Original Article

DOI: 10.7860/JCDR/2026/87373.23604

Pathology Section

Quantifying Tumour Stroma Ratio and Desmoplastic Stroma in Colorectal Cancer: A Cross-sectional Study

RAMYA CHITTURI[1], MUNI BHAVANI ITHA[2], SANDHYA KRUPAL VARIGANJI[3], APARNA CHINNAM[4], SATYA SAIKUMAR LAXMI PRASANNA KANTUBHUKTA[5], GONJI SUMA[6]

(cc) BY-NC-ND

ABSTRACT

Introduction: Tumour microenvironment plays an important role in the progression and invasion of cancer. There has been search for newer prognostic markers in colorectal cancers. Tumour Stroma Ratio (TSR) is an estimate of proportion of epithelial and stromal cells. Desmoplastic Reaction (DR) is the growth of fibrous tissue around tumour cells. DR and TSR have been found to have prognostic significance in colorectal cancers.

Aim: To evaluate TSR and DR and determine their association with clinicopathological features in colorectal carcinoma.

Materials and Methods: This was a retrospective cross-sectional study conducted in the Department of Pathology, Guntur Medical College, Kanna Vari Thota, Guntur, Andhra Pradesh, India, from June 2021 to May 2024. The study included all consecutive resected cases of histopathologically confirmed colorectal adenocarcinoma received in the Department of Pathology during the study period. TSR and DR were characterised by two independent pathologists. Chi-square test was used to assess the association of TSR, types of desmoplastic response with clinicopathological parameters evaluated included age, gender, tumour location, histological grade, pathological T stage, lymphovascular invasion, perineural invasion, lymph node metastasis, TSR, and DR.

Results: A total of 53 cases of colorectal carcinomas were identified with the median age being 60 years. Stroma High (SH) tumours were seen in 19 (35.8%) cases and Stroma Low (SL) tumours in 34 (64.2%) cases. SH tumours were associated with advanced pathological stage, suggesting a potentially poorer prognosis. SL tumours were associated with mature stroma and favourable outcomes. Mature type of DR was seen in 31 (58.5%) cases, intermediate type in 18 (34%) cases and immature type in 4 (7.5%) cases. Chi-square test was used to assess the association between TSR, DR, and clinicopathological parameters. A statistically significant association was observed between TSR and pathological T stage (p=0.03) as well as DR (p=0.023).

Conclusion: TSR showed statistically significant association with T stage and DR, suggesting its potential as a supportive histomorphological parameter. Incorporation of these newer parameters in pathology reports may aid in treatment decisions.

Keywords: Colorectal neoplasm, Desmoplastic reaction, Fibroblasts, Stromal cells

INTRODUCTION

Colorectal Malignancies (CRC) are the second most common cause of cancers and the third leading cause of cancer-related deaths [1]. Current research is focusing on establishing new prognostic factors and investigating their relationship with aggressive cancer phenotypes [2]. Two such promising prognostic markers were TSR and DR. The tumour-stroma ratio is an estimate of the proportion of epithelial and stromal cells [3]. It has been shown to be a prognostic factor in several types of malignant epithelial neoplasms like breast [4], patients with adverse prognosis have been documented to have high proportion of stroma and tumours with abundant carcinomatous tissue had better prognosis. The stroma facilitates the survival and proliferation of neoplastic cells and promotes Epithelial-Mesenchymal Transition (EMT), and local and metastatic dissemination. Cancer-Associated Fibroblasts (CAF's) play a central role in mediating the EMT program [5]. DR is the proliferation of myofibroblasts in the stroma of invasive cancer which is generated by CAF's [3]. DR can be morphologically categorised on the basis of the presence of specific types of stroma. Hence, the primary objective was to evaluate TSR and DR and determine their association with clinicopathological features in colorectal carcinoma. Secondary objectives were to grade TSR in colorectal carcinomas, to categorise DR in colorectal carcinomas; to find the association between TSR, DR, and clinicopathological parameters-age, gender, tumour grade, tumour stage, lymphovascular invasion, perineural invasion and lymph node metastases.

MATERIALS AND METHODS

This was a retrospective cross-sectional study conducted in the department of Pathology, Guntur Medical College, Kanna Vari Thota, Guntur, Andhra Pradesh, India, from June 2021 to May 2024. Institutional Ethics Committee approval was taken, (IEC No.: GMC/IEC/038/2024; dated 22 August 2024). Relevant data was collected from medical records.

Sample size calculation: Interobserver agreement was substantial for TSR (κ=0.70; 95% CI: 0.55-0.85) and DR (κ=0.71; 95% CI: 0.56-0.86), both indicating substantial agreement (Landis and Koch criteria). In cases of disagreement (n=8/53 for TSR; n=6/53 for DR), a consensus opinion was reached by simultaneous re-review of the slides by both pathologists. The κ values with CIs provide a measure of the precision and reliability of the agreement beyond chance.

Inclusion criteria: The study included all consecutive resected cases of histopathologically confirmed colorectal adenocarcinomas received in the Department of Pathology during the study period.

Exclusion criteria: Colorectal carcinomas with prior history of Neoadjuvant Chemotherapy (NACT), radiotherapy, non epithelial tumours like Gastrointestinal Stromal Tumour (GIST), neuroendocrine carcinomas and melanomas were excluded from the study.

Study Procedure

The pathological variables were obtained from the reanalysis of the histological slides and include histological grade, perineural invasion, lymphovascular invasion, lymph node metastasis and pathologic T-stage. Slides have been reviewed by two independent pathologists. If there was any discrepancy then a consensus opinion was taken with mutual agreement.

Tumour stroma ratio was assessed on the same slide used to determine pathologic T stage. Slide with deepest point of invasion was selected. Then with the help of 4X objective, areas with highest percentage of stroma were identified. Then 10X field containing both tumour cells and stroma was selected. For proper assessment, tumour clusters should be located at four sides of microscopic field and were approximately 90^0 (right-angled) to each other. For statistical analysis, TSR groups were divided into SH and SL. Under 10X objective, tumours with >50% stroma were reported as SH and with ≤ 50% stromal area were reported as SL [2]. The reason for taking 50% as cut-off value was it allows for maximum discriminative power [6]. Native constituents like smooth muscle tissue, lymphoid follicles and large vessels were disregarded while scoring. Areas containing mucin, necrosis and Tumour Budding (TB) were also avoided.

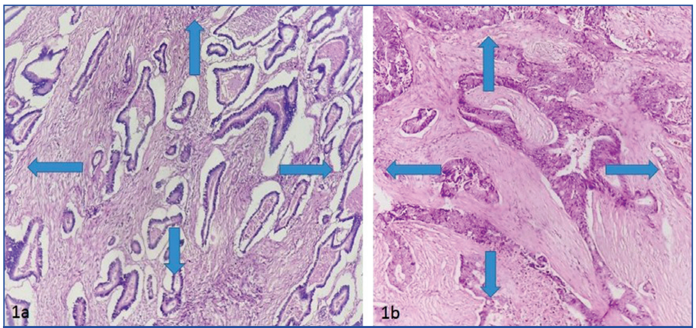
For categorising DR, myxoid stroma and keloid like hyalinised bundles are the two most important criteria [7]. The categories include mature, intermediate and immature type of DR. First, tumour with maximum depth of invasion was selected. Using 10X objective, tumour at infiltrating edge was selected. Extramural stroma of tumour was scanned at 10X magnification to search for myxoid stroma and keloid like collagen. At 40X magnification, any focus of myxoid stroma was searched for. A myxoid stroma was defined as an amorphous stromal substance comprised of an amphophilic or slightly basophilic Extracellular Matrix (ECM), usually intermingled with randomly oriented hyalinised collagen molecules. Immature DR was defined as the presence of myxoid stroma at the tumour invasive front involving at least one high microscopic field (400X). Cases without myxoid stroma larger than the 40X objective field and with the presence of keloid-like collagen (broad bands of collagen with eosinophilic hyalinisation) at the tumour invasive front were classified as intermediate DR. Mature DR was identified by the presence of fine mature collagen fibres stratified in multiple layers and without any myxoid areas or keloid like collagen. Presence of immune cells does not affect DR status.

STATISTICAL ANALYSIS

Data was analysed using Statistical Package for Social Sciences (SPSS) version 26.0. Descriptive statistics like frequencies and percentages for categorical variables were used to represent the data. Chi-square test was used to test the association of TSR, types of DR with clinicopathological parameters. The p-value of ≤0.05 taken as statistically significant.

RESULTS

There were total of 53 cases of colorectal carcinomas, among which males were 31 (58.5%) and females were 22 (41.5%). The age of the patients ranged from 32 years to 88 years with the median age being 60 years. The location of the tumour was rectosigmoid in 29 (54.7%) cases, right-sided in 18 (34%) cases and left-sided in 6 (11.3%) cases. Well-differentiated tumours were 48 (31 SL and 17 SH), moderately differentiated tumours were 2 (0 SL and 2 SH) and poorly cohesive were 3 (3 SL &0 SH). Lymphovascular invasion was seen in 28 (52.8%) cases and perineural invasion in 6 (11.4%) cases. Proximal margin was positive for invasive carcinoma in three cases. Proximal margin was positive for invasive carcinoma in three cases and for dysplasia in one case, while distal margin was positive in one case. Out of 53 cases, lymph nodes were not submitted in 6 (11.4%) cases, lymph node metastases was found in 21 (39.6%) cases and nodes negative in 26 (49%) cases. Pathological stage T1 was seen in 2 cases, T2 in 18 cases, T3 in 26 cases and T4 in 7 cases. SH tumours were seen in 19 (35.8%) cases and SL tumours in 34 (64.2%) cases [Table/Fig-1a,b]. T stage and DR category have significant association with TSR When calculated for any association between TSR and other parameters, significant association was found with T stage and DR [Table/Fig-2]. Odds ratio (OR) was calculated using binary logistic regression, so the estimated effect size was 0.38, and the 95% CI for the odds of SH tumours in advanced T stage (T3/T4 vs. T1/T2) was OR=4.2 (95% CI: 1.2-14.6), indicating a clinically meaningful association despite the modest sample size. Other parameters like age, gender, location, tumour grade, lymphovascular invasion, perineural invasion and lymph node metastases did not show any statistically significant association with TSR.



[Table/Fig-1]: a) Stroma Low (SL) tumour (H&E 100X); b) Stroma High (SH) tumour (H&E 100X). (Images from left right)

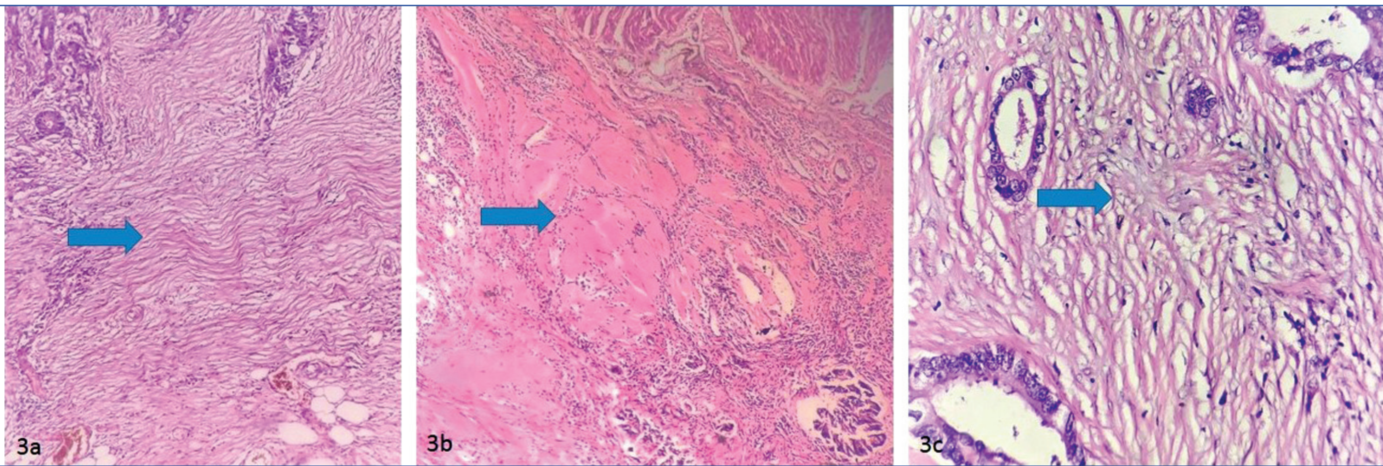
S. No.	Parameters	SL	SH	p-value
1	**Age (in years)**			0.78
	<65	21	11	
	>65	13	8	
2	**Gender**			0.22
	Male	22	9	
	Female	12	10	
3	**Location**			0.28
	Left-sided	5	1	
	Right-sided	13	5	
	Rectosigmoid	16	13	
4	**Differentiation**			0.26
	Well-differentiated	31	17	
	Moderately differentiated	0	2	
	Poorly cohesive	3	0	
5	**Lymphovascular invasion**			0.26
	Present	16	12	
	Absent	18	7	
6	**Perineural invasion**			0.09
	Present	2	4	
	Absent	32	15	
7	**Lymph node metastases**			0.25
	Present	12	9	
	Absent	19	7	
8	**T stage**			0.03 Significant
	T1	2	0	
	T2	16	2	
	T3	13	13	
	T4	3	4	
9	**DR category**			0.023 Significant
	Immature	3	1	
	Intermediate	7	11	
	Mature	24	7	

[Table/Fig-2]: Association of TSR with clinicopathological parameters.
Note: 95% Confidence Intervals (CI) for key effect sizes are provided in the text. κ=0.70 (95% CI: 0.55-0.85) for TSR agreement. Lymph node status analysis was performed on 47 evaluable cases after excluding six cases where lymph nodes were not submitted; SL: Stroma low; SH: Stroma high; DR: Desmoplastic reaction

DR was mature type in 31 (58.5%) cases, intermediate in 18 (34%) cases and immature in 4 (7.5%) cases [Table/Fig-3a-c]. No significant association was found between DR and other clinicopathological parameters like age, gender, location, tumour differentiation, lymphovascular invasion, perineural invasion, lymph node metastases and T stage but significant association was found with TSR [Table/Fig-4]. In the present study, mature DR showed a statistically significant association with stroma-low tumours (p=0.023) [Table/Fig-4]. The 95% CI for the proportion of mature DR among SL tumours was 70.6% (95% CI: 52.5-84.9%) compared to 36.8% (95% CI: 16.3-61.6%) among SH tumours. The absolute risk difference was 33.8% (95% CI: 8.2-59.4%).

DISCUSSION

The TNM staging stratifies colorectal cancer patients based on the extent of spread of tumour. Treatment regimens vary from local tumour excision to neoadjuvant therapy with surgery and adjuvant therapy. Apart from TNM staging, several other factors can vary the outcome [8,9]. The benefit of adjuvant chemotherapy is higher in average-risk stage III patients compared to average-risk stage II patients. Adjuvant chemotherapy can be tried to stage II tumours with high-risk features such as pathologic T4 stage, poorly differentiated histology, lymphovascular invasion, perineural invasion, TB, bowel obstruction, perforation and positive margins. Current National Comprehensive Cancer Network (NCCN) guidelines recommend either three or six months of adjuvant chemotherapy or simple observation in stage II patients with high-risk features, whereas chemotherapy is recommended for all patients with stage III disease [10]. Also, Microsatellite Instability (MSI) is an important factor to consider when determining the benefit from adjuvant therapy. So these complex situations highlight the limitations of extent-based staging and the need for robust biomarkers.



[Table/Fig-3]: a) Mature stroma-Mature collagen in layers (H&E 100X); b) Intermediate stroma -Intermediate stroma-hyalinised collagen (H&E 100X); c) Immature stroma-Myxoid stroma (H&E 400x).

S. No.	Parameters	Immature stroma	Intermediate stroma	Mature stroma	
1	**Age (in years)**				0.49
	<65	3	9	20	
	>65	1	9	11	
2	**Gender**				0.42
	Male	4	9	18	
	Female	0	9	13	
3	**Location**				0.49
	Left-sided	0	4	2	
	Right-sided	2	4	12	
	Rectosigmoid	2	10	17	
4	**Tumour differentiation**				0.5
	Well-differentiated	4	15	29	
	Moderately differentiated	0	2	0	
	Poorly cohesive	0	1	2	
5	**Lymphovascular invasion**				0.18
	Present	4	11	13	
	Absent	0	7	18	
6	**Perineural invasion**				0.70
	Present	0	3	3	
	Absent	4	15	28	
7	**Lymph node metastases**				0.398
	Present	3	7	11	
	Absent	1	8	17	
8	**T stage**				0.48
	T1	0	1	1	
	T2	1	3	14	
	T3	3	11	12	
	T4	0	3	4	

[Table/Fig-4]: Association of Desmoplastic Reaction (DR) with clinicopathological parameters.

The prognostic role of TSR in colorectal cancers was first described by Mesker WE et al., [6]. The tumour stroma is an important determinant of initiation and progression of many solid cancers [11]. The stroma facilitates the survival and proliferation of neoplastic cells and also promotes EMT [12,13]. The prognostic significance of TSR has been studied in various malignancies [14-17]. Zunder SM et al., identified that patients with SH tumours had significantly more cancer related deaths and shorter Distant Recurrence Free Survival (DRFS) compared to patients with SL tumours in stage II colorectal carcinomas [18]. In their study multivariate analysis has validated TSR as an independent prognostic factor for DRFS and carcinoma related death. In the present study, SH tumours were 35.8%, which is slightly high compared to Zunder SM et al., and Liang Y et al., [Table/Fig-5] [18,19]. In the present study, more number of SH tumours were seen in advanced stage (T3 &T4) compared to early stage cancers and it was found to be statistically significant (p=0.03). This suggests that TSR may serve as a potential supportive prognostic marker and the association of SH tumours with bad prognosis.

S. No.	Studies	SL	SH	Stroma intermediate
1.	Present study 2026 (N=53)	64.2%	35.8%	----
2.	Zunder SM et al., [18] 2020 (N=174)	79.3%	20.7%	-----
3.	Liang Y et al., [19] 2021 (N=248)	33.5%	32.7%	33.9%

[Table/Fig-5]: Comparison of SL and SH with other study.
SH: Stroma high; SL: Stroma low

Van Pelt devised a scoring method for TSR and proved to have low interobserver variability in colorectal cancers [9]. There was initial difficulty in assessing TSR, but following the protocol strictly and by initially viewing the slides multiple times helped us to master TSR estimation. De Souza Silva RM et al., clarified TSR to be simple, economical, reproducible and reliable scoring method in colorectal carcinomas. They found that SL tumours have greater interoberver agreement. They proposed that TSR based on routine histological material is faster without extra costs, easy to understand and reproducible. They suggested brief participation in an educational session, specific training, certification and participation by more number of pathologists, with considerable professional experience can result in high reproducibility of the method [2]. Firmbach D et al., identified accuracy of 86.5% and 86.7% using artificial intelligence networks, Basic Prototype Network (BPN) and U-Net, respectively and stated that TSR estimates by humans were not reliable as previously thought [20].

The prognostic role of DR was studied in malignancies like pancreatic ductal adenocarcinoma, cutaneous squamous cell carcinoma and cervical SCC [21-23]. In the DR, intermediate stroma and immature stroma were seen at tumour invasive front and the tumour center contains mature stroma. These findings suggest that intermediate and immature fibrotic stroma are transitory phenotypes which facilitate dedifferentiation of cancer cells whereas mature stroma is a later and more stable phenotype which may halt the invasive activity of neoplastic cells [24]. Ueno H et al., found that five year and 10 year survival rates were worst in the immature stroma group and best in the mature stroma group. In the present study, intermediate type of stroma was found to be high compared to other studies [Table/Fig-6] [5,25]. Kobayashi T et al., found that Immature DR was significantly correlated with a higher p T stage, presence of lymph node metastasis, lymphatic, venous, and perineural invasion, and also higher TB compared to intermediate/mature types of DR. They also concluded that immature type DR was significantly correlated with the presence of Tumour Deposits (TD's) [25]. According to Ueno H et al., the distribution of DR was significantly associated with tumour grade and T stage [5]. In the present study, mature stroma was found more commonly associated with SL tumours and it was statistically significant.

S. No.	Studies	Immature stroma	Intermediate stroma	Mature stroma
1.	Present study 2026 (N=53)	7.5%	34%	58.5%
2.	Fan S et al., [3] 2022 (N=207)	21.2%	30%	48.8%
3.	Ueno H et al., [5] 2021 (N=991)	6%	29.7%	64.4%
4.	Kobayashi T et al., 2022 [25] (N=443)	63.7%	20.5%	15.8%

[Table/Fig-6]: Comparison of DR with other studies [3,5,25].

Limitation(s)

One limitation of the study was the small sample size. Additional studies with large number of cases are needed. The other limitation was as this was a retrospective study prospective study with follow-up of patients might have thrown light on survival rates.

CONCLUSION(S)

The TSR has been associated with pathological T stage and DR. SH tumours were commonly associated with advanced stage disease with poor outcome. Mature stroma was more commonly associated with SL tumours. Thus, TSR and DR could be the newer prognostic markers which can be implemented in routine histopathology reporting as they are simple and cost effective. They help in optimising patient treatment by identifying subset of colorectal cancer patients who benefit from adjuvant therapy.

REFERENCES

[1] Sullivan L, Pacheco RR, Kmeid M, Chen A, Lee H. Tumour stroma ratio and its significance in locally advanced colorectal cancer. Curr Oncol. 2022;29(5):3232-41.
[2] Souza da Silva RM, Queiroga EM, Paz AR, Neves FF, Cunha KS, Dias EP. Standardized assessment of the tumour-stroma ratio in colorectal cancer: Interobserver validation and reproducibility of a potential prognostic factor. Clinpathol. 2021;14:2632010X21989686.
[3] Fan S, Cui X, Zheng L, Ma W, Zheng S, Wang J, et al. Prognostic value of desmoplastic stromal reaction, tumour budding and tumour-stroma ratio in stage II colorectal cancer. J Gastrointest Oncol. 2022;13(6):2903.
[4] Downey CL, Simpkins SA, White J, Holliday DL, Jones JL, Jordan LB, et al. The prognostic significance of tumour-stroma ratio in oestrogen receptor-positive breast cancer. Br J Cancer 2014;110(7):1744-47.
[5] Ueno H, Ishiguro M, Nakatani E, Ishikawa T, Uetake H, Murotani K, et al. Prognostic value of desmoplastic reaction characterisation in stage II colon cancer: Prospective validation in a Phase 3 study (SACURA Trial). Br J Cancer. 2021;124(6):1088-97.
[6] Mesker WE, Junggeburt JM, Szuhai K, de Heer P, Morreau H, Tanke HJ, et al. The carcinoma-stromal ratio of colon carcinoma is an independent factor for survival compared to lymph node status and tumour stage. Cell Oncol. 2007;29(5):387-98.
[7] Ueno H, Jones AM, Wilkinson KH, Jass JR, Talbot IC. Histological categorisation of fibrotic cancer stroma in advanced rectal cancer. Gut. 2004;53(4):581-86.
[8] Kannarkatt J, Joseph J, Kurniali PC, Al-Janadi A, Hrinczenko B. Adjuvant chemotherapy for stage II colon cancer: A clinical dilemma. J. Oncol Pract. 2017;13(4):233-41.
[9] van Pelt GW, Kjær-Frifeldt S, van Krieken JHJM, Al Dieri R, Morreau H, Tollenaar RAEM, Sørensen FB, Mesker WE. Scoring the tumor-stroma ratio in colon cancer: Procedure and recommendations. Virchows Arch. 2018 Oct;473(4):405-412. doi: 10.1007/s00428-018-2408-z.
[10] National Comprehensive Cancer Network. NCCN Guidelines version 5.2024-Colon Cancer. Available online: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed on 10 October 2024).
[11] Wu J, Liang C, Chen M, Su W. Association between tumour-stroma ratio and prognosis in solid tumour patients: A systematic review and meta-analysis. Oncotarget. 2016;7(42):68954-65.
[12] Park JH, Richards CH, McMillan DC, Horgan PG, Roxburgh CSD. The relationship between tumour stroma percentage, the tumour microenvironment and survival in patients with primary operable colorectal cancer. Ann Oncol. 2014;25(3):644-51.
[13] Huijbers A, Tollenaar RAEM, Pelt GWV, Zeestraten ECM, Dutton S, McConkey CC, et al. The proportion of tumourstroma as a strong prognosticator for stage II and III colon cancer patients: Validation in the VICTOR trial. Ann Oncol. 2013;24(1):179-85.
[14] Conti J, Thomas G. The role of tumour stroma in colorectal cancer invasion and metastasis. Cancers (Basel). 2011;3(2):2160-68.
[15] Unlu M, Cetinayak HO, Onder D, Ecevit C, Akman F, Ikiz AO, et al. The prognostic value of tumour-stroma proportion in laryngeal squamous cell carcinoma. Turk Patoloji Derg. 2013;29(1):27-35.
[16] Panayiotou H, Orsi NM, Thygesen HH, Wright AI, Winder M, Hutson R, et al. The prognostic significance of tumour-stroma ratio in endometrial carcinoma. BMC Cancer. 2015;15(1):955.
[17] Chen Y, Zhang L, Liu W, Liu X. Prognostic significance of the tumour-stroma ratio in epithelial ovarian cancer. Biomed Res Int. 2015;2015(1):589301.
[18] Zunder SM, Gerger A, Moser RS, Greil R, Hofmann TB, Bareck E, et al. Prognostic and Predictive Value of the Tumour-Stroma Ratio in STAGE II Colon Cancer. Clinical oncology and Research. 2020;3(4):02-08.
[19] Liang Y, Zhu Y, Lin H, Zhang S, Li S, Huang Y, et al. The value of the tumour-stroma ratio for predicting neoadjuvant chemoradiotherapy response in locally advanced rectal cancer: A case control study. BMC Cancer. 2021;21(1):729.
[20] Firmbach D, Benz M, Kuritcyn P, Bruns V, Lang-Schwarz C, Stuebs FA, et al. Tumour-stroma ratio in colorectal cancer-comparison between human estimation and automated assessment. Cancers (Basel). 2023;15(10):2675.
[21] Wang LM, Silva MA, D'Costa Z, Bockelmann R, Soonawalla Z, Liu S, et al. The prognostic role of desmoplasticstroma in pancreatic ductal adenocarcinoma. Oncotarget. 2016;7(4):4183-94.
[22] Hernández-Ruiz E, Hernández-Muñoz I, Masferrer E, Ferrándiz-Pulido C, Andrades E, Gimeno J, et al. A myxoid fibrotic reaction pattern is associated with metastatic risk in cutaneous squamous cell carcinoma. Acta Derm Venereol. 2019;99:89-94.
[23] Cao L, Sun P-L, He Y, Yao M, Gao H. Desmoplastic reaction and tumour budding in cervical squamous cell carcinoma are prognostic factors for distant metastasis: A retrospective study. Cancer Manag Res. 2020;12:137-44.
[24] Henke E, Nandigama R, Ergün S. Extracellular matrix in the tumour microenvironment and its impact on cancer therapy. Front Mol Biosci. 2020;6:160.
[25] Kobayashi T, Ishida M, Miki H, Hatta M, Hamada M, Hirose Y, et al. Significance of desmoplastic reactions on tumour deposits in patients with colorectal cancer. Oncol Lett. 2022;25(1):1.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, Guntur Medical College, Guntur, Andhra Pradesh, India.
2. Assistant Professor, Department of Pathology, Guntur Medical College, Guntur, Andhra Pradesh, India.
3. Assistant Professor, Department of Pathology, Guntur Medical College, Guntur, Andhra Pradesh, India.
4. Professor and Head, Department of Pathology, Guntur Medical College, Guntur, Andhra Pradesh, India.
5. Postgraduate Student, Department of Pathology, Guntur Medical College, Guntur, Andhra Pradesh, India.
6. Assistant Professor, Department of Preventive Medicine, Guntur Medical College, Guntur, Andhra Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ramya Chitturi,
D. No. 57-15-7A, Flat No. T3, Krishna Sai Enclave, New Postal Colony,
Vijayawada, Andhra Pradesh, India.
E-mail: drchramya@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 01, 2026
- Manual Googling: Apr 21, 2026
- iThenticate Software: Apr 24, 2026 (1%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 20, 2026**
Date of Peer Review: **Feb 09, 2026**
Date of Acceptance: **Apr 27, 2026**
Date of Publishing: **Jun 01, 2026**