Exploring heterogeneity of HER2 immunohistochemistry staining in patients undergoing neoadjuvant breast cancer treatment in two centers of South America

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INTRODUCTION

Intratumoral heterogeneity (ITH) in HER2-positive breast cancer has been reported as a negative predictive factor of pathological complete response (pCR) after neoadjuvant treatment.

In a pivotal study, Metzger and colleagues found 0% of pCR in the subgroup of patients with ITH determined by FISH after anti-HER2 based therapies[1].

OBJECTIVES

Assess whether HER2 heterogeneity determined by immunohistochemistry (IHC) predicts residual disease and pathological complete response in patients with HER2-3+ early breast cancer, and describe clinical features associated with ITH

MATERIALS AND METHODS

This was a retrospective cohort study including patients with HER2-3+ early breast cancer treated with neoadjuvant therapy in two Institutions: Instituto Alexander Fleming (Argentina) and INCAN (Paraguay).

HER2 ITH was defined according to ASCO/CAP 2013 and 2018 guidelines. It was considered present when ≥10% of tumor cells showed a distinct HER2 copy number and/or HER2/CEP17 ratio, with a separate count of at least 20 non-overlapping cells. The 2018 guideline also acknowledged the presence of unusual HER2 IHC patterns, including strong complete staining in <10% of tumor cells.

Associations between ITH and pathologic complete response (pCR) were assessed using univariate tests and logistic regression, considering other potential confounders such as estrogen receptor (ER) expression, axillary status and tumor size.

RESULTS

Table 1. Clinical and biological characteristics according to HER2 heterogeneity status

	No ITH	ITH	p value
n	95	21	
Age (median)	49 [43, 56.5]	51 [43-56]	0.535
ER positive (%)	49 (51.6)	14 (66.7)	0.31
PR positive (%)	45 (47.4)	15 (71.4)	0.079
Tumor stage (%)			0.117
T1	27 (28.4)	4 (19.0)	
T2	60 (63.2)	12 (57.1)	
T3	8 (8.4)	5 (23.8)	
Clinically positive axilla	47 (49.5)	14 (66.7)	0.235
Tumor size, cm (median)	2 [2-4]	3 [2-4]	0.38
Breast-conserving surgery	47 (49.5)	3 (14.3)	0.007
Sentinel lymph node biopsy (%)	76 (80.0)	11 (52.4)	0.3

Heterogeneity



Figure 1. pCR according to HER2 ITH

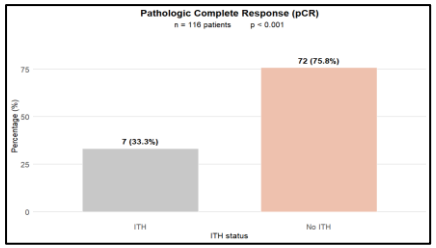


Figure 2. ypN+ Rates According to HER2 ITH

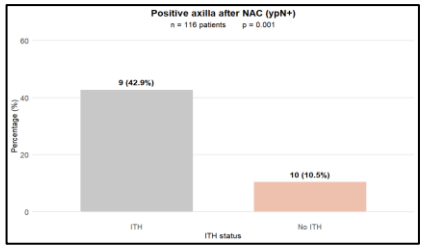
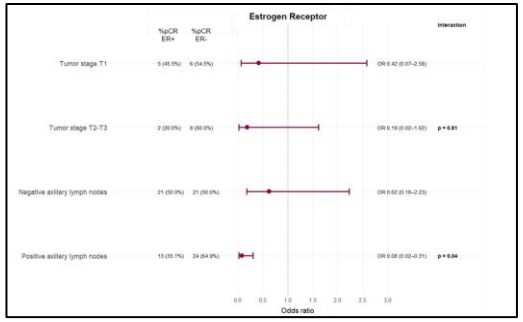
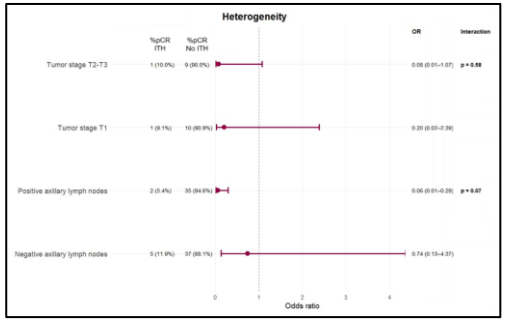


Table 2. Univariate and multivariate analysis

Variable	OR univariate	95% CI	p value	OR multivariate	95% CI	p value
Age >50 vs <50	1.28	0.58 - 2.81	0.539	-	-	-
Clinically positive axilla	0.48	0.21 - 1.07	0.072	1.56	0.31- 7.73	0.58
Tumor size	0.62	0.22 - 1.79	0.378	0.91	0.69 - 1.19	0.49
ER positive	0.21	0.08 - 0.51	0.0006	0.32	0.07 - 1.50	0.15
HER2 ITH	0.16	0.06 - 0.44	0.0004	0.21	0.03- 1.34	0.09

Figures 3 and 4 Subgroup and interaction analysis





CONCLUSIONS

Our findings suggest that HER2 heterogeneity is associated with a poorer treatment response, reflected in lower pCR rates, especially in tumors of higher size.

Further recognition of its prognostic relevance, along with a better understanding of its specific biological features, will be essential for tailoring therapy in patients with this tumor characteristic.

REFERENCES

1. Metzger Filho O, Clinical Discov 2021

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