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Caracterización inmunohistoquímica del cáncer de mama correlacionado con histopatología, estudio realizado en un hospital de Ecuador

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Abstract

Breast cancer is the most common type in the female population, and ranks first in mortality with 10.9 % and an incidence of 38.2 % of all causes of cancer in women. The objective of this study was to determine the immunohistochemical characteristics of breast cancer and its histopathology correlation. An observational, retrospective, and correlational study was carried out that involved from 2019 to 2021 with information obtained from the pathology department of the Luis Vernaza hospital in Guayaquil, Ecuador. In this research, the results were that the most frequent breast tumor, according to pathology, was invasive ductal carcinoma in 78 %. All patients with ductal carcinoma in situ were estrogen, progesterone, and Ki67 receptors < 10 % in the vast majority (83 %). Patients with invasive lobular carcinoma had the vast majority of estrogen receptors, progesterone positive, and Ki67 > 10 %. In patients diagnosed with invasive ductal carcinoma, the overexpressed intrinsic molecular subtype HER2/neu predominated. Molecular markers obtained by immunohistochemistry are important for the classification of breast cancer subtypes, treatment selection, and prediction of prognosis. In this study, great variability and heterogeneity were noted in the different tumors, which gives them a different prognosis and therapeutic approach.

Resumen

El cáncer de mama es el tipo más frecuente en la población del sexo femenino, y ocupa el primer lugar en mortalidad con 10.9 % y una incidencia de 38.2 % de todas las causas de cáncer en mujeres. El objetivo de este estudio fue determinar las características inmunohistoquímicas del cáncer de mama y su correlación histopatología. Se efectuó un estudio observacional, retrospectivo y correlacional que involucró desde el año 2019 al 2021 con información obtenida del departamento de patología del hospital Luis Vernaza en Guayaquil-Ecuador. En esta investigación se obtuvo como resultados que el tumor de mama más frecuente, según patología fue el carcinoma ductal invasivo en un 78 %. Todas las pacientes con carcinoma ductal in situ presentaron receptores de estrógeno, progesterona positivos y Ki67 < 10 % en su gran mayoría (83%). Las pacientes con carcinoma lobulillar invasor presentaron en su gran mayoría receptores de estrógenos, progesterona positivo y Ki67 > 10 %. En las pacientes diagnosticadas con carcinoma ductal invasor predominó el subtipo molecular intrínseco HER2/neu sobre expresado. Los marcadores moleculares que se obtienen mediante inmunohistoquímica son importantes para la clasificación de los subtipos de cáncer de mama, la selección de tratamiento y la predicción del pronóstico. En este estudio se notó una gran variabilidad y heterogeneidad en los diferentes tumores lo que les otorga un pronóstico y enfoque terapéutico diferente.

Introduction

There is currently a high prevalence of breast cancer (BC)[1]. Ecuador in 2022 presented an increase of 23.0 % in new cases of BC with a total of 3903, the incidence and mortality according to statistics published by the Global Cancer Observatory of the International Agency for Cancer Resources that belong to the World Health Organization (WHO) indicate that BC ranks first in mortality in the female population[2]. This occurs when the cells of the mammary gland grow uncontrollably, evading mechanisms that control cell multiplication, causing proliferation without response to regulation, causing a heterogeneous disease that presents different clinical, pathological, molecular, prognostic and therapeutic forms[3]. It is appropriate to highlight the prevention and early screening of BC, since, when detected in early stages, there is a lower risk of metastasis, as well as a greater chance of survival and cure, up to 80 %, in women treated in early stages[4]. BC is not a single entity, but a heterogeneous group of diseases with highly variable clinical behavior[5]. p53, a gene that participates in cell division and mobility, preventing irregular growth[5]. When BRCA genes are defective, cellular repair and regulation are impaired, leading to the formation of cancer cells[6].

Breast carcinoma in situ is a neoplasm of the ducts and lobules, which can progress to invasive carcinoma, the presentation includes, breast tumor that may be palpable, discharge through the nipple and Paget's disease of the nipple[7,8].

Of the types of invasive carcinoma, infiltrating ductal carcinoma, the most common of the BC, occupies 70-75 % of cases, and reveals a spiculated mass that is sometimes associated with microcalcifications, is firm, poorly defined, with a yellow or grayish surface of a stellate shape[9]. Lobular carcinoma, a type of tumor with poorly defined borders, variable size, from inapparent lesions or tumors that can occupy the entire breast, bilateral in 25 to 50 %. Its immunohistochemistry (IHC) is positive for hormone receptors, and it is rarely reactive for HER2/neu[10,11]. Medullary carcinoma is macroscopically 4 to 6 cm in diameter, rounded, soft, pale to gray, and may present hemorrhage and necrosis, less than 10 %, positive for hormone receptors[10].

The Nottingham grading system assesses, i) degree of tubule formation, ii) nuclear grade: assesses the size and shape of the tumour cell nucleus, iii) mitotic rate: they are given a score from 1 to 3, "1" means that the cells and tumour tissue look mostly the same as usual tissue, and the score of "3" means that the cells and tissue look mostly defective. Hence, there are 3 grades: i) total score 3-5: G1 (low grade, well differentiated), ii) total score 6-7: G2 (intermediate grade, moderately differentiated), iii) total score 8-9: G3 (high grade, poorly differentiated)[12].

IHC has important applications in the diagnosis of breast pathology, from supporting and differentiating between benign epithelial hyperplasias and neoplastic proliferations, to serving as a predictive and prognostic biomarker that intervenes to guide the patient's treatment[13].

Molecularly, BC is classified into 4 intrinsic subtypes that include luminal A, luminal B, enriched with HER2/neu, normal-like and claudin-low according to the presence or absence of the 3 primary markers (ER, PR and HER2)[14].

The main biomarkers are ER, PR, HER2/neu and (Ki67 antigen)[14]. The term "luminal" is used because this type of BC is present in the luminal (internal) epi

thelial cells of the breast[14]. The luminal subtype was separated as luminal A and B, depending on the expression of HER2/neu, thus, luminal A is HER2/neu - and luminal B is HER2/neu positive[11,14], luminal group A is likely to benefit from hormone therapy alone, while luminal B tumors with their greater proliferation may be candidates for chemotherapy[14].

Regarding hormone receptors, there is evidence of an association between the presence of hormone receptor and a more favorable prognosis, its presence identifying tumors that are sensitive to hormonal treatment. The estrogen receptor was recognized for a long period as the most important predictive and prognostic biomarker in BC[15].

HER2/neu gene amplification, or overexpression, is found in 15-20 % of BCs, and is related to aggressive clinical behavior. Clinically, HER2 has an application to know the prognostic and predictive value of the disease. An accurate HER2/neu result is paramount for optimal patient management. Its overexpression occurs in approximately 20 % of the BCs. With the development of monoclonal antibodies against HER2/neu, many studies reported that therapies directed at it improve survival in HER2-positive patients with early and advanced BC[16].

Ki67, a protein of the non-histone nuclear cortex, involved in the first steps of polymerase I-dependent ribosomal RNA synthesis. The molecule was named Ki after the University of Kiel and 67 after the number of antibody clones capable of detecting it. Ki67 expression varies throughout the cell cycle, reaching the maximum level during mitosis[17].

Ki67 measures tumor cell proliferation that occurs during mitosis, using IHC techniques. IHC Ki67 has limited value for treatment decisions due to its questionable analytical validity[18]. The Breast Cancer Working Group (IKWG) evaluated the analytical validity and clinical utility of Ki67 IHC in BC and concluded that clinical utility is evident only for the estimation of prognosis in anatomically favorable estrogen receptor-positive, HER2/neu-negative patients to identify those who do not need adjuvant chemotherapy[18].

Triple-negative BC lacks biomolecular expression, is characterized by rapid disease progression, and has limited therapy regimens and lower survival compared to other types because it does not respond to hormonal therapy due to the lack of expression of (ER, PR, and HER2)[19].

IHC is an essential constituent in the screening of breast pathology, it allows us to know the presence or not of the hormone receptor (HR), the presence of the HER2/neu receptor and the percentage of KI67 that each type of BC[18].

Histological grading and immunohistochemical evaluation of EP, PR, HER2, and the Ki67 proliferation index play a crucial role in the differential diagnosis between the different types of breast carcinoma, and this is where the importance of correlating IHC with histopathology lies[20].

The objective was to determine the immunohistochemical characteristics of breast cancer and its histopathological correlation.

Materials and methods

Prior authorization from the Research Headquarters of the Luis Vernaza Hospital in Guayaquil, Ecuador, by Dr. Daniel Tettamanti, who authorized the use of instruments for data collection and thus be able to carry out the observational, retrospective and correlational study that covered from 2019 to 2021, complying with the ethical requirements for its development. By means of an Excel data sheet that rested in

the databases of the hospital's pathology department, granted and reviewed by an expert pathologist Dr. Maritza Guerrero, Head of the hospital's pathology service, information was collected from patients who were treated for a malignant breast tumor, the results of IHC (estrogen receptor positive, low positive, negative, progesterone receptor positive or negative, HER2/neu Score 0, Score1+ Score 2+ Score 3 +, Ki67 < 10%) or Ki67> 10 % and histopathology (ductal-lobular-in situ-invasive), nuclear grade (grade 1, 2 or 3).

For its analysis, the information was divided into groups according to the subtype of tumor diagnosed. The data sheet contained variables such as: age, histopathological diagnosis and IHC. The data were tabulated and entered into an Excel spreadsheet and analyzed by the Epi Info 7 program.

Type and design of the study. Observational, retrospective and correlational study that covered from 2019 to 2021.

Universe and sample. 68 reports of women treated in the outpatient clinic of the Luis Vernaza Hospital during the years 2019 to 2021.

Inclusion criteria: i) Women > 15 years of age diagnosed with malignant breast tumour. ii) Women with malignant breast tumors who underwent histopathology and IHC tests.

Exclusion criteria. i) Patients with benign breast tumours. ii) Patient with malignant breast tumor who only had a histopathological examination and no IHC examination was performed at the institution and therefore did not appear in the database of the pathology department. iii) Patients with hemodynamic compromise.

Results

Table 1 Distribution of breast cancer by age group

Age (years)	N	%
15-49	21	31
> 50	47	69
Total	**68**	**100**

Figure 1 Distribution of breast cancer according to histopathology

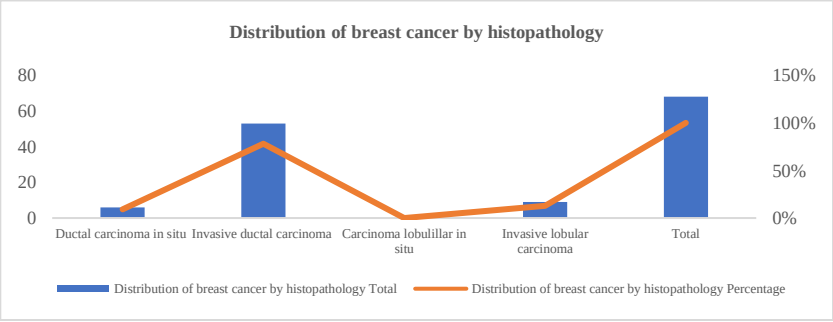

Table 2 Nuclear grade according to histopathological type

Histological type	Nuclear grade				
	Grade 1 low	Grade 2 intermediate	%	Grade 3 high	%
Ductal carcinoma in situ	0	5	83	1	17
Invasive ductal carcinoma	0	22	42	31	58
Lobular carcinoma in situ	0	0	0	0	0
Invasive lobular carcinoma	0	1	11	8	89
Total	**0**	**28**	**41**	**40**	**59**

Figure 2 Distribution according to nuclear grade - histopathology

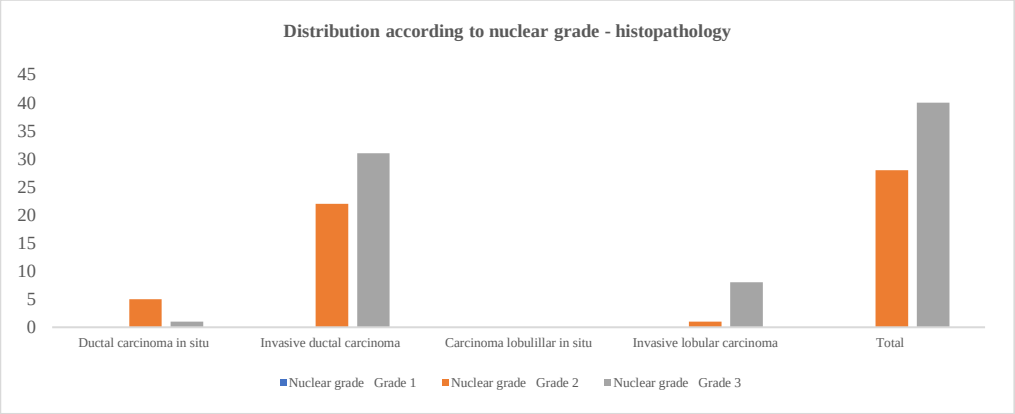

Table 3 Immunohistochemistry of the estrogen hormone receptor according to histopathological type

Immunohistochemistry	Estrogen receptor					
	Positive > 10 %	%	Positive low 1-10 %	%	Negative	%
Ductal carcinoma in situ	6	100	0	0	0	0
Invasive ductal carcinoma	24	45	8	15	21	40
Lobular carcinoma in situ	0	0	0	0	0	0
Invasive lobular carcinoma	8	89	1	11	0	0
Total	**38**	**56**	**9**	**13**	**21**	**31**

Table 4 Immunohistochemistry of the progesterone hormone receptor according to histopathological type

Immunohistochemistry	Progesterone receptor			
	Positive	%	Negative	%
Ductal carcinoma in situ	6	100	0	0
Invasive ductal carcinoma	24	45	29	55
Lobular carcinoma in situ	0	0	0	0
Invasive lobular carcinoma	8	89	1	11
Total	**38**	**56**	**30**	**44**

Tabla 5 Inmunohistoquímica del HER2/neu según el subtipo histopatológico

Immunohistochemistry	HER2/neu							
	Score 0	%	Score 1+	%	Score 2+	%	Score 3+	%
Ductal carcinoma in situ	1	17	5	83	0	0	0	0
Invasive ductal carcinoma	12	23	5	9	6	11	30	57
Lobular carcinoma in situ	0	0	0	0	0	0	0	0
Invasive lobular carcinoma	8	89	0	0	0	0	1	11
Total	**21**	**31**	**10**	**15**	**6**	**9**	**31**	**46**

Table 6 Immunohistochemical distribution according to Ki67 according to histopathological subtype

Immunohistochemistry	Ki67/less 10 %	%	Ki67/mas 10 %	%
Ductal carcinoma in situ	5	83	1	17
Invasive ductal carcinoma	3	6	50	94
Lobular carcinoma in situ	0	0	0	0
Invasive lobular carcinoma	1	11	8	89
Total	**9**	**13**	**59**	**87**

Figure 3 Distribution by HER2/neu score according to histopathological subtype

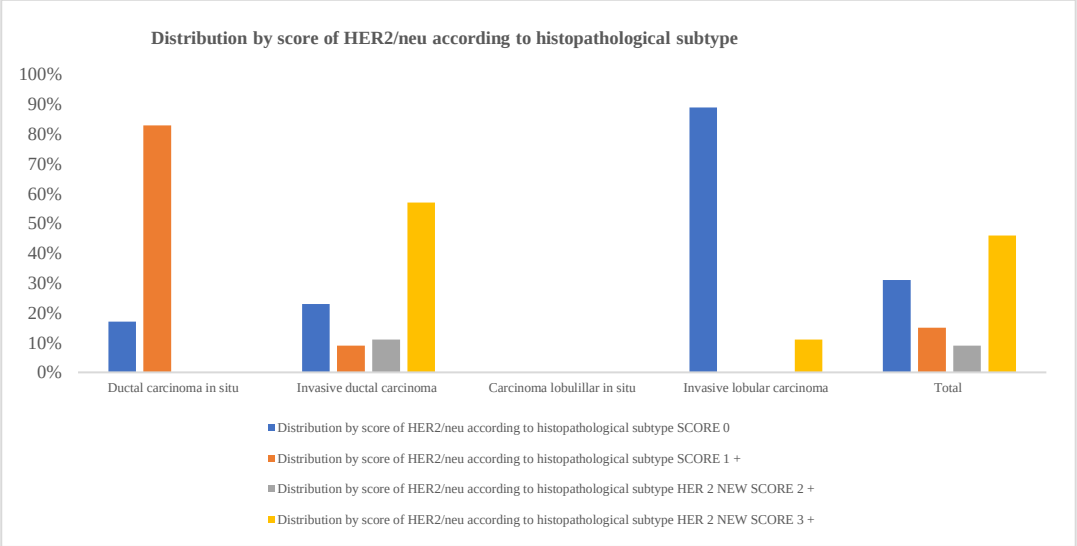

Table 7 Correlation of histopathology with immunohistochemistry

Histopathological type	Immunohistochemistry				
	Luminal A	**Luminal B**	**HER2/neu**	**Basal like**	**Total**
Ductal carcinoma in situ	6	0	0	0	6
Invasive ductal carcinoma	2	19	30	2	53
Invasive lobular carcinoma	8	0	1	0	9
Total	**16**	**19**	**31**	**2**	**68**
Probability (%)	23	28	46	3	100

Table 8 Statistical distribution by age according to histopathological diagnosis

Histopathology	Middle Age
Invasive ductal carcinoma	58
Ductal carcinoma in situ	59
Infiltrating lobular carcinoma	43

Freq ductal, IC 93.84 %, Freq lobulillar IC 55.75 %, ER negativo < 1 % IC 83.89 %, Freq in situ IC 63.06 %, Freq invasor IC 93,94%, Freq HER2/neu score 0 IC 83.16 %, Freq HER2/neu score 1+ IC 71.51 %, Freq HER2/neu score 2 + IC 54.07 %, Freq HER2/neu score 3 + IC 88.06 %, Freq Ki67 mas 10 % 93.62 %, Freq Ki 67/menos 10 % 69.15 %.

Discussion

Molecular markers obtained by IHC are important for the classification of BC subtypes, treatment selection, and prediction of prognosis. The expression of estrogen receptors and/or progesterone receptors determines the luminal type of BC and the target of antihormonal therapy, as well as the expression of human epidermal growth factor receptor 2 (HER2/neu), a key marker to determine tumor behavior and the use or not of anti-HER2/neu therapy. When there is an absence of molecular target, i.e., negative ER, negative PR, and negative HER2/neu, it is considered

a subtype of triple-negative SC that indicates a worse prognosis for the patient[21].

In hormone receptor-positive BCs account for 70-80 % of all BCs, these hormone-dependent cancers can often be successfully treated with a variety of estrogen receptor-modulating or estrogen-reducing drugs, in this research the receptor-positive molecular subtype was present in 100 % of patients diagnosed with ductal carcinoma in situ and 89 % of invasive lobular carcinoma, which indicates that these types of tumors have a better prognosis, will respond better to antihormonal therapy and agrees with the data obtained in the world literature in which they comprise a high percentage and a better prognosis, however, patients with the subtypes of BC with a single hormone receptor positive (ER+PR- and ER-PR+) are more likely to have unfavorable characteristics and worse survival than the ER+PR+ subtype and should be considered clinically distinct from these[22-24].

HER2/neu is overexpressed in approximately 15 % of breast carcinomas[25-27], which contrasts with the data obtained in this study in which the intrinsic molecular subtype HER2/neu was the most frequent, predominating in invasive ductal carcinoma, in which it was positive in 30 patients, representing 57 % of cases. The importance of manifesting a positive HER2 result in the histological subtype of BC confers a poor prognosis, but at the same time offers the possibility of using a targeted treatment with Trastuzumab, a monoclonal antibody, and the use of chemotherapy would be avoided in some cases[26,27].

When there are doubts about HER2/neu positivity, an in situ hybridization analysis with fluorescence or enhanced with silver can be performed, which is another test different from IHC[28].

Regarding the basal-like or triple-negative molecular subtype, these are tumors that lack the 3 standard molecular markers and occupy 15 % of all BC[29], in this study it was only observed in 2 patients with invasive ductal carcinoma, representing 3 % of the patients studied, occupying a minority group being the subtype with the worst prognosis and with the lowest survival[29].

The age group of women > 50 years had the highest percentage with a diagnosis of BC, representing 69 % compared to patients aged 15 to 49 years, who occupied 31 %, indicates that the age group where BC occurs most is in women over 50 years of age[30,31], however, in this study the case of moderately differentiated infiltrating ductal carcinoma was presented in a 16-year-old adolescent.

In a study by Kwon et al.[21], in a total of 284 patients, observed that the histopathological classification identified invasive ductal carcinoma in 242 cases, invasive lobular carcinoma in 16 cases, and others (carcinoma with medullary features in 4 cases, carcinoma with neuroendocrine differentiation in 1, microinvasive carcinoma in 2, papillary carcinoma in 8, cribriform carcinoma in 1, metaplastic carcinoma in 3, mucinous carcinoma in 8, and (tubular carcinoma in 4)[21]. In our study, the most frequent histological type was also invasive ductal carcinoma, followed by invasive lobular carcinoma and finally ductal carcinoma in situ, but other histological types of BC were not identified in the study group.

It is evident that the vast majority of patients with ductal carcinoma in situ had nuclear grade 2, in invasive ductal carcinoma they had grade 2 and grade 3 almost equally, and in invasive lobular carcinoma the majority of patients had nuclear grade 3, which indicates that there are differences in nuclear grades according to the histopathological type. In our study, it

was observed that, in all patients diagnosed with BC, there was no case of nuclear grade 1 (low), with a predominance of nuclear grade 3 (high) representing 59 % of the total number of patients, and nuclear grade (intermediate), representing 41 % of patients. This would indicate that most malignant breast tumors are of high and intermediate grade and means that the cells observed were mostly large with irregular chromatin with multiple prominent nucleoli, with frequent mitoses and usually not polarized towards the luminal space[32]. Histopathological classification[21,33] and nuclear grade also differed significantly between the subtypes of BC[21,33].

There is a significant association between classification and Ki67 levels [34], well-differentiated carcinomas exhibited predominantly low levels of Ki67, intermediate and poorly differentiated carcinomas reported higher levels of Ki67 with a wider range[34]. In the study carried out on invasive ductal carcinoma, most patients had Ki67 > to 10 %, which indicates that this tumor has a high level of cell proliferation, compared to ductal carcinoma in situ, most patients had Ki67< 10 %, which indicates that this tumor has a low level of cell proliferation. invasive lobular carcinoma mostly had Ki67 >10 %, which indicates that, like invasive ductal carcinoma, it is a tumor with high cell proliferation.

Invasive ductal carcinoma and invasive lobular carcinoma have low or poorly differentiated high nuclear grades and (high ki67)[34].

IHC is a necessary method for the diagnosis and categorization of the different histopathological subtypes in breast cancer[35].

The objective of reporting the results of IHC is to provide the patient with BC with the opportunity to receive immunotherapy to improve their survival in both newly diagnosed and metastatic cancers. Clinical trials in recent years have reported that immunotherapy is an effective therapeutic option, highlighting the need for personalized treatment strategies aimed at maximizing patient outcomes, such as in the case of triple-negative breast cancer, pembrolizumab is currently approved for use in combination with chemotherapy[35,36].

Tumors with low HER2 are defined as tumors with an IHC score of 1+ or 2+ without genetic amplification. Most studies have indicated that HER2-low BC has a higher prevalence of hormone receptor positivity (HR+), lower nuclear and histological grades, and a lower Ki67 proliferation index than HER2-zero BC. Kang & Kim[37] performed a multivariate logistic regression analysis to elucidate the association between HER2-low and hormone receptor (HR) status and revealed that HR+ had a strong association with HER2-low, indicating that HR status is significantly related to the characteristics of HER2-low BC[37].

In this study, great variability and heterogeneity were noted in the different tumors, which gives them a different prognosis and therapeutic approach. Invasive ductal carcinoma was the most common malignant breast tumor according to histopathology. The second most observed was invasive lobular carcinoma, the third in frequency was ductal carcinoma in situ, and no other types of BC were present.

Ductal carcinoma in situ and lobular carcinoma was mostly of the luminal molecular subtype A and invasive ductal carcinoma had the overexpressed molecular subtype HER2/neu.

In the patients studied, the triple-negative molecular subtype was observed only in 2 patients, both with a diagnosis of invasive ductal carcinoma. Heterogeneity was observed in terms of age 22 and 65 years. This subtype has a poor prognosis, high mortality,

greater recurrences and distant metastases compared to other tumor subtypes, but thanks to the IHC correlated with histopathology, breast cancers have better survival, with the use of targeted therapies according to the molecular subtype.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Ethical considerations

All the participants as authors of the research contributed freely to propose, execute or present the results of the research, the data were obtained from the pathology department of the Luis Vernaza Hospital, without directing the research and the search, joint analysis was carried out to avoid manipulation of the data, guaranteeing their availability and reproducibility, complying with the ethical aspects of research.

Limitations in research

The limitation in this study was that many patients did not undergo the immunohistochemistry test and could not be part of the study, therefore, we obtained a small sample, so more studies are needed that cover a larger population.

Future prospects

Future research could focus on larger studies and multicenter to evaluate treatment related to the new guidelines

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Contribution of the authors in the article

Identification of the responsibility and contribution of the authors: The authors declare to have contributed to the original idea (*María Calderón*), study design (*Diego Cabrera*), data collection (*Jorge Cárdenas, María Calderón, Andrea Saltos*), data analysis (*María Calderón, Paula Vázquez, Maryoli González*), drafting and writing of the article (*María Calderón, Diego Cabrera, Jorge Cárdenas, Andrea Saltos, Paula Vázquez, Maryoli González*).

Use of artificial intelligence

We assume that the entire document was written based on ethical and professional criteria, and AI was not used to make the images or text

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