to enhance decision-making, especially in primary care settings, where delays often begin. These interventions would likely lead to more timely diagnoses and treatments, ultimately improving patient outcomes.

Besides, our findings underscore the challenges in adhering to existing cancer care guidelines in Colombia, particularly regarding timely diagnosis and treatment initiation. According to the guidelines set by the Colombian Ministry of Health and Social Protection, cancer patients are expected to receive a diagnosis and begin treatment within specific timeframes to improve outcomes. However, the delays observed in this study, particularly those related to diagnostic results and the initiation of treatment, suggest that these guidelines are not always being followed. This discrepancy may be due to systemic issues such as limited healthcare resources, inefficient referral systems, and delays in obtaining

pathology results. These barriers prevent the guidelines from being fully implemented in practice. Addressing these gaps through policy improvements and healthcare infrastructure enhancements is crucial to align the system more closely with the established guidelines.

Limitations

The analysis was based on retrospective data, which introduces inherent limitations. Moreover, the study was conducted in a single geographic area, which may limit the generalizability of the findings to other regions. To achieve greater representativeness of various cancer types and patient populations, especially those with rare cancers, it is recommended to replicate the study in larger and more diverse samples. Besides, the study did not examine the impact of patients' socioeconomic status variables, such as income and education because they affect patients' actions and access to healthcare. Finally, other variables that could account for clinical relationships, such as comorbidities and characteristics of patients, were not taken into consideration.

Conclusion

This study highlights the prevalence of advanced-stage cancer diagnoses, particularly among women and patients with solid tumors, such as skin, breast, and prostate cancers. A significant finding was the identification of delays in the diagnostic and treatment initiation process, with quality of care being the most substantial barrier. Notably, delays in pathology results and treatment initiation were more pronounced in hematologic cancers, with a higher proportion of delays observed in comparison to solid tumors. Furthermore, delays were more frequent among incident cases, especially in terms of obtaining pathology results and executing procedures. These delays were attributed to systemic inefficiencies, such as limitations in healthcare infrastructure and referral logistics. The evidence underscores the need for targeted policies to reduce these delays, particularly by improving the healthcare system's infrastructure and ensuring timely access to care. These efforts are critical to improving patient outcomes and survival rates in Colombia.

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Conflicts of interest

The authors declare no financial conflicts of interest or personal relationships that may have influenced the work presented in this article.

Supplementary data

Supplementary data are available at DOI: 10.24875/j.gamo.25000028. This material is provided by the corresponding author and posted online for the benefit of the reader. The content of the supplementary data is the sole responsibility of the authors.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ARTÍCULO ORIGINAL

Irradiación cráneo-espinal pediátrica. Déficit de crecimiento y aspectos dosimétricos

*Alejandra P. Zárate-Gómez[1], Heynar J. Pérez-Villanueva[1], Aida A. López-Azcárraga[1], Juan M. Vázquez-Peralta[1] y Gabriel A. Sánchez-Marín[2]**

[1]Servicio de Radioterapia, Hospital Infantil de México Federico Gómez; [2]Servicio de Oncología, Hospital Juárez de México. Secretaría de Salud, Ciudad de México, México

Resumen

Antecedentes: *La irradiación cráneo-espinal (ICE) tiene un impacto decisivo en el control de tumores pediátricos con alta probabilidad de diseminación por líquido cefalorraquídeo, pero se asocia a defectos del desarrollo de la columna vertebral en etapa de crecimiento.* **Objetivo:** *Analizar las alteraciones de columna posteriores a ICE, y la comparación dosimétrica de las técnicas de radioterapia conformada (RC) y arco volumétrico de intensidad modulada (VMAT).* **Método:** *Se presenta una serie institucional de 101 casos, con resultados clínicos a 5 años.* **Resultados:** *En los casos analizados (n = 12) se observó una media de talla alcanzada de 136.1 cm con una talla media proyectada de 147.7 cm (p < 0.001) y una velocidad de crecimiento (VC) alcanzada de 3.2 cm/año con una VC promedio proyectada de 7.1 cm/año (p < 0.001). Hubo una diferencia de 11.6 cm entre la talla media actual y la proyectada y de 3.9 cm/año entre la VC alcanzada y la esperada, con un aumento del 58% en la incidencia de talla baja. La técnica de VMAT mostró una mejor homogeneidad a cambio de una mayor distribución de dosis bajas a tejidos periféricos.* **Conclusiones:** *Las alteraciones del desarrollo de la columna son multifactoriales, resultado de factores genéticos, nutricionales y del tratamiento. La edad y la dosis son los mayores predictores de los efectos.*

Palabras clave: *Irradiación cráneo-espinal. Tumores pediátricos. Déficit de crecimiento.*

Pediatric craniospinal irradiation. Growth deficit and dosimetric aspects

Abstract

Background: *Craniospinal irradiation (CSI) has a decisive impact on the control of pediatric tumors with a high probability of dissemination through cerebrospinal fluid, but is associated with developmental defects in the spinal column during growth.* **Objective:** *To analyze spinal alterations after CSI, and to compare dosimetric techniques of conformal radiotherapy (CR) and volumetric intensity-modulated arc (VMAT).* **Method:** *An institutional series of 101 cases is presented, with clinical results at 5 years.* **Results:** *In the analyzed cases (n = 12), a mean achieved height of 136.1 cm was observed with a projected mean height of 147.7 cm (p < 0.001) and a growth velocity (GV) of 3.2 cm/year with a projected mean GV of 7.1 cm/year (p < 0.001). There was a difference of 11.6 cm between the current and projected mean height and of 3.9 cm/year between the achieved and expected GV, with a 58% increase in the incidence of short stature. The VMAT technique showed better homogeneity in exchange for a greater distribution of low doses to peripheral tissues.* **Conclusions:** *Alterations in spinal development are multifactorial, resulting from genetic, nutritional and treatment factors. Age and dose are the greatest predictors of effects.*

Keywords: *Craniospinal irradiation. Pediatric tumors. Growth deficit.*

***Correspondencia:**
Gabriel A. Sánchez-Marín
E-mail: gabriel.sanchezma@anahuac.mx

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Introducción

Los tumores del sistema nervioso central (SNC) y las leucemias agudas son la primera y segunda causa de cáncer en niños y adolescentes[1,2].

La radioterapia constituye la segunda modalidad de tratamiento más efectiva en el control de los tumores del SNC y las neoplasias hematológicas. El beneficio como la terapia adyuvante para la curación de estos tumores se ha demostrado a lo largo del tiempo[3,4].

La irradiación cráneo-espinal (ICE) tiene un impacto en la supervivencia del 70% en tumores del SNC con alta probabilidad de diseminación por líquido cefalorraquídeo como el meduloblastoma, ependimoma, y tumores rabdoides atípicos y de células germinales[5-8].

Se ha determinado que la radioterapia afecta el desarrollo óseo en las etapas de crecimiento. La fisiopatología de la lesión ósea compromete todas las fases de la actividad fisaria como consecuencia del daño de las células del tejido conectivo; específicamente al efecto sobre los condroblastos en proliferación y a los vasos de pequeño calibre. La disminución del crecimiento óseo resultante se atribuye a la pérdida de células proliferativas en la placa de crecimiento, la reducción de la capacidad de las células sobrevivientes para la síntesis matriz osteoide o la producción de una matriz anormal que no logra calcificarse[9-11].

La ICE puede producir efectos en el desarrollo vertebral que dan lugar a déficits como la detención del crecimiento y deformidades de la columna, que se traducen clínicamente en baja estatura y escoliosis que se manifiestan a largo plazo[5,7,11,12]. La relación dosis-efecto está descrita a partir de los 15-18 Gy, con estudios que documentan un retraso significativo del crecimiento a dosis totales > 33 Gy y déficits proporcionales en dosis ≥ 18-20 Gy[5,7,8,12].

Método

Se presenta una serie institucional de niños y adolescentes con tumores del SNC y neoplasias hematológicas con edad ≤ 18 años tratados con ICE en el periodo 2018-2022. Se hizo la documentación retrospectiva de variables iniciales del paciente, la enfermedad y la técnica de radioterapia, con toma de los registros antropométricos al corte del estudio en diciembre del 2024. El diseño sigue los lineamientos de las guías STROBE (*Strengthening the Reporting of Observational studies in Epidemiology*).

El objetivo primario del estudio fue describir y analizar la incidencia del retraso en el crecimiento y escoliosis en los casos de seguimiento ≥ 5 años. El objetivo secundario fue la comparación dosimétrica de las técnicas de tratamiento de radioterapia utilizadas.

La ICE fue administrada con simulación y planeación 3D mediante dispositivos de fijación craneal y colchón de vacío en posiciones dorsal o ventral según las condiciones de cada caso y uso de sedación en los casos necesarios en los menores de 5 años. Los volúmenes de tratamiento fueron cráneo y columna con sus extensiones meníngeas siguiendo las recomendaciones de la *Société Internationale d'Oncologie Pédiatrique* (SIOP)[12,13] y los órganos de riesgo y restricciones con base en el QUANTEC y protocolos clínicos[14], se utilizó un fraccionamiento convencional de 1.8 a 2 Gy/día con dosis terapéutica según la patología, con prescripción al 95% del volumen de tratamiento planeado.

El seguimiento fue mediante parámetros antropométricos para comparar la talla y la VC. Se realizaron radiografías de columna para determinar la incidencia de la escoliosis en función del método de Cobb[15,16].

Los valores de la estatura final se compararon con las tablas de percentiles por edad y sexo del Centro de Control y Prevención de Enfermedades (CDC). Se consideró talla baja una VC final por debajo del percentil 25[17] y VC proyectada, el promedio del crecimiento anual esperado por edad en el periodo, calculado en centímetros por año (talla proyectada) de acuerdo con los parámetros de Barstow et al.[18]. El periodo evaluado fue del término de la radioterapia al corte del estudio.

Para el reporte de la dosimetría de columna se dividió en regiones cervical, torácica y lumbar, tomando como referencia cuatro puntos de cada vértebra en los cuerpos de C4, T7 y L3, de los cuales tres correspondían a los centros de osificación primarios: de los arcos vertebrales la lámina derecha y la lámina izquierda, la región central del cuerpo vertebral y la porción media de la apófisis espinosa, especificando la dosis media en cada punto.

Se excluyeron del análisis primario los casos de defunción, pérdidas, referencia a otros centros, esquemas incompletos y paliación.

Los datos se presentan mediante estadística descriptiva y se realizó comparación de medias según su distribución normal, con un valor de significación estadística de p ≤ 0.05, mediante el programa estadístico SPSS-27.

Resultados

Fueron tratados 101 casos con ICE, de los cuales 64 constituyen pérdidas al corte por defunción, contrarreferencia o pérdida del seguimiento con 37 casos activos. Los datos descriptivos del total de la serie se muestran en la tabla 1.

Debido al periodo de latencia tardío de los efectos, se analizaron los datos de 12 pacientes con un periodo de seguimiento ≥ 5 años, cuyos parámetros antropométricos se muestran en la tabla 2.

El promedio de edad al tratamiento fue de 7 años (2-14), con una dosis media a columna de 27.2 Gy. Al inicio del tratamiento de ICE, la media del percentil de talla fue de 38, con 5 casos (41.7%) arriba del percentil 75, 2 (16.7%) en el rango 50-75, 2 (16.7%) en 25-50 y 3 casos (25%) estuvieron por debajo del percentil 25 (talla baja).

La media de talla alcanzada al final del periodo fue de 136.1 cm, con una media de talla proyectada de 147.7 cm ($p < 0.001$) y la VC alcanzada de 3.2 cm/año con una VC promedio proyectada de 7.1 cm/año ($p < 0.001$). El percentil de la VC alcanzada al final del periodo fue < 25% en el 83.3% de los casos. Así entonces, se observó una diferencia de 11.6 cm entre la media de talla actual y la proyectada y de 3.9 cm/año entre la VC alcanzada y la esperada; con un aumento del 58% en la incidencia de talla baja en comparación al inicio. De los 10 casos evaluados mediante radiografía, ninguno presentó escoliosis al corte. La media de seguimiento del subgrupo fue de 5.6 años (5-6.7).

En lo referente a las técnicas del tratamiento se utilizaron técnicas 3D: RC y VMAT, esta última a partir de 2020.

Para efectos de comparación, se muestran los datos de los dos esquemas de dosis de mayor prescripción, de 15 Gy (37% en RC y 40% en VMAT) y 36 Gy (34% en RC y 40% en VMAT). En la tabla 3 se presentan los datos de comparación de dosis por segmentos de ambas técnicas para el esquema de 15 Gy.

En la tabla 4 se presentan los datos de comparación de dosis por segmentos de ambas técnicas para el esquema de 36 Gy. En la tabla 5 se muestra la comparación de gradientes por segmentos de columna para ambas técnicas de tratamiento.

En la figura 1 se muestra la comparación de las técnicas de tratamiento; se observa una mayor conformación de la dosis al volumen cráneo-espinal en el plan realizado con VMAT. En la figura 2 se muestra la homogeneidad de distribución de la dosis en columna.

Tabla 1. Características de la serie (n = 101)

Parámetro	
Edad* (años)	9.3 (2 18)
Grupo de edad	n (%)
≤ 5	26 (25.7%)
6 10	34 (33.8%)
11 15	27 (26.7%)
> 15	14 (13.8%)
Sexo	
Masculino	66 (65.3%)
Femenino	35 (34.7%)
Diagnósticos principales	
LLA	40 (39.7%)
Meduloblastoma	32 (31.7%)
Tumor germinal	13 (12.9%)
Otros	16 (15.7%)
Dosis a cráneo (Gy)*	41.9 (22.5-59.4%)
Dosis a columna (Gy)*	25.1 (15-36%)
Técnica de tratamiento	
RC	76 (75.2%)
VMAT	25 (24.8%)

*Expresada en media y rango.
LLA: leucemia linfoblástica aguda; Gy: Gray; RC: radioterapia conformada; VMAT: terapia de arco volumétrico de intensidad modulada.

Discusión

En nuestra serie la media de edad del tratamiento fue de 9.3 años, el grupo de edad predominante fue el de 6-10 años en el 33.8%, lo cual coincide con lo documentado por otras series[5,7,8]. Así mismo, la LLA fue el diagnóstico más frecuente en pacientes, con una incidencia del 39.8% de los casos tratados, seguida por el meduloblastoma en el 31.7%.

Se observó un déficit del crecimiento final de 11.6 cm y de 3.9 cm/año en la VC. Debido a la heterogeneidad del reporte de resultados no es posible hacer una comparación directa con otras series que los reportan con otros parámetros, sin embargo todos son consistentes en la afectación del crecimiento. Mizumoto et al. reportaron en una serie de niños tratados por tumores embrionarios una tasa de crecimiento para los mayores de 15 años de 0.43 ± 0.84 cm/año en los hombres y 0.20 ± 0.54 cm/año en mujeres con un deterioro de la altura del 8.1 y 4.4% respectivamente a los 20 años de edad[8]. Probert y Parker concluyen un déficit de dos desviaciones estándar en la altura en el 36% de los casos tratados por meduloblastoma[11]. A diferencia de otros estudios nosotros utilizamos la media de VC

Tabla 2. Datos clínicos y antropométricos de casos con seguimiento ≥ 5 años (n = 12)

Edad	Sexo	Diagnóstico	Año de Tx	Dosis a columna (Gy)	Talla inicial (cm)	Percentil inicial	VC	Percentil VC	Talla actual (cm)	Talla proyectada (cm)	Escoliosis	Seguimiento (años)
9	M	Pineoblastoma	2018	23.4	126	10.7	5.2	1	152	156	No	6.7
4	M	Meduloblastoma	2018	36	110	96	4	8	132	145	No	6.2
5	M	Meduloblastoma	2018	36	109.5	55	2.9	1	124	139	No	6.1
5	M	PNET	2019	36	112	75	2.5	1	122	137	-	5.7
7	F	Tumor germinal	2019	18	112	3	2.25	1	121	132	No	5.7
4	F	Meduloblastoma	2019	36	111	98	3.75	1	126	137	No	5.5
8	F	Meduloblastoma	2019	36	119	6	3	1	131	140	No	5.5
2	F	Meduloblastoma	2019	23.4	95	99	6.25	50	120	125	No	5.4
10	M	Tumor germinal	2019	36	146	87	0.75	1	149	174	-	5.3
14	M	LLA	2019	15	162	40	0.87	75	165.5	175	No	5.2
9	M	LLA-recaída	2019	15	145	97	2.5	1	155	171	No	5.1
7	M	LLA-recaída	2019	15	120	37	4	9	136	141	No	5

LLA: leucemia linfoblástica aguda; PNET: tumor neuroectodérmico primitivo; Tx: tratamiento; VC: velocidad de crecimiento cm/año.

Tabla 3. Comparación de dosis media por segmentos de columna en técnicas de radioterapia 3D para dosis de 15 Gy (n = 38)

Segmento de columna	Técnica	Media*	p	IC 95%
Cervical derecha	RC	16.09	0.999	–0.372-0.371
	VMAT	16.09		
Cervical izquierda	RC	16.02	0.701	–0.472-0.321
	VMAT	16.15		
Cervical anterior	RC	15.37	0.323	–0.993-0.336
	VMAT	15.70		
Cervical posterior	RC	16.58	0.009	0.261-1.740
	VMAT	15.58		
Torácica derecha	RC	16.55	< 0.001	0.454-1.432
	VMAT	15.60		
Torácica izquierda	RC	16.43	0.006	0.254-1.381
	VMAT	15.61		
Torácica anterior	RC	15.46	0.062	–0.030-1.135
	VMAT	14.91		
Torácica posterior	RC	16.83	< 0.001	0.910-2.885
	VMAT	14.93		
Lumbar derecha	RC	16.21	0.030	0.062-1.147
	VMAT	15.60		
Lumbar izquierda	RC	16.21	0.014	0.141-1.162
	VMAT	15.55		
Lumbar anterior	RC	15.08	0.048	0.007-2.154
	VMAT	14.00		
Lumbar posterior	RC	16.71	< 0.001	0.967-2.684
	VMAT	14.89		

*Expresada en Gy.
IC 95%: intervalo de confianza del 95%; RC: radioterapia conformada; VMAT: terapia de arco volumétrico de intensidad modulada.

Tabla 4. Comparación de dosis media por segmentos de columna en técnicas de radioterapia 3D para dosis de 36 Gy (n = 36)

Segmento de columna	Técnica	Media*	p	IC 95%
Cervical derecha	RC	38.03	0.952	–0.983-0.925
	VMAT	38.06		
Cervical izquierda	RC	38.10	0.776	–0.706-0.937
	VMAT	37.98		
Cervical anterior	RC	36.33	0.029	–2.628 a –0.153
	VMAT	37.72		
Cervical posterior	RC	39.44	0.062	–0.067-2.706
	VMAT	38.12		
Torácica derecha	RC	39.87	0.001	1.318-4.673
	VMAT	36.88		
Torácica izquierda	RC	40.13	< 0.001	1.627-4.598
	VMAT	37.01		
Torácica anterior	RC	37.36	0.076	–0.157-3.041
	VMAT	35.92		
Torácica posterior	RC	40.84	< 0.001	1.945-5.873
	VMAT	36.93		
Lumbar derecha	RC	38.90	0.012	0.362-2.748
	VMAT	37.35		
Lumbar izquierda	RC	38.59	0.071	–0.112-2.583
	VMAT	37.35		
Lumbar anterior	RC	36.36	0.052	–0.115-3.002
	VMAT	34.86		
Lumbar posterior	RC	41.01	< 0.001	2.931-6.586
	VMAT	36.25		

*Expresada en Gy.
IC 95%: intervalo de confianza del 95%; RC: radioterapia conformada; VMAT: terapia de arco volumétrico de intensidad modulada.

alcanzada, pues consideramos que es un parámetro que mejor describe las condiciones individuales. Al final del periodo hubo un aumento del 58% de talla baja en el grupo analizado en comparación con el estado inicial, lo cual se asemeja a lo documentado por Karadag et al. en niños con meduloblastoma, donde el 92.5% de los casos estuvieron por debajo del percentil 50 de la curva de altura para su edad a 37 meses[19].

No observamos escoliosis al corte a los 5 años, debido posiblemente al periodo de latencia tardío. Paulino et al., en su serie de ICE en niños con meduloblastoma tratados antes de los 12 años, describen que la incidencia acumulada de escoliosis a los 15 años fue del 34.6%, con una media de tiempo a la ocurrencia de 7.1 años (rango: 5-11) posterior al tratamiento[15].

Los efectos de la irradiación sobre el crecimiento óseo se manifiestan a largo plazo; la gravedad del

Tabla 5. Comparación de gradientes por segmentos de columna en técnicas de radioterapia 3D (n = 101)

Segmento	Técnica	Mediana (rango)*	p
Cervical D-I	RC	0.6 (0.1-10.1)	0.853
	VMAT	0.5 (0.1-4.20)	
Cervical A-P	RC	10.3 (0.3-22.0)	< 0.001
	VMAT	2.2 (0.1-15.4)	
Torácico D-I	RC	0.9 (0.1-5.2)	0.019
	VMAT	1.6 (0.2-11.6)	
Torácico A-P	RC	8.9 (0.4-18.1)	< 0.001
	VMAT	2.1 (0.4-18.4)	
Lumbar D-I	RC	1.1 (0.1-12.1)	0.747
	VMAT	1.0 (0.1-3.4)	
Lumbar A-P	RC	11.0 (0.6-21.8)	< 0.001
	VMAT	3.0 (0.1-15.1)	

*Expresada en porcentaje.
A-P: antero-posterior; D-I: derecha-izquierda; RC: radioterapia conformada; VMAT: terapia de arco volumétrico de intensidad modulada

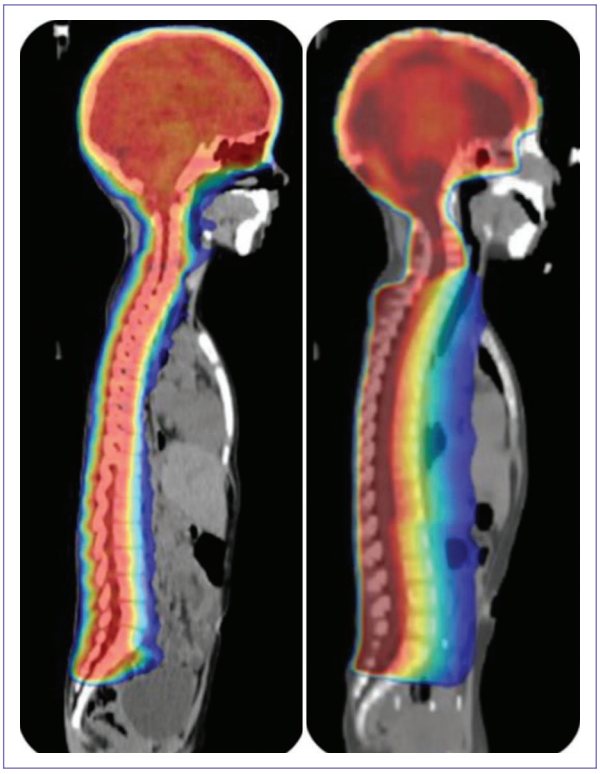

Figura 1. Tomografías en corte sagital en posición supina. Se muestra la distribución de las curvas de dosis en plano lineal. El color rojo representa el 100% y el azul, el 50. La imagen derecha corresponde a la técnica conformada y la izquierda a VMAT.

efecto es difícil de predecir y puede verse afectado por factores como la edad al tratamiento, la dosis total, el fraccionamiento, el volumen, la distribución de dosis, el estado de desarrollo de las placas de crecimiento y otros tratamientos como la quimioterapia, cirugía u otras condiciones como las anomalías endocrinas, nutricionales y las alteraciones del crecimiento óseo[12,16].

La edad temprana en el momento del tratamiento es un factor altamente predictor del efecto. Nanda et al. reportan en una revisión de la literatura que puede ocurrir escoliosis clínicamente significativa con dosis ≥ 15 Gy en menores de 2 años y que los niños menores 3 años fueron los más susceptibles aun a dosis más bajas[16]. Mizumoto et al. informan una tasa de crecimiento significativamente más baja en aquellos pacientes con edad menor de 10 años al momento del tratamiento[8]. Probert y Parker documentan que los niños menores de 6 años al tratamiento fueron más sensibles a los efectos de la irradiación a columna, respecto a la tasa de crecimiento, y que este efecto se observó en dosis menores, como 25 Gy[11].

En lo referente a la dosis a columna Hoben et al., en una revisión de la literatura concluyen un efecto proporcional de la dosis que inicia a partir de los 15 Gy con efectos significativos de retraso en el crecimiento a partir de los 25 Gy[12]. Oshiro et al., en su estudio de ICE pediátrica en tumores del SNC, confirman una relación proporcional dosis-efecto entre los 20-30 Gy y de mayor severidad a partir de los 36 Gy[7]. Hartley et al., en una serie de niños con meduloblastoma y PNET reportaron una mayor reducción en la VC en dosis ≥ 36 Gy[5].

En lo que respecta a la comparación de las técnicas de tratamiento, para la técnica de VMAT observamos una mejor homogeneidad tanto en dosis medias con respecto de la prescripción, como una menor diferencia de gradientes para los distintos segmentos de columna. La conformación a la columna y los tejidos paravertebrales fue mejor con la técnica de VMAT, sin embargo hay una mayor distribución de dosis bajas en el rango del 5-10% de la prescripción a los tejidos periféricos en comparación con la RC. Este aspecto queda a consideración bajo el principio de riesgo-beneficio, debido al riesgo de segundas neoplasias en niños y adolescentes. Meadows et al. describen una incidencia de segundas neoplasias del 9.3% a 30

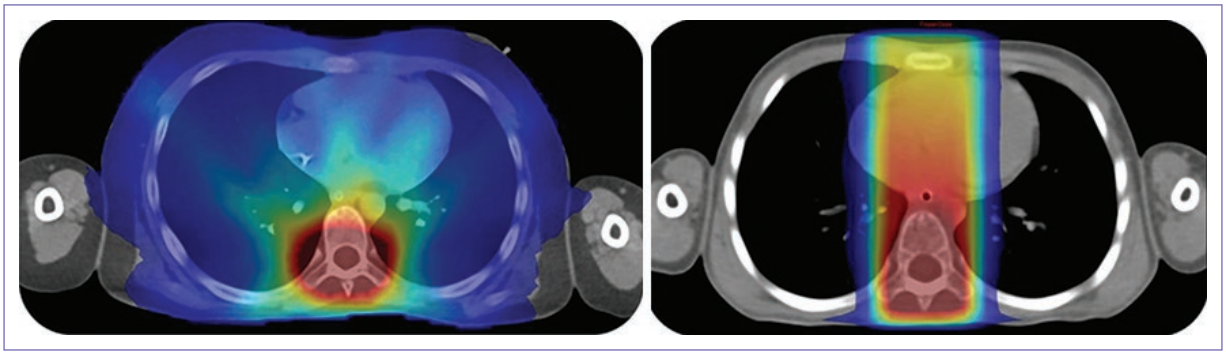

Figura 2. Tomografías en corte transversal. Se observa una irradiación simétrica tanto transversal como anteroposterior con un gradiente de dosis < 5 Gy en los centros de osificación primaria. El color rojo representa el 100% de la dosis y el azul, el 10. La imagen de la derecha corresponde a la técnica conformada y la izquierda a VMAT.

años para la técnica de RC y no disponemos en la actualidad del riesgo correspondiente para la técnica de VMAT[20].

Las limitaciones del estudio fueron la documentación retrospectiva de variables, el tiempo medio de seguimiento de 5 años en los casos analizados, debido a la latencia tardía de los efectos y el número de pérdidas debidas principalmente al pronóstico de la enfermedad. Se requiere de un diseño prospectivo, multicéntrico, con un análisis multivariable para una mejor estimación de los factores predictores de las alteraciones del desarrollo de columna posteriores a ICE. Nuestros resultados deben considerarse como una estimación aproximada, debido a que las referencias antropométricas disponibles no proceden de población infantil mexicana.

En conclusión, las alteraciones del desarrollo de la columna son multifactoriales, resultado de la interacción de factores genéticos, nutricionales y del tratamiento. La edad al tratamiento y la dosis son los mayores predictores de los efectos.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Consideraciones éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad, consentimiento informado y aprobación ética. Los autores han obtenido la aprobación del Comité de Ética para el análisis de datos clínicos obtenidos de forma rutinaria y anonimizados, por lo que no fue necesario el consentimiento informado. Se han seguido las recomendaciones pertinentes.

Declaración sobre el uso de inteligencia artificial. Los autores declaran que no utilizaron algún tipo de inteligencia artificial generativa para la redacción de este manuscrito.

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ORIGINAL ARTICLE

Tumor stromal infiltrating lymphocytes as a prognostic biomarker of survival in human epidermal growth receptor 2-positive early breast cancer

Xiaomei Chavarría-Arriaga[1], *Rocío C. Grajales-Álvarez*[1]*, *Raquel Valencia-Cedillo*[2], *and Abdel K. Dip-Borunda*[1]

[1]*Department of Medical Oncology;* [2]*Department of Anatomical Pathology. Hospital de Oncología, Centro Médico Nacional Siglo XXI, IMSS, Mexico City, Mexico*

Abstract

Background: *Anti-human epidermal growth receptor 2 (HER2) therapies have significantly improved the survival rates of patients with HER2-positive breast cancer. Achieving a pathological complete response (pCR) following neoadjuvant treatment correlates with better prognosis, underscoring the need to identify prognostic biomarkers such as tumor stromal infiltrating lymphocytes (TILs).* **Objective:** *To analyze the expression of TILs as a prognostic marker for disease-free survival (DFS) in patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy with trastuzumab.* **Method:** *This retrospective, analytical, observational cohort study included patients with HER2-positive breast cancer treated at the oncology hospital between January 2018 and December 2021. Histopathological slides were reviewed to determine the proportion of TILs. DFS and overall survival (OS) were estimated using the Log-Rank test and Kaplan-Meier method. The association between categorical variables was assessed with Pearson's χ^2 test. A $p < 0.05$ was considered statistically significant.* **Results:** *One hundred and twenty-one patients were included. The DFS was 72.6 versus 61.9 months (hazard ratio [HR] 0.79, $p = 0.006$), and OS was 76.7 versus 66.1 months (HR 0.83, $p = 0.015$) in patients with TILs ≥ 10% compared to those with < 10%, respectively. The pCR rate was higher in the group with TILs ≥ 10% ($p = 0.03$).* **Conclusions:** *The presence of TILs ≥ 10% in patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy and trastuzumab was associated with increased DFS, OS, and pCR rates.*

Keywords: *Breast cancer. Human epidermal growth receptor 2. Trastuzumab. Tumor stromal infiltrating lymphocytes.*

TIL como biomarcador pronóstico de supervivencia en cáncer de mama temprano HER2-positivo

Resumen

Antecedentes: *Las terapias anti-HER2 han incrementado la supervivencia de pacientes con cáncer de mama HER2 positivo. El impacto en supervivencia al lograr respuesta patológica completa (pCR) a la neoadyuvancia conduce a la necesidad de identificar biomarcadores pronósticos, como los linfocitos infiltrantes del estroma tumoral (TIL).* **Objetivo:** *Analizar la expresión de TIL como marcador pronóstico de supervivencia libre de enfermedad (SLE) en pacientes con cáncer de mama HER2 positivo tratadas con quimioterapia más trastuzumab neoadyuvante.* **Método:** *Cohorte retrospectiva, analítica, observacional. Se incluyeron pacientes con cáncer de mama HER2 positivo tratadas en el Hospital de Oncología entre enero 2018 y diciembre 2021. Se revisaron laminillas histopatológicas para*

***Correspondence:**
Rocío C. Grajales-Álvarez
E-mail: chiograjales@yahoo.com

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determinar la proporción de TIL. La SLE y supervivencia global (SG) se obtuvo por medio del Log Rank test y el método de Kaplan Meier; la dependencia entre variables categóricas, con el test de Chi cuadrada de Pearson (χ^2); tomando una p < 0.05 para la significancia estadística. **Resultados:** *Se incluyeron 121 pacientes. La SLE fue de 72.6 vs. 61.9 meses (HR: 0.79; p = 0.006) y la SG de 76.7 vs. 66.1 meses (HR: 0.83; p = 0.015) con TIL ≥ 10% vs. < 10, respectivamente. La pCR fue mayor en el grupo con TIL ≥ 10% (p = 0.03).* **Conclusiones:** *La expresión de TIL ≥ 10% en pacientes con cáncer de mama HER2 positivo tratadas con quimioterapia más trastuzumab neoadyuvante presentó un incremento en SLE, SG y pCR.*

Palabras clave: *Cáncer de mama. Receptor de crecimiento epidérmico humano tipo 2. Trastuzumab. Linfocitos infiltrantes del estroma tumoral.*

Background

The incorporation of anti-human epidermal growth receptor 2 (HER2) targeted therapies into neoadjuvant chemotherapy for HER2-positive breast cancer has successfully increased the rates of pathological complete response (pCR), defined as the absence of invasive tumor in the breast and lymph nodes (ypT0/is ypN0 or ypT0 ypN0)[1], to approximately 60-68%, with greater benefit observed in patients with hormone receptor-negative tumors[2-6]. Despite these advances, up to 50% of patients do not achieve this response. The impact of pCR as a surrogate marker for survival[7] has prompted a focus on new strategies based on the evaluation of immunological biomarkers capable of providing predictive and prognostic information, such as tumor stromal infiltrating lymphocytes (TILs)[8].

TILs are a diverse set of immune cells located within the tumor microenvironment, reflecting the host's immune activity against the tumor. They are predominantly composed of CD8+ T cells[9]. *In vitro* studies have demonstrated that these cells can proliferate up to 10 times more than normal immune cells, limiting tumor growth by 40-50% and achieving complete regression in 10-20% of patients undergoing oncological treatment[10]. The presence of TILs has been associated with high-grade tumors, HER2-positive or triple-negative breast cancers, and correlates with a better response to chemotherapy, as well as a reduced risk of relapse and mortality, with reductions of up to 10%[11-13].

This study aims to analyze the presence of TILs as a prognostic marker for disease-free survival (DFS) in patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy combined with trastuzumab. In addition, the study seeks to evaluate the association between TILs and pCR. Our objective is to provide relevant data regarding the value of TILs in Mexican women, with the ultimate goal of optimizing therapeutic decision-making and promoting a more personalized and effective approach to HER2-positive breast cancer management.

Materials and methods

An observational, longitudinal, retrospective, and analytical study was conducted. Patients with a histopathological diagnosis of HER2-positive breast cancer, confirmed by immunohistochemistry or amplification by *in situ* hybridization (ISH), and treated at the Oncology Hospital of the Centro Médico Nacional Siglo XXI between January 1, 2018, and December 30, 2021, were included. The patients received neoadjuvant chemotherapy in combination with trastuzumab, had evaluable histopathological and immunohistochemical slides, and a complete surgical report. Patients with metastatic disease, a second primary cancer, incomplete treatment, or trastuzumab discontinuation due to toxicity were excluded. In addition, patients with non-evaluable slides were eliminated from the study.

In collaboration with the pathology department, the histopathological slides of each patient were evaluated to identify TILs, categorizing them as low (< 10%) and high (≥ 10%). In addition, variables such as age, neoadjuvant chemotherapy regimen, clinical stage, histological grade, lymphovascular invasion, hormone receptor expression, and Ki67 proliferation index were incorporated. For univariate analysis, measures of central tendency and dispersion were used for quantitative variables, whereas frequencies and proportions were employed for qualitative variables. Overall survival (OS) and DFS were calculated according to TIL levels using the Log-Rank test and the Kaplan–Meier method. The association between categorical variables was assessed using the Pearson χ^2 test, with a $p < 0.05$ considered statistically significant.

The Epi-Info 7 software facilitated the development of databases and data analysis through statistical methods, graphical representations, and epidemiological mapping. Data analysis was conducted using SPSS version 25.

The protocol received approval from the research and ethics committees, in accordance with the General Health Law and the Declaration of Helsinki. This

observational study was reported in accordance with the strengthening the reporting of observational studies in epidemiology guidelines. This is retrospective and non-risk, and does not require informed consent, as there was no direct contact with patients; data were obtained from clinical records and pathology materials. Information was handled confidentially and anonymously, with access restricted solely to the principal investigator, who held the encrypted data. Confidentiality agreements were signed, and a privacy notice was issued. No external support or funding was utilized, and the authors declare no conflicts of interest.

Results

Between January 2018 and December 2021, a total of 145 HER2-positive patients received neoadjuvant treatment with chemotherapy and trastuzumab. Of these, 24 patients were excluded due to the lack of adequate pathological material for analysis or incomplete follow-up data in their medical records. Consequently, 121 patients were included in this study, as depicted in the CONSORT diagram **(**Fig. 1). The median follow-up duration was 40 months. The mean age was 54.9 years (± 10.96). A total of 86% of patients (n = 103) presented with locally advanced disease (stages IIB-IIIC), and 40.3% (n = 49) expressed estrogen receptor positivity. Two-thirds of the cohort (67.8%, n = 82) exhibited TILs ≥ 10%. The clinical and pathological characteristics are summarized in table 1.

More than 90% of the patients received chemotherapy regimens including anthracyclines (AC-TH, EC-TH) (doxorubicin/epirubicin, cyclophosphamide, taxane, and trastuzumab). Radical surgery was performed in 90% of cases; 93.4% received adjuvant trastuzumab, and 94.2% underwent radiotherapy.

DFS

DFS at 2 years was 79.3%. A significant benefit was observed in patients with TILs ≥ 10%, with a median DFS of 72.6 months (95% confidence interval [CI], 68.8-74.7) compared to 61.9 months (95% CI, 53.8-69.9) in patients with TILs < 10%. The hazard ratio (HR) was 0.79 (95% CI, 0.73-0.97; p = 0.006), as shown in figure 2. Among the 20.7% of patients who experienced recurrence, 8.26% had local or nodal recurrence, followed by 3.3% with bone metastases and 3.3% with pulmonary metastases, which were the most frequent sites (Table 2).

OS

Patients with TILs ≥ 10% showed a median OS at 2 years of 76.7 months (95% CI, 74.0-79.4), compared to 66.1 months (95% CI, 60.2-71.9) in patients with TILs < 10% (HR 0.83; 95% CI, 0.81-0.98; p = 0.015), as shown in figure 3.

TILs

Univariate analysis demonstrated that the proportion of TILs was independent of histological type, clinical stage, or tumor grade; however, statistically significant associations were found regarding recurrence (p = 0.004), absence of progression during neoadjuvant chemotherapy (p = 0.03), pCR (p = 0.03), and lower breast cancer-specific mortality (p = 0.007) in the group with TILs ≥ 10%. This information is summarized in table 3.

pCR

Sixty-one point seven percent of patients achieved a pCR (n = 51). Of these, 78.4% had TILs ≥ 10%, while 21.6% had TILs < 10%. The pCR rate with TILs ≥ 10% was 60.8%, compared to 39.2% with TILs < 10% (p = 0.03) as shown in figure 4.

An exploratory analysis was conducted to evaluate DFS in relation to TIL expression and pCR. In patients with TILs ≥ 10% and pCR, DFS was 73.5 months versus 59.9 months in patients without pCR. In those with TILs < 10% and pCR, DFS was 58.0 months versus 52.4 months in patients without pCR (HR 2.07, 95% CI 1.35-3.17; p = 0.002), as illustrated in figure 5.

Discussion

The association between immune cell infiltration in breast cancer and its prognostic impact has been recognized over the past decade. TILs can enhance the efficacy of chemotherapy, induce tumor cell death, and play a role in controlling cancer progression. Although various studies have demonstrated that TILs are an independent factor for predicting the effectiveness of neoadjuvant therapy in breast cancer patients, these results vary due to tumor heterogeneity[14].

Regarding DFS, it has been shown that TILs are a favorable prognostic factor, meaning they decrease the risk of breast cancer recurrence, particularly in HER2-positive and triple-negative tumors. A meta-analysis by Li et al. evaluated 9,145 patients with

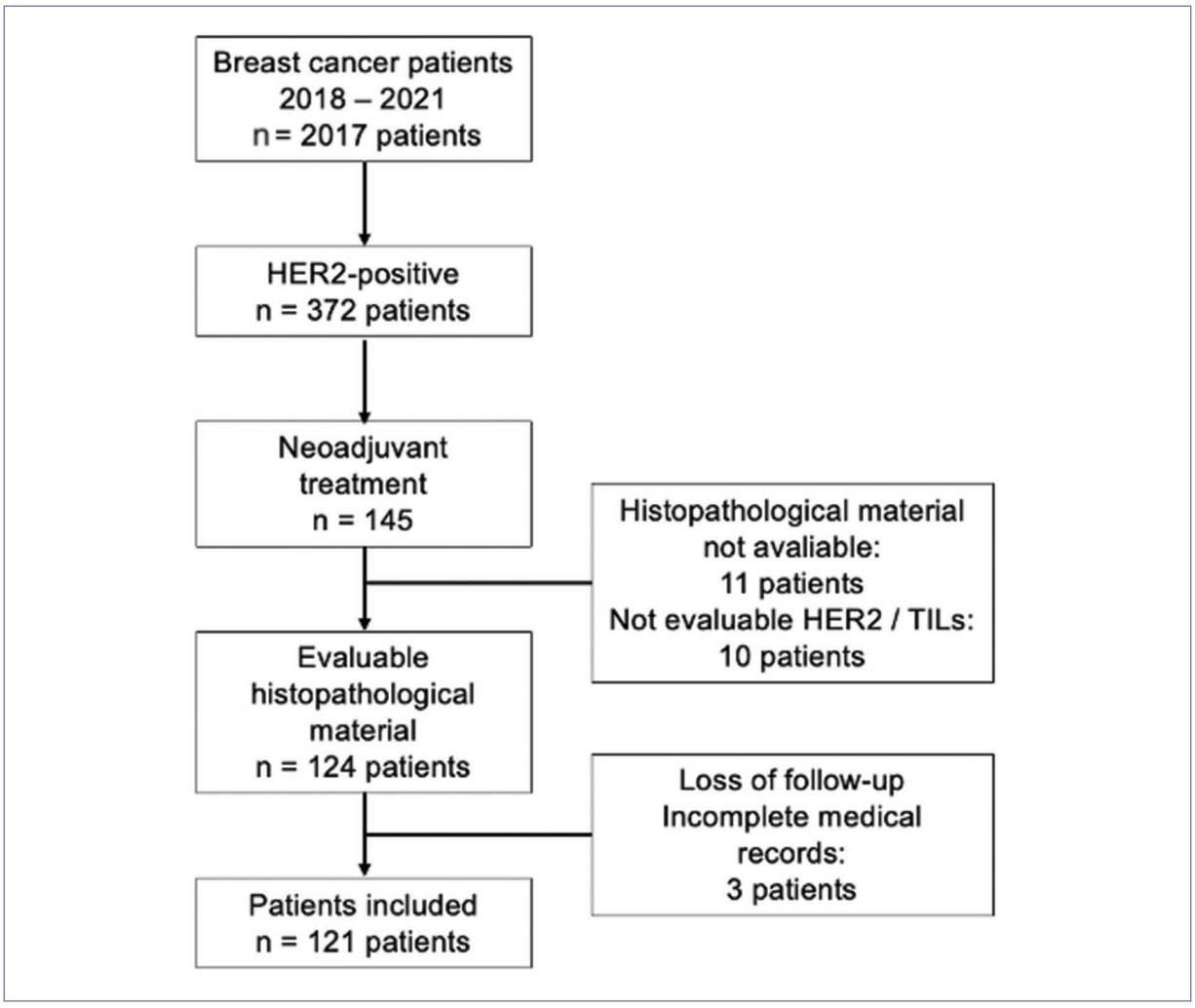

Figure 1. CONSORT diagram.

HER2-positive breast cancer. Elevated TIL levels were associated with greater benefit in DFS (HR 0.96) and OS (HR 0.90); in addition, a TIL threshold of 20% was most effective in predicting pCR in these patients (p = 0.035)[15].

In the Latin American population, specifically in Mexico, there are few relevant studies on this topic. Initially, research was conducted in patients with triple-negative breast cancer; in a study involving 62 patients, low TIL infiltration was associated with more advanced clinical stages, suggesting that TILs may serve as a useful prognostic factor. This study represents one of the first investigations in Mexico to evaluate this relationship, proposing the inclusion of TIL assessment as a routine parameter in pathology reports[16].

Subsequently, TILs were analyzed as a predictive factor for treatment response in 53 patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy and trastuzumab. Although no statistical significance was observed for the primary endpoint, a trend toward better DFS and higher response rates was noted in patients with a higher percentage of TILs (> 25%). However, this study highlights the limited sample size[17].

In our study, we demonstrated that, similar to findings in Asian and European populations, in the Mexican population treated in a neoadjuvant setting with anti-HER2 therapy, TILs ≥ 10% serve as a prognostic factor. This is evidenced by a significant benefit in 2-year DFS, with a median of 72.6 months in patients with TILs ≥ 10% compared to 61.9 months in those with TILs < 10%, and a 21% reduction in recurrence risk (HR 0.79, 95% CI 0.73-0.97; p = 0.006). These findings support the role of TILs as a useful prognostic biomarker, as their presence reflects heightened immune activity

Table 1. Clinical and histopathological characteristics of the patients

Variable	Frequency (n = 121) No.	%
Age, mean±SD	54.9±10.96	
Histological type		
Ductal	112	92.56
Lobular	7	5.79
Others	2	1.65
Clinical stage		
I	2	1.6
IIA	15	12.4
IIB	25	20.7
IIIA	47	38.8
IIIB	16	13.2
IIIC	16	13.2
Histological grade		
G1	1	0.8
G2	60	49.6
G3	60	49.6
Tumor-infiltrating lymphocytes in the tumor stroma (TILs %)		
Low (TILs < 10%)	39	32.2
High (TILs ≥ 10%)	82	67.8
Neoadjuvant treatment		
AC-TH	67	55.4
EC-TH	45	37.2
TCb-HP	3	2.5
TCbH	6	5
Type of surgery		
Radical mastectomy	109	90
Breast-conserving surgery	12	10
Adjuvant Trastuzumab		
Yes	113	93.4
No	8	6.6
Adjuvant radiotherapy		
Yes	114	94.2
No	7	5.8

SD: standard deviation; G: grade; A: doxorubicin; C: cyclophosphamide; E: epirubicin; H: trastuzumab; T: docetaxel; Cb: carboplatin, P: pertuzumab; TIL: tumor stromal infiltrating lymphocytes.
Source: Medical Oncology Department, Oncology Hospital. Centro Médico Nacional Siglo XXI.

Table 2. Recurrence patterns

Site of recurrence	(n = 25) No.	%
Local/regional	5	4.13
Nodal	5	4.13
Bone	4	3.31
Pulmonary	4	3.31
Lymphangitic carcinomatosis	1	0.83
Liver	1	0.83
Central nervous system	1	0.83
Soft tissues/skin	3	2.48
Progression during neoadjuvant chemotherapy	2	1.65
Yes	119	98.35
No		

Source: Medical Oncology Department, Oncology Hospital. Centro Médico Nacional Siglo XXI.

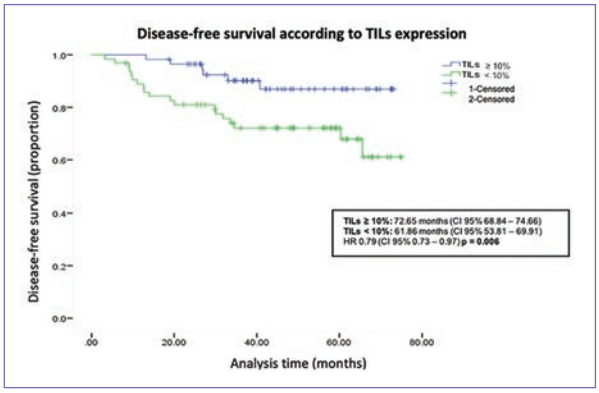

Figure 2. Disease-free survival according to tumor-infiltrating lymphocytes (TILs) expresión. Kaplan-Meier curve for DFS based on the percentage of TILs. A significantly longer DFS was observed in patients with TILs ≥ 10%, with a median of 72.65 months (95% confidence interval [CI], 68.84-74.66), compared to 61.86 months (95% CI, 53.81-69.91) in the group with TILs < 10%. The hazard ratio was 0.79 (95% CI, 0.73–0.97; p = 0.006). *Source: Medical Oncology Department. Oncology Hospital, Centro Médico Nacional Siglo XXI.*

within the tumor microenvironment, which may restrict disease progression or eliminate residual disease post-treatment. Similarly, the low recurrence rate observed in patients with TILs ≥ 10% reinforces the premise that these patients could be more responsive to standard therapies, potentially avoiding exposure to more intensive treatments.

Regarding 2-year OS, patients with TILs ≥ 10% exhibited improved OS (76.7 months) compared to those with TILs < 10% (66.1 months), with a 17% reduction in the risk of death (HR 0.83, 95% CI 0.81-0.98; p = 0.015). The markedly low mortality rate in the TILs ≥ 10% group (2 of 82 patients, with no cancer-specific deaths) contrasts sharply with the TILs < 10% group, which experienced 10 deaths, 8 directly attributable to breast cancer.

Table 3. Univariate analysis for factors associated with TILs expresion

Cathegory	TILs				χ^2	p
	TILs ≥ 10%		TILS < 10%			
	n	%	n	%		
Histological type						
Ductal invasive	79	65.3	33	27.3	5.6	0.06
carcinoma	2	1.7	5	4.1		
Lobular carcinoma	1	0.8	1	0.8		
Others						
Clinical stage						
I	2	1.7	0	0.0	5.03	0.41
IIA	12	9.9	3	2.5		
IIB	17	14.0	8	6.6		
IIIA	27	22.3	20	16.5		
IIIB	12	9.9	4	3.3		
IIIC	12	9.9	4	3.3		
Histologic grade						
G1	1	0.8	0	0.0	0.51	0.77
G2	40	33.1	20	16.5		
G3	41	33.9	19	15.7		
Neoadjuvant treatment						
AC-TH	49	40.5	18	14.9	16.68	0.406
EC-TH	28	23.1	17	14.0		
EC-THP	2	1.7	1	0.8		
TCH	3	2.5	3	2.5		
Recurrence						
Yes	11	9.1	14	11.6	8.15	0.004
No	71	58.7	25	20.7		
Site of recurrence						
Local/regional	1	0.8	4	3.3	14.79	0.06
Nodal	2	1.7	3	2.5		
Bone	3	2.5	1	0.8		
Pulmonary	3	2.5	1	0.8		
Lymphangitic	0	0.0	1	0.8		
carcinomatosis	0	0.0	1	0.8		
Liver	0	0.0	1	0.8		
Centrall nervous system						
Soft tissues/skin	2	1.7	1	0.8		
Progression during neoadjuvant treatment						
Yes	0	0.0	2	1.7	4.27	0.03
No	82	67.8	37	30.6		
Site of progression						
Local	0	0.0	2	1.7	4.27	0.03
NA	82	67.8	37	30.6		
pCR						
Yes	31	60.8	20	39.2	4.58	0.03
No	26	37.1	44	62.9		
Cancer-specific mortality						
Death	4	3.3	8	6.6	7.23	0.007
Alive	78	64.5	31	25.6		

G: grade; A: doxorubicin; C: cyclophosphamide; E: epirubicin; H: trastuzumab; T: docetaxel; Cb: carboplatin, P: pertuzumab; pCR: pathological complete response; NA: not apply; TIL: tumor stromal infiltrating lymphocytes.
Source: Medical Oncology Department. Oncology Hospital, Centro Médico Nacional Siglo XXI.

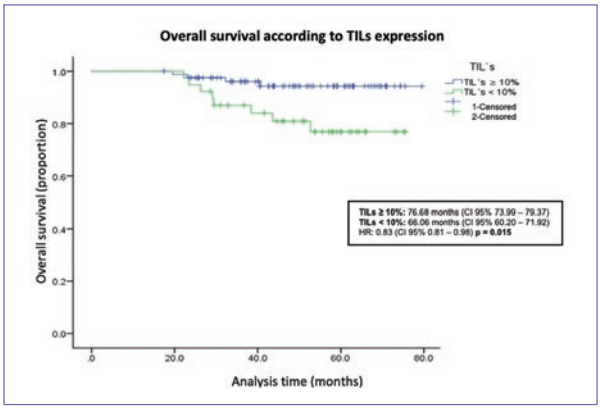

Figure 3. Overall survival according to tumor-infiltrating lymphocytes (TILs) expression. Kaplan-Meier survival curve for OS according to the percentage of TILs. Patients with TILs ≥ 10% demonstrated a median overall survival (OS) of 76.7 months (95% confidence interval [CI]: 73.99-79.37), which was superior to that of the group with TILs < 10%, who exhibited a median OS of 66.1 months (95% CI: 60.20-71.92). The difference between the groups was statistically significant (Hazard ratio 0.83, 95% CI: 0.81-0.98; p = 0.015). *Source: Medical Oncology Department. Oncology Hospital, Centro Médico Nacional Siglo XXI.*

In terms of treatment response, we observed a significant association between elevated TILs levels (≥ 10%) and higher rates of pCR. Of the patients achieving pCR, 78.4% had TILs ≥ 10%, compared to 21.6% with TILs < 10% (p = 0.03). This difference further underscores the utility of TILs not only as a prognostic marker but also as a predictive indicator of treatment response.

These findings are consistent with international literature. The meta-analysis by Li et al. demonstrated that TILs are a prognostic biomarker, particularly in triple-negative and HER2-positive breast cancers–subtypes where immunogenicity is more pronounced–and identified TILs as an independent predictor of pCR. An immunologically active tumor microenvironment appears to enhance the efficacy of chemotherapy by promoting tumor cell destruction. The nearly 11-month difference in DFS and OS between the groups suggests a dynamic interaction between the tumor and the host immune system, which can significantly influence disease progression and survival. A tumor microenvironment rich in TILs confers better disease control, possibly due to a more effective immune response or residual sensitivity to subsequent treatments, as previously demonstrated in the NeoALTTO trial[13].

Recently, the ShortHER trial compared the standard sequential regimen of four cycles of anthracyclines

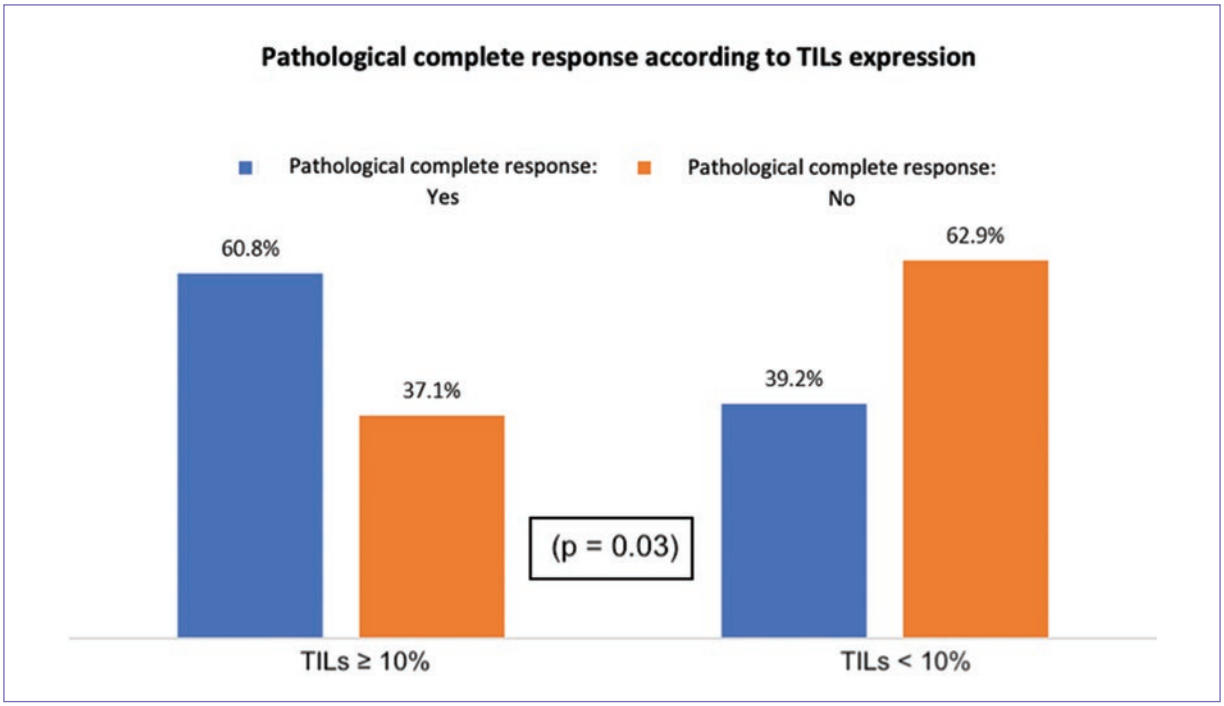

Figure 4. Pathological complete response (pCR) according to tumor-infiltrating lymphocytes (TILs) expression. Patients with a higher proportion of TILs achieved a pCR of up to 60.8%, compared to 39.2% in those with TILs < 10%. *Source: Medical Oncology Department. Oncology Hospital, Centro Médico Nacional Siglo XXI.*

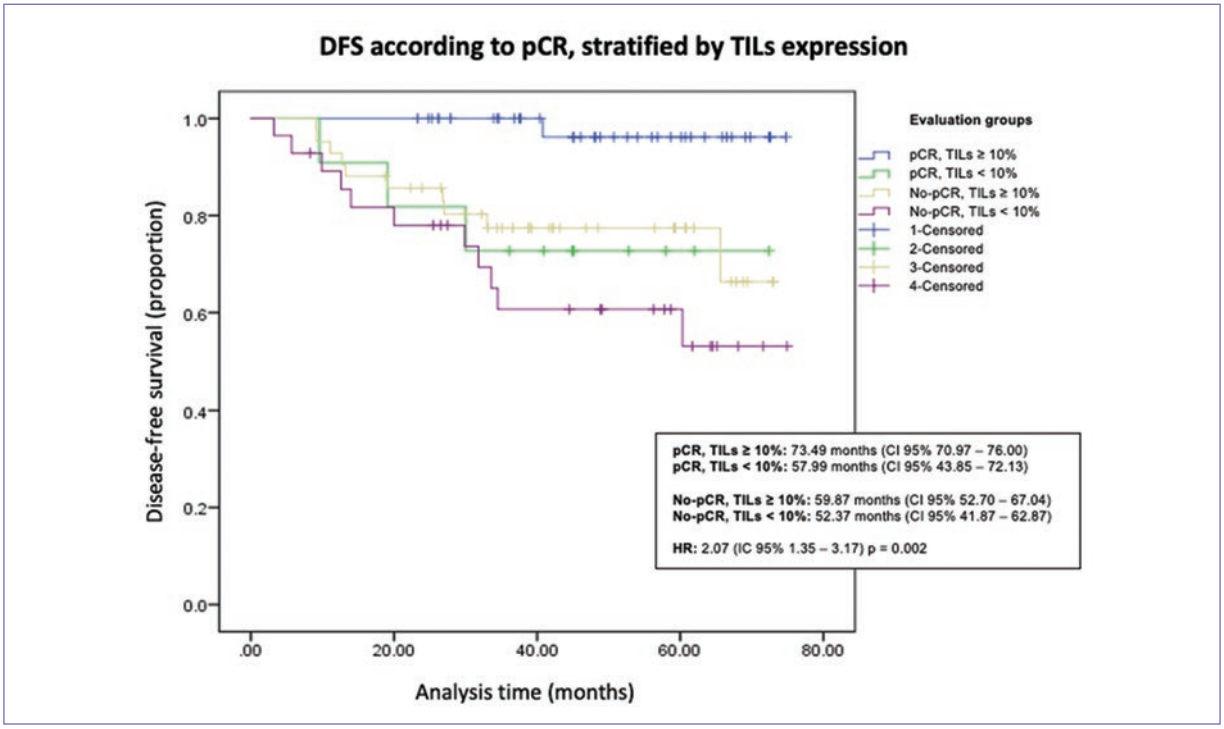

Figure 5. Disease-free survival according to pathological complete response (pCR), stratified by tumor-infiltrating lymphocytes (TILs) expression. Kaplan-Meier curve of EFS according to pCR and TILs percentage.Patients with TILs ≥ 10% and pCR had a longer EFS (73.49 months) compared to 57.99 months in patients with TILs < 10% and pCR. In patients with non-pCR, EFS was 59.87 months for TILs ≥ 10% and 52.37 months for TILs < 10%, hazard ration 2.07, 95% confidence interval, 1.35-3.17; p = 0.002. *Source: Medical Oncology Department. Oncology Hospital, Centro Médico Nacional Siglo XXI.*

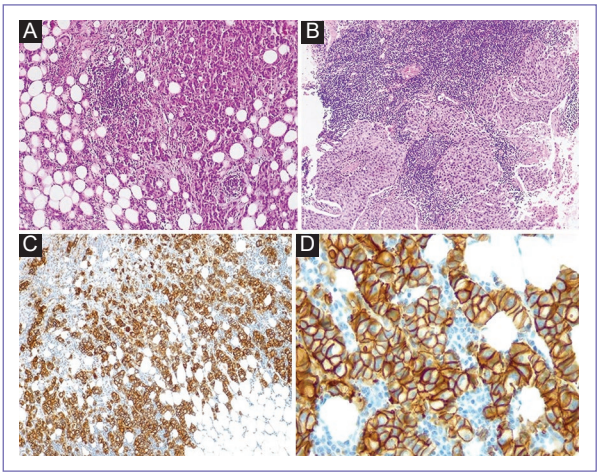

Figure 6. Photograph of tissue sections from a patient with human epidermal growth receptor 2 (HER2)-positive breast cancer, with an 80% tumor-infiltrating lymphocytes (TILs) report. **A:** invasive ductal carcinoma with a non-special pattern, grade 3 according to the Scarff-Bloom-Richardson grading system, accompanied by TILs. (HE10×). **B:** invasive ductal carcinoma with a non-special pattern, grade 3 according to the Scarff-Bloom-Richardson grading system, accompanied by intratumoral and peritumoral infiltrating lymphocytes (HE10×). **C:** HER2-positive breast cancer and TILs, exhibiting HER2 overexpression (3+) (HE10×). **D:** (HE40×). *Source: Medical Oncology Department. Oncology Hospital, Centro Médico Nacional Siglo XXI.*

followed by four cycles of taxanes and trastuzumab for 1 year with a shorter regimen consisting of three cycles of anthracyclines followed by three cycles of taxanes and a total of nine doses of trastuzumab in an adjuvant setting. With a 10-year follow-up, DFS was 91.3% in patients with TILs ≥ 20%, 93.3% in those with TILs ≥ 30%, and 98% in patients with TILs ≥ 50%, with statistically significant differences. Patients with TILs < 20% experienced greater benefit from the extended treatment (DFS at 10 years: 88.7 vs. 81.0%), whereas those with TILs ≥ 20% showed better DFS with the shorter regimen (87.1 vs. 92.2%; p = 0.01)[18].

These findings suggest that TILs could be useful for risk stratification, aiding in the selection of patients who may benefit from more intensive treatments or, conversely, from treatment de-escalation–particularly in contexts with limited access to targeted therapies.

It is noteworthy that, in the exploratory analysis conducted in our study, patients with TILs ≥ 10% and pCR had a median DFS of 73.5 months, compared to 59.9 months in patients without pCR. Conversely, patients with TILs < 10% exhibited a DFS of 58.0 months versus 52.4 months in those with and without pCR, respectively (p = 0.03). This underscores the expression of TILs as a more relevant prognostic factor than pCR in patients with HER2-positive breast cancer.

Overall, the interaction between TILs and pCR not only enhances DFS but could also be utilized to identify patients with a favorable prognosis even in the presence of residual disease. This supports their integration into personalized prognostic models.

These findings also highlight the need to standardize cutoff points in the assessment of TILs. Although a threshold of ≥ 10% proved useful in our study–primarily based on Asian studies–other research has proposed values such as 20 or even 30%, indicating methodological heterogeneity that currently limits universal application[19,20].

Among the limitations identified in this work is the retrospective nature of the study, where TILs measurement on slide review was performed by a single pathologist with specialized expertise in breast cancer. Consequently, there was no double verification or assessment of interobserver concordance. However, evaluating TILs through optical microscopy on hematoxylin and eosin-stained sections **(**Fig. 6) is feasible within routine clinical practice at secondary and tertiary care levels. Nonetheless, specific training in TILs interpretation is necessary for general pathologists reviewing breast cancer specimens. The reproducibility of TILs reporting is achievable, but heterogeneity remains a source of bias. It would be advisable to automate this assessment universally, as results may vary depending on the experience of different pathologists interpreting TILs.

Another significant limitation of our study is that it was based solely on the use of trastuzumab as an anti-HER2 therapy, due to limited access to dual blockade regimens with pertuzumab in our hospital unit. Therefore, we consider it ideal to replicate this methodology using these treatment schemes to compare results.

At the oncology hospital, approximately 600 breast cancer patients are treated annually, of whom 20% are HER2 positive. This highlights the necessity of having reliable biomarkers to categorize patients according to their risk, thereby guiding (de)escalation of therapies. The measurement of TILs expression does not require the implementation of additional equipment or materials.

Prospective trials are needed to validate the utility of TILs with longer follow-up periods and updated therapies, with the aim of incorporating their assessment into routine histopathological reports and establishing their use as an accessible, reproducible, and clinically relevant prognostic biomarker.

Conclusions

The expression of TILs ≥ 10% in patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy plus trastuzumab was associated with improved DFS, OS, and complete pathological response.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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