ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 8, Issue – 4, August - 2025, Page No.: 179 – 184

Alpha – SMA and the Cancer – Stroma Crosstalk: Unveiling the Invisible Player in Breast Carcinogenesis

[1]Dr. Roshini Rodrigues, Final Year Post Graduate, BMCRI, Bengaluru

[2]Dr. Anusree VT, Senior Resident, BMCRI, Bengaluru

[3]Dr. Natarajan M, Professor, Department of Pathology, BMCRI, Bengaluru

[4]Dr Siddiq Ahmmed, HOD, Department of Pathology, BMCRI, Bengaluru

Corresponding Author: Dr. Anusree VT, Senior Resident, BMCRI, Bengaluru

How to citation this article: Dr. Roshini Rodrigues, Dr. Anusree VT, Dr. Natarajan M, Dr Siddiq Ahmmed, "Alpha – SMA and the Cancer – Stroma Crosstalk: Unveiling the Invisible Player in Breast Carcinogenesis", IJMACR- August - 2025, Volume – 8, Issue - 4, P. No. 179 – 184.

Open Access Article: © 2025 Dr. Anusree VT, et al. This is an open access journal and article distributed under the terms of the creative common's attribution license (http://creativecommons.org/licenses/by/4.0). Which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Introduction: Breast cancer is a heterogeneous group of diseases that exhibit various clinical characteristics, course of disease, and response to treatment. In carcinomas, neoplastic epithelial cells are found alongside a biologically diverse stroma made up of multiple stromal cell types and extracellular matrix (ECM) components, all contributing to the complexity of the tumor microenvironment. A significant presence of myofibroblasts, identified by their expression of alpha-smooth muscle actin (α-SMA), has been consistently detected in the stroma of most invasive human breast cancers. However, their exact role in tumor progression remains not well understood. Therefore, this study aims to examine the relationship between the desmoplastic reaction and the clinicopathological features of invasive breast cancer using immunohistochemical analysis.

Objectives: The study aims;

- To evaluate the expression of alpha smooth muscle actin (α- SMA) in the stromal component of invasive breast carcinoma using immunohistochemistry.
- To correlate α- SMA expression with histopathological features such as lymphovascular invasion, lymph node involvement.

Methodology: Retrospective study, study period - 2 years, gross examination, followed by tissue processing and staining with h and e. Representative block of each lesion subjected to IHC marker Alpha SMA and its expression is evaluated.

Results

- Total 34 cases were included
- Mean age of presentation was 52.94
- Gender – 32 females and 2 males
- Majority cases studied were invasive breast carcinoma, followed by invasive lobular carcinoma,

1 case each of mucinous carcinoma and carcino sarcoma.

- Alpha SMA under expression (score 0 and 1) in 17 cases and overexpression (score 2) in 17 cases.
- Alpha SMA overexpression showed statistical significance with lymph node metastasis and lymphovascular invasion

Conclusion: This study demonstrates a statistically significant association between alpha SMA expression and adverse prognostic indicators, including lymph node metastasis and lymphovascular invasion, in invasive breast carcinoma. These findings suggest that alpha SMA may serve as a potential marker of tumor aggressiveness and stromal activation, reinforcing its role in the cancer – stroma interplay. Assessing alpha SMA expression could thus offer valuable insights into tumor behaviour and aid in risk stratification of breast carcinoma patients

Keywords: Breast carcinoma, Alpha SMA

Introduction

- Breast cancer development involves not only malignant epithelial cells but also the tumor microenvironment (TME).
- Cancer-associated fibroblasts (CAFs) are critical stromal components.
- Alpha-smooth muscle actin (α-SMA) is a well-recognized marker of activated CAFs.
- CAFs contribute to tumor progression through paracrine signaling, ECM remodeling, and immune modulation.
- α-SMA is an actin isoform typically expressed by:
  - Myofibroblasts o Pericytes
  - Vascular smooth muscle cells
- In cancer:
  - Denotes CAF activation
  - Facilitates tumor cell migration, angiogenesis, and stromal reorganization High α-SMA expression = Aggressive tumor behavior

Cancer–Stroma Crosstalk

- Bidirectional interaction between tumor epithelial cells and stromal fibroblasts:
- Tumor cells secrete TGF-β, PDGF, IL-6 → fibroblast activation
- CAFs release VEGF, FGF, MMPs → promotes tumor growth
- Effects:
  - Enhanced tumor proliferation and invasion
  - Immune evasion and resistance to therapy

Objectives

The study aims;

- To evaluate the expression of alpha smooth muscle actin (α- SMA) in the stromal component of invasive breast carcinoma using immunohistochemistry.
- To correlate α- SMA expression with histopathological features such as lymphovascular invasion, lymph node involvement etc.

Materials and Methods

Type of Study: Retrospective study

Duration of Study: March 2023 to Feb 2025

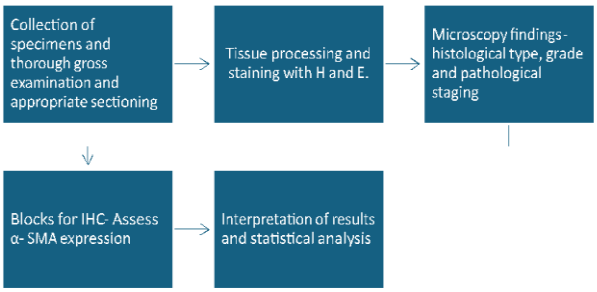
Inclusion Criteria

- Patients willing to give informed consent
- Patients with primary breast carcinoma confirmed as invasive breast carcinoma on histopathology.

Exclusion Criteria

- Patients not willing to give informed consent.
- Patients with breast carcinoma post neoadjuvant therapy.
- Patients with recurrent breast carcinoma

©2025, IJMACR



Alpha SMA Interpretation

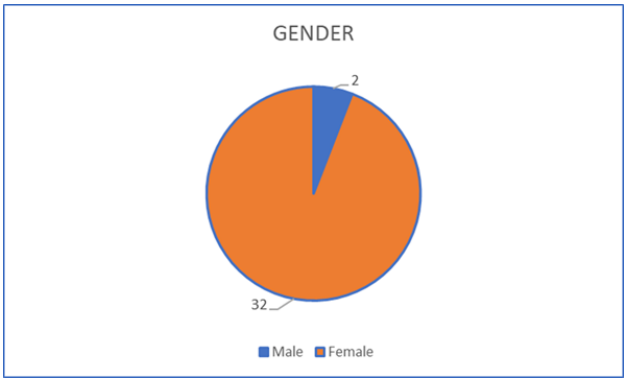
- Immunoreactivity is regarded as positive when brown staining is localized in the cytoplasm of stromal myofibroblasts.
- Semi-quantitative intensity score (H score) : (done manually [not computer assisted analysis])

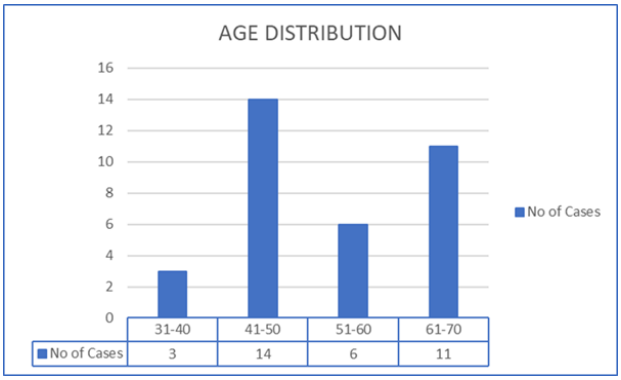
Score 0	Negative staining
Score 1	Weak staining
Score 2	String staining

- Interpretation:
- Alpha SMA low-expression - H score between 0 and 1
- Alpha SMA high-expression - H score as 2

Results

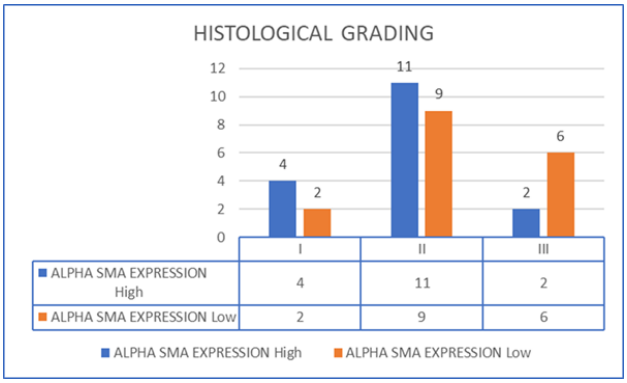
- Total 34 MRM Cases Were Included, Out Of Which 2 Were Male Patients.
- Age Range From 33 To 70 Years
- Mean Age Of Presentation Was 52.94





Alpha SMA Expression

- Out of 34 cases, 2 cases were score 0, 15 cases were score 1 and 17 cases were score 2.
- Hence, total 17 cases showed low alpha SMA expression and 17 cases showed high alpha SMA expression.



PATHOLOGICAL STAGING - SIZE	ALPHA SMA EXPRESSION				P Value
	High		Low		
	No	%	No	%	
T1	0	0	1	6	0.59 (not statistically significant)
T2	10	59	8	47	
T3	5	29	7	41	
T4	2	12	1	6	
Total	17	100	17	100	

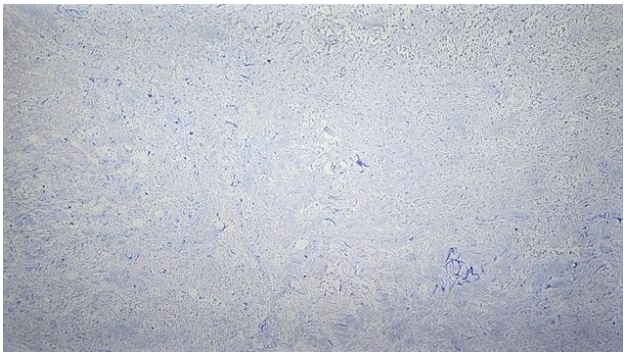
MOLECULAR SUBTYPE	TUMOR BUDDING				P Value
	High		Low		
	No	%	No	%	
LUMINAL A	3	18	3	17,6	0.39 (not statistically significant)
LUMINAL B	6	35	2	11,8	
TRIPLE NEGATIVE	6	35	8	47,1	
HER 2 ENRICHED	2	12	4	23,5	
Total	17	100	17	100	

©2025, IJMACR

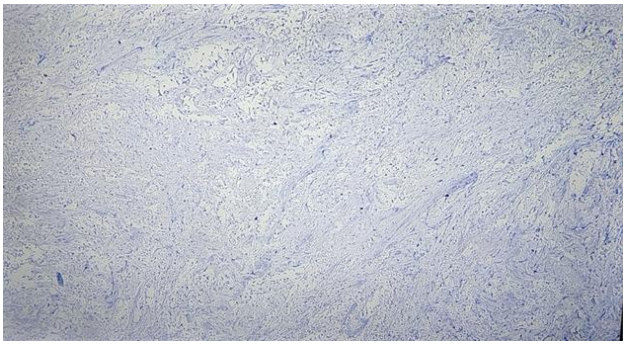
LYMPHOVASCULAR INVASION	ALPHA SMA EXPRESSION				
	High		Low		p VALUE
	No	%	No	%	0.005 (statistically significant)
PRESENT	13	76	5	29	
ABSENT	4	24	12	71	
Total	17	100	17	100	

LYMPH NODE METS	ALPHA SMA EXPRESSION				P Value
	High		Low		
	No	%	No	%	
PRESENT	14	82	8	47	0.03 (statistically significant)
ABSENT	3	18	9	53	
Total	17	100	17	100	

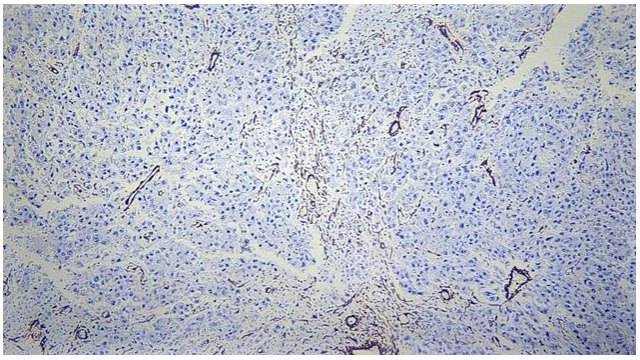
Negative Staining



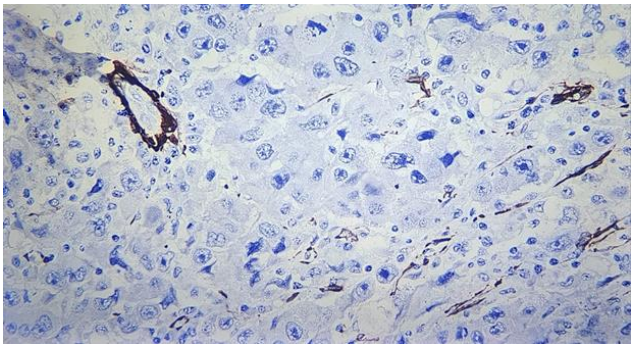
Score 0 (BIOPSY NO 7673/24)



Weak Staining

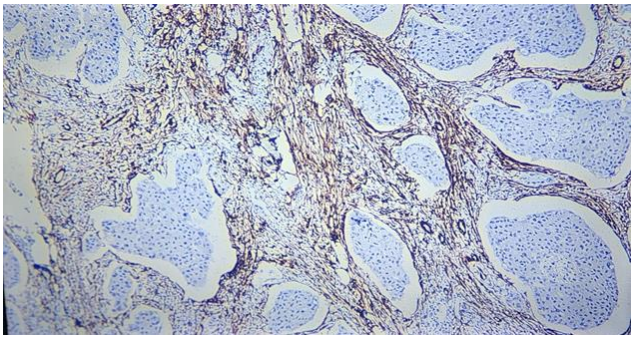


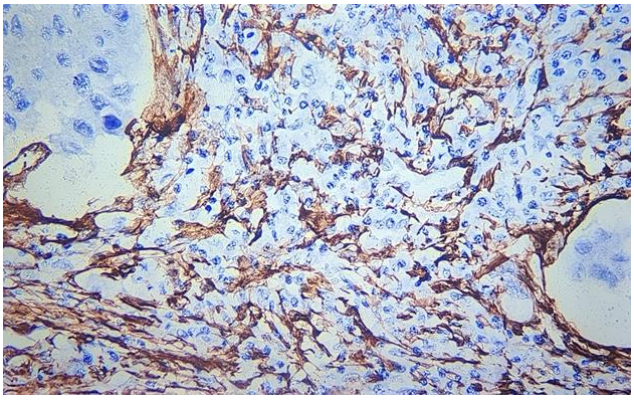
Score 1 (7016/23)



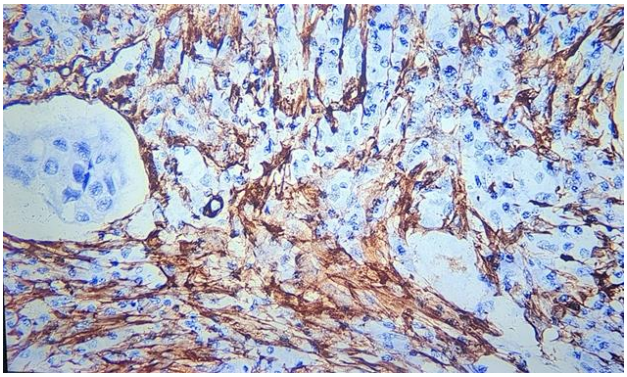
Strong Expression

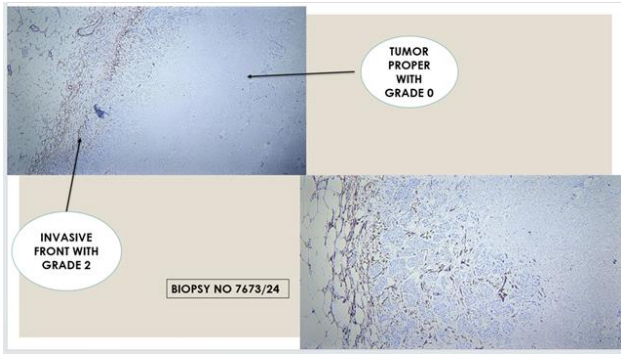
Score 2 (Biopsy NO. 8743/24)





©2025, IJMACR





Discussion

In this study majority of the cases (82%) showing high expression of alpha SMA, presented with lymph node metastasis

STUDY	LYMPH NODE METASTASIS			LYMPHOVASCULAR INVASION		
	PRESENT	ABSENT	p VALUE	PRESENT	ABSENT	p VALUE
Yamashita M et al	7	4	<0.05	-	-	-
Catteau X et al	52	40	<0.05	-	-	-
Pasca Fenesan MM et al*	Not specified	Not specified	0.048	Not specified	Not specified	<0.001
PRESENT STUDY	14	3	0.03	13	4	0.005

* In all other studies, histological parameters are compared with high Alpha SMA expression, where as in this study, it is compared with medium alpha SMA expression

- Study also shows that majority of cases with high expression of alpha SMA showed lympho vascular invasion.
- Our analysis revealed no statistically significant correlation between alpha SMA expression and either tumor size or molecular subtype of breast cancer, consistent with findings of Yamashita M et al, who similarly reported no such association.

Conclusion

- α-SMA marks CAF activity and plays a crucial role in breast cancer progression.
- Strong correlation between α-SMA and poor prognostic indicators such as lymph node metastasis and lymphovascular invasion
- Also our findings suggest that there is no statistically significance between increased stromal alpha SMA expression and either tumor size or molecular subtype. This aligns with the study conducted by Andreas et al (2022), which proposed that they are mutually exclusive of each other, as advanced and larger tumors can have necrotic stroma and CAFs exhaustion.

Clinical Implication for future:

- α-SMA could serve as a prognostic biomarker if multiple clinical trials confirm that its high expression predicts positive margins or recurrence when combined with other markers. Limitation
- Smaller sample size
- Short duration of study
- Manual grading method

References

1. Yamashita M, Ogawa T, Zhang X, et al. Role of stromal myofibroblasts in invasive breast cancer: stromal expression of alpha-smooth muscle actin correlates with worse clinical outcome. *Breast Cancer*. 2012;19(2):170-176.
2. Singh A, Bandyopadhyay A, Mukherjee N, Basu A (2020) α-Smooth Muscle Actin and TLR9 Expression and Correlation in Breast Cancer. Int J Pathol Clin Res 6:108.

©2025, IJMACR

3. Catteau X, Simon P, Noël JC. Myofibroblastic stromal reaction and lymph node status in invasive breast carcinoma: possible role of the TGF-β1/TGF-βR1 pathway. *BMC Cancer*. 2014;14:499
4. Muchliń ka A, Nagel A, Popęda M, Szade J, Niemira M, Zieliń ki J, et al. Alpha-smooth muscle actin-positive cancer-associated fibroblasts secreting osteopontin promote growth of luminal breast cancer. Cell Mol Biol Lett [Internet]. 2022 [cited 2024 Jun 28];2
5. Pasca Fenesan MM, Cosma AA, Melnic E, Cimpean AM, Cozma GV, Negru AG. Heterogeneity of the Alpha-Smooth Muscle Actin Tumor Score in Breast Cancer Cells Significantly Affects Tumor Invasiveness, Recurrence, and Patient Survival. *Cureus*. 2024;16(12):e75908.
6. Sappino AP, Skalli O, Jackson B, Schurch W, Gabbiani G. Smooth-muscle differentiation in stromal cells of malignant and nonmalignant breast tissues. Int J Cancer 1988; 41:70712.

©2025, IJMACR