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P53 expression in colorectal carcinomas study at a tertiary health care center in South Kerala

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Abstract

Introduction: Colorectal carcinoma (CRC) ranks as the third most ubiquitous cancer globally and the fourth primary source of cancer-related mortality. Loss of the p53 gene is vital in the conversion of colorectal adenoma into carcinoma. The study aims to evaluate the prevalence of p53 expression and investigate its correlation with diverse clinicopathological parameters, providing valuable insights into the dynamics of colorectal cancer in the specified region.

Methods: A total of 42 CRC cases from tertiary healthcare center in South Kerala, India, were sampled between December 2018 and January 2021. Comprehensive clinical data and clinicopathological parameters were collected, followed by histomorphological and immunohistochemical evaluations. The results were then correlated with clinicopathological variables.

Results: Patients aged 45 to 82 years (mean 63.5) exhibited a predilection for the left colon (57%) and rectum (33%), with symptoms ranging from abdominal pain to weight loss. Histologically, 95.2% were adenocarcinomas, mostly moderately differentiated (57.1%). Tumor extension (T3: 57%) and lymph node involvement (N1: 29%) were prevalent, with Stage II tumors (38.1%) most frequent. P53 immunoreactivity was observed in 83.3% of cases, correlating with moderately differentiated grades, higher tumor extensions (T3/T4), N1/N2 lymph node statuses, and Stage II/III tumors. No significant associations were found with age, sex, lesion site, or tumor type. P53 nuclear positivity, identified through IHC analysis, provides crucial insights into cancer biology, prognosis, and potential therapeutic implications. The finding highlights significant associations between p53 expression and key clinicopathological parameters. P53 positivity is notably higher in moderately differentiated tumors (Grade) and T3/T4 tumor extensions compared to well and poorly differentiated grades and T1/T2 extensions, respectively. Significant links were also observed with lymph node status (N1/N2 > N0) and tumor stage (S2/S3 > S1), indicating a strong correlation between p53 expression and advanced disease characteristics. However, no significant associations were found with age, sex, lesion site, or tumor type. The novelty of our study lies in the focused exploration of p53 expression in colorectal carcinomas. By specifically investigating the correlation between p53 expression and various clinicopathological parameters, we contribute a unique perspective to the understanding of the molecular characteristics of colorectal cancer. This targeted approach enhances the visibility of novel insights that our study brings to the field of p53 expression in the context of colorectal carcinomas.

Conclusion: Our investigation underscores that p53 overexpression is particularly prominent in advanced-stage colorectal cancer cases and those having LNM, further supporting its role as an adverse prognostic marker in this context.

Keywords: Colorectal carcinoma, P53, Immunohistochemistry, Lymph node, Prognosis

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Introduction

Colorectal carcinoma (CRC), a prevalent malignancy worldwide, poses a significant health challenge due to its high ubiquity and associated morbidity and mortality In 2020, it resulted in approximately 1.9 million new cases and 930,000 deaths. Factors such as age, family history, genetics, and lifestyle choices, including diet, physical activity, smoking, and alcohol consumption, influence the risk of developing CRC. Incidence and mortality rates vary significantly worldwide, with Europe and Australia/New Zealand experiencing the highest rates and Africa and Asia the lowest. Projections suggest a 63% increase in incidence and a 73% rise in mortality by 2040 (1), driven by population growth, ageing, and evolving risk factors. While CRC is preventable and treatable, early detection and proper management are crucial, emphasizing the importance of effective strategies for primary prevention, screening, diagnosis, and treatment

Also, it is the third most ubiquitous cancer in men along with the second most ubiquitous cancer in women across the globe. However, in India, the incidence rates of colon cancer are notably lower in comparison to other cancer types (2) In India, the annual incidence of CRC stands at 4/100, 000, with Kerala reporting a slightly higher rate at 5.5/100, 000. In recent years, extensive research has focused on identifying specific biomarkers and clinicopathological variables that can provide valuable insights into the prognosis and management of CRC. One such key molecular player in the context of colorectal cancer is the p53 protein a critical tumor suppressor protein, which plays a fundamental role in preserving genomic stability along with regulating cell cycle progression. Dysregulation of the p53 pathway, often associated with p53 protein overexpression, has been involved in the development along with progression of CRC (3).

CRC stands as a complex malignancy characterized by a spectrum of clinical and pathological features. Our study, encompassing various demographic and tumor-related factors to unravel the intricacies of this disease. This investigation offered insights into key aspects such as age distribution, gender variations, preferred carcinoma sites, histological grading, tumor extension patterns, lymph node involvement, and tumor staging (4). Additionally, our scrutiny extended to the pivotal biomarker, p53, known for its association with cancer development and prognosis. By comprehensively examining these demographic and tumor-related factors, our study adds valuable insights to the intricate landscape of colorectal adenocarcinoma. The focus on p53 expression further contributes to the understanding of molecular markers with potential implications for prognosis and targeted therapeutic interventions (Harris and Hollstein, 2013) (5). The study aimed to determine the correlation between p53 expression and clinicopathological parameters in CRC, focusing on tumor grade, extension, lymph node status, and stage to elucidate the molecular implications for prognosis and therapy.

Methods

This cross-sectional study involved CRC patients' cases presented to the Department of Pathology at Pushpagiri Institute of Medical Sciences and Research Centre, Thiruvalla, Kerala, India, between December 2018 and January 2019. The study included a cohort of 42 patients for analysis and relevant clinical data, encompassing variables such as age, gender, colon subsite distribution, clinical presentation at diagnosis, histopathological type, tumor grade, disease stage, and presence of LNM, were collected from medical records for evaluation and correlation analysis.

Inclusion criteria encompassed all histopathologically diagnosed cases of carcinoma in the colon and rectum, comprising both biopsies and resected specimens.

Exclusion criteria

Comprised endoscopic biopsies with corresponding resected specimens of the colon and resection specimens from patients who underwent neoadjuvant chemotherapy.

Immunohistochemical (IHC) Staining for p53

IHC staining for the p53 protein was conducted using 5-micrometer sections acquired from formalin-fixed paraffin-embedded blocks. These IHC-stained sections were evaluated alongside H&E-stained specimens to determine the expression of p53 in CRC . The interpretation of p53 immunostaining was based on whether it was positive or negative. Also, positive

staining was demarcated as the presence of nuclear staining in ≥5% of cells per high-power field.

Data Analysis

The collected data was input into Microsoft Office Excel 2019 spreadsheets and subsequently analysed using SPSS version 16.0 software. Associations between p53 expression and clinicopathological parameters were assessed using Fisher's exact test. A p-value less than 0.05 was deemed to be significant in statistical terms. The study findings were presented in appropriate charts and tables.

Ethical Considerations

All procedures performed in this study received approval from the Institutional Review Board (IRB) with reference number 19666/2018, dated 17/01/2019. The research followed the guidelines established in the Helsinki Declaration of 1964 along with its following revisions. Written informed consent was not required, as determined by the IRB, with a waiver granted for this purpose.

Results

The results demonstrate the patient population and the characteristics of the colorectal adenocarcinoma cases under investigation. In a cohort of 42 cases, we observed a diverse range of demographic and tumor-related factors. As shown in Figure 1, the study group, patients' ages spanned from 45 to 82 years, with the most substantial representation observed in the 61-70 years age category. The mean age at diagnosis was 63.5±10.60 years, and a minority of patients, specifically 11.9% (n=5), were under the age of 50.

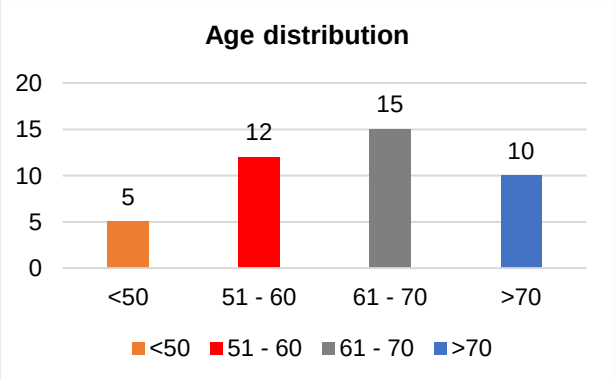

Figure 1. Age Distribution within the study population.

Among the 42 cases examined (as depicted in Figure 2), 19 were male, while 23 were female, resulting in a male-to-female ratio of 0.8:1.

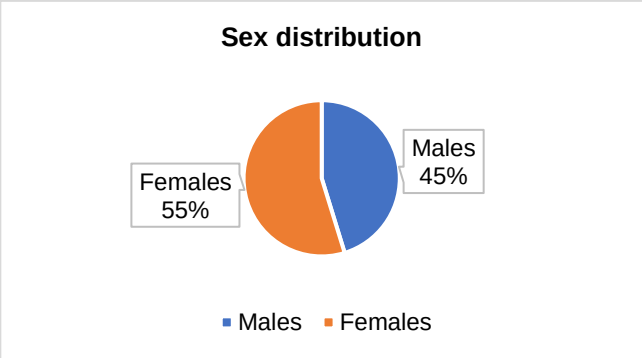

Figure 2. Gender wise distribution among study population.

As illustrated in Figure 3, the observed tumor growth exhibited a predilection for the colon and rectum's left side, with 24 (57%) cases occurring in this region, whereas 33 % cases were observed under rectum site and 10 % were on left side Clinical presentations among these cases varied and included symptoms such as abdominal pain, rectal bleeding, altered bowel habits, signs indicative of intestinal obstruction, weight loss, and anaemia.

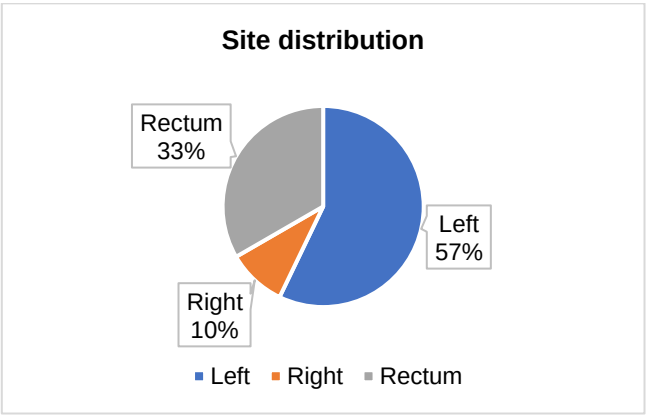

Figure 3. Distribution of Carcinoma Sites within the Study Population.

As depicted in Figure 4, histological grading show vast majority of colorectal carcinomas, accounting for 95.2% (n=40), were categorized as adenocarcinoma NOS. Within this category, 57.1% (n=24) were moderately differentiated, 38.1% (n=16) were well-differentiated, and a smaller proportion, 4.8% (n=2), were poorly differentiated.

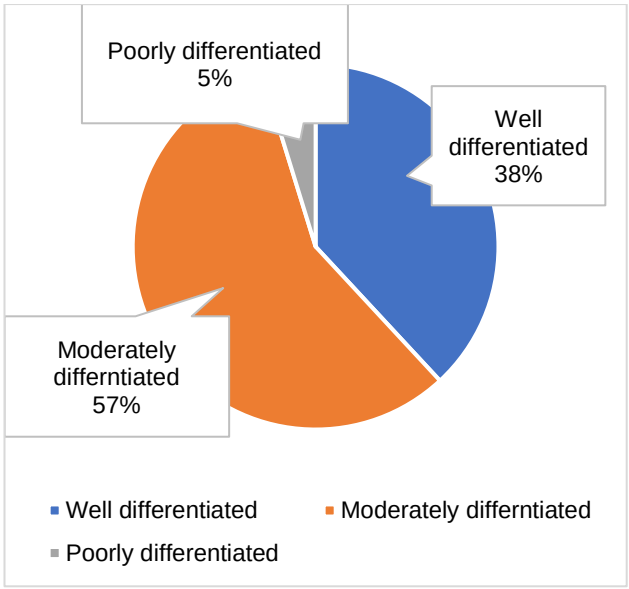

Figure 4. Histological grading among study population.

This histology image (Figure 4.1) demonstrates that moderately differentiated adenocarcinomas were predominantly observed in the left colon within the study population.

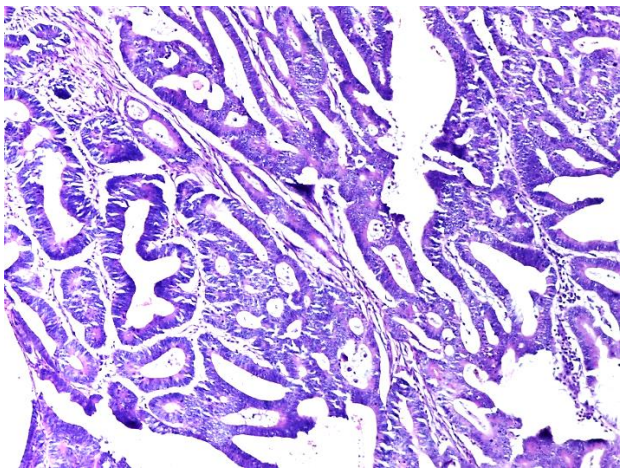

Figure 4.1. Moderately differentiated adenocarcinoma – left colon (H&E).

As shown in Figure 5 the remaining cases comprised two instances of mucinous carcinoma. Among the tumors, 57% (n=24) exhibited infiltration extending beyond the muscularis propria into the adjacent pericolic adipose tissue, designated as T3, while 31% (n=13) were restricted to the muscularis propria, categorized as T2 A smaller subset, 9.5% (n=4), showed infiltration into the visceral peritoneum or adjacent organs, classified as pT4. Additionally, only one case (2.4%) was identified as an early-stage T1 tumor.

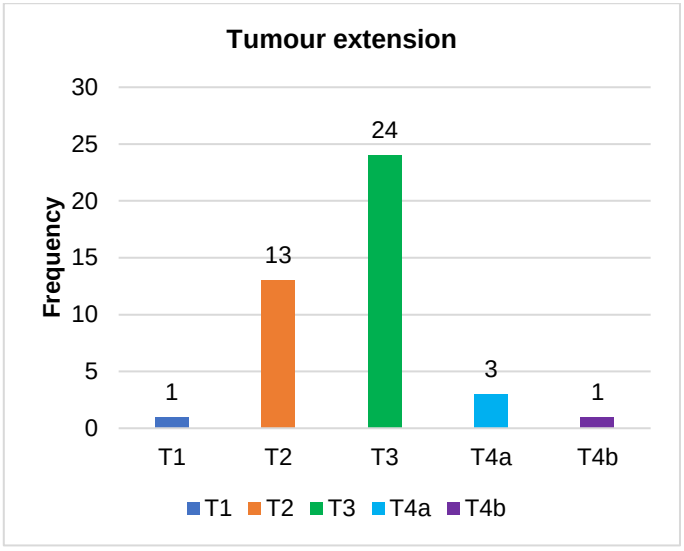

Figure 5. Distribution of tumor extension among study population.

As indicated in Figure 6 in half of the cases, there was no evidence of nodal involvement, whereas 29% were categorized as N1 and 21% as N2 were observed in study population.

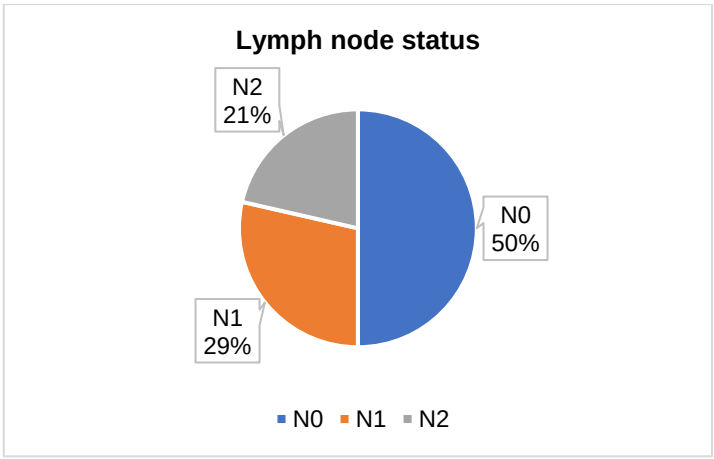

Figure 6. Distribution of Lymph node status among study population.

As demonstrated in Figure 7, the most frequently observed tumor stage was Stage II, with 38.1% (n=16) of cases, followed by Stage I tumours at 33.3% (n=14), and Stage III at 28.6% (n=12).

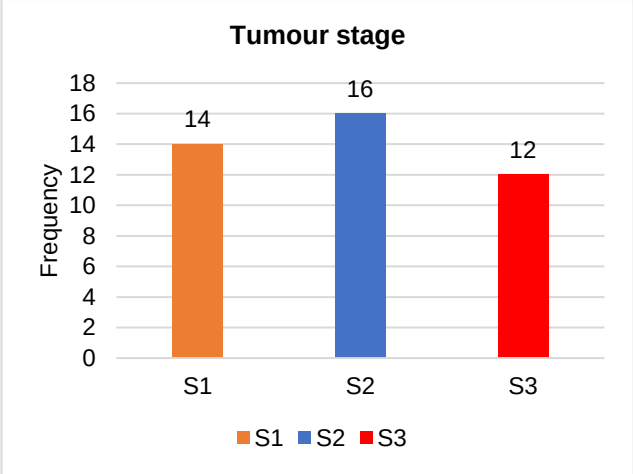

Figure 7. Distribution of tumour staging among study population.

As depicted in Figure 8, p53 immunoreactivity expression was detected in 35 cases of CRC, making up 83.3% of the study cohort. Only seven cases (16.7%) displayed no p53 expression.

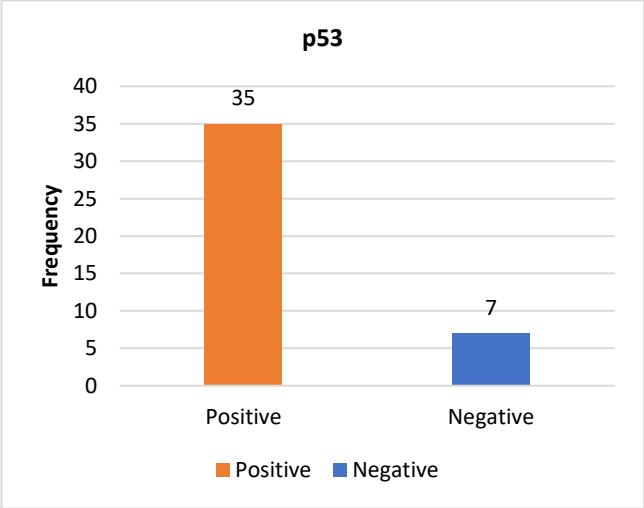

Figure 8. Expression of p53 immunoreactivity among study population.

P53 nuclear positivity, as observed in Figure 8.1 (IHC), signifies the presence of the p53 protein within the cell nuclei. In this context, p53 nuclear positivity suggests that the p53 protein is actively present and localized within the nuclei of the cells in the examined tissue sample. This finding can be significant in cancer research and diagnosis, as alterations or overexpression of the p53 protein are associated with various cancer types and can provide insights into the molecular characteristics of the tumor, its prognosis, and potential therapeutic implications. Therefore, identifying p53 nuclear positivity through IHC analysis is vital in comprehending the biology and behaviour of cancer cells in the context of the studied tissue or tumor specimen.

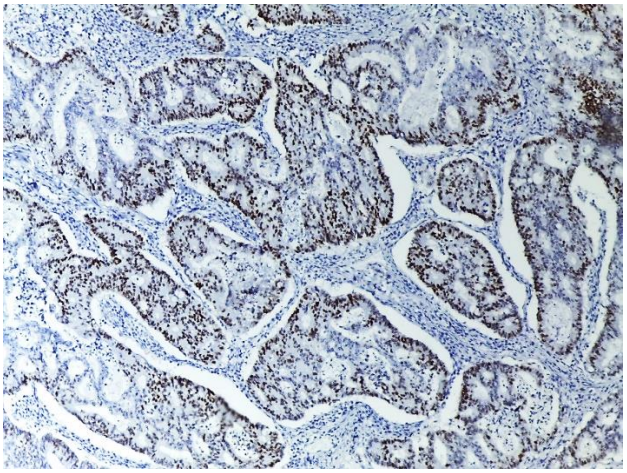

Figure 8.1. p53 nuclear positivity corresponding to Image 1 (IHC).

In table 1, the study revealed a noteworthy association between p53 expression and various clinical-pathological characteristics. Notably, p53 positivity was more frequent in moderately differentiated tumor grades compared to well and poorly differentiated tumors. There was also a significant link between p53 expression and tumor extension, with T3 and T4 tumors showing higher p53 positivity compared to T1 and T2. Similarly, lymph node status and tumor stage exhibited significant associations with p53 expression, indicating that N1 and N2 lymph node statuses and stages S2 and S3 were more likely to be p53-positive. However, no noteworthy links were observed between p53 expression and other clinicopathological factors like age, sex, site of lesion, or tumor type.

Table 1. Correlation of clinicopathologic parameters with the expression of p53.

Clinical pathological Characteristic	Fisher's Exact Value	P-Value	Association with p53 Expression
Grade of the Tumor	7.255	0.024	Significant
			Moderately > Well & Poorly
Tumor Extension	5.355	0.031	Significant
			T3 & T4 > T1 & T2
Lymph Node Status	7.177	0.012	Significant
			N1 & N2 > N0
Stage of the Tumor	14.053	0.000	Significant
			S2 & S3 > S1

Discussion

The findings of our study provide valuable insights into the clinicopathological characteristics and p53 expression in colorectal adenocarcinoma cases within our patient population. The study discusses age distribution in Figure 1 depicts a diverse age distribution, with a significant representation in the 61-70 years age category. The male-to-female ratio of 0.8:1, as illustrated in Figure 2, aligns with existing literature. These demographic observations are consistent with previous studies, mean age distribution in previous studies ranged from 55.23 to 59 years, with varying gender ratios, while our study showed a predominance of females, consistent with study by (Mardi et al., 2017) (4). In this study Figure 3 highlights a predilection for tumor growth on the left side of the colon and rectum, consistent with known distribution. Clinical presentations varied, encompassing symptoms such as abdominal pain, rectal bleeding, altered bowel habits, signs of intestinal obstruction, weight loss, and anemia.

Histological grading, showcased in Figure 4, reveals a predominance of adenocarcinoma NOS, with moderately differentiated tumors being the most prevalent. Figure 5 illustrates diverse tumor extension patterns, with a notable frequency of infiltration beyond the muscularis propria (T3). Figure 6 indicates diverse lymph node status, with notable associations in half of the cases, and Figure 7 portrays a varied distribution of tumor staging, with Stage II being the most frequently observed. In our investigation, colorectal carcinomas were primarily classified as adenocarcinoma NOS, with a predominance of moderately differentiated tumors, followed by well-differentiated and poorly differentiated subtypes. The T staging system revealed diverse tumor extension patterns, ranging from infiltration beyond the muscularis propria (pT3) to confined muscularis propria involvement (pT2), as well as infiltration into the visceral peritoneum or adjacent organs (pT4) and rare early-stage T1 tumors, while lymph node status and tumor stage indicated significant prognostic variability, with Stage II being the most common, followed by Stage I and Stage III.

Moderately differentiated adenocarcinoma displayed a higher frequency of p53 positivity (95.8%) compared to well-differentiated tumors, with a statistically noteworthy link between p53 expression and tumor grade, consistent with findings (Harris & Hollstein, 2013) (5) reported an increased frequency of p53 expression in 95% of moderately differentiated adenocarcinomas, further supporting this correlation.

Our study revealed a predilection for tumor growth on the left side of the colon and rectum, a finding consistent with the known distribution of colorectal cancers. (Fearon & Vogelstan, 2010) (6). reported a comparable histological type distribution to our study, where conventional adenocarcinomas were predominantly located in the left colon, consistent with existing literature, and most cases in our study were moderately differentiated (57.1%), in line with the findings by (Dignam et al., 2016) (7).

The evaluation of lymph nodes continues to be the primary method for determining prognosis and determining the need for adjuvant treatment. We noted LNM in 21 cases (50%) which was comparable to the investigation by (Chithra et al., 2018) (8).

Similarly, Kim et al.,(2022) (9) summarize the role of p53 signaling in colorectal cancer, including the molecular mechanisms, the clinical implications, and the therapeutic strategies results have reported a high frequency of p53 expression in colorectal carcinomas and its association with tumor grade, extension, lymph node status, and stage. Another study by (Cotran et al., 2014) (10) compares the clinical effect of p53

expression and TP53 variation status in colorectal cancer patients, using immunohistochemistry and next-generation sequencing hence finding suggest that p53 expression rather than TP53 variation status has more significant impact on the overall survival of colorectal cancer patients and also suggest However, some studies have also found significant correlations between p53 expression and age, sex, lesion site, or tumor type , which were not observed in our study.

Another relevant stud done by Tomicic et al., (2021) (11) which investigates the role of mutant p53 in colon cancer, using human and mouse genetic studies and explain the possible mechanisms and functions of mutant p53 in colorectal carcinogenesis and progression. Additionally, a study done by Scott et al., (2011) (12) explores the epigenetic alterations upstream and downstream of p53 signaling in colorectal cancer, including DNA methylation, histone modifications, and micro-RNAs, insights into the complex regulation of p53 signaling by epigenetic factors and its implications for colorectal cancer diagnosis and therapy.Finally, study by Mizuho et al.,(2019) (13) which examines the correlation between p53 expression and clinicopathological parameters in colorectal cancer, using immunohistochemistry and corroborate with current finding that p53 expression is associated with tumor grade, extension, lymph node status, and stage in colorectal cancer patients.

Similarly, overexpression was observed in cases with LNM (100%), indicating a poor prognosis associated with p53 detection in CRC. A statistically noteworthy link was found between p53 expression, tumor extension, and LNM. In Figure 8, p53 immunoreactivity is detected in 83.3% of cases, with a notable nuclear positivity (Figure 8.1). Table 1 underscores significant associations between p53 expression and clinicopathological characteristics, emphasizing its prevalence in moderately differentiated tumors, advanced tumor stages, and lymph node involvement. Our findings offer a comprehensive understanding of the clinicopathological landscape of colorectal adenocarcinoma, highlighting the significance of p53 expression as a potential prognostic indicator. These insights contribute to the ongoing efforts to unravel the complexities of this malignancy and pave the way for targeted therapeutic interventions. According to study by (Dabiri et al., 2019) (14) contributes to a comprehensive understanding of the clinicopathological landscape of colorectal adenocarcinoma. The prevalence of p53 expression in specific tumor grades and stages emphasizes its potential as a prognostic marker. These insights not only validate prior research but also add nuanced details to the intricate interplay between p53 and the progression of colorectal carcinoma.Similarly (Russo et al., 2012)(15) observed associations underscore the significance of p53 expression as a potential prognostic indicator in colorectal adenocarcinoma. Identification of p53 as a molecular marker holds promise for predicting the behavior of tumors and guiding therapeutic interventions. Given its prevalence in advanced stages and lymph node involvement, p53 expression could aid in risk stratification and decision-making regarding the intensity of therapeutic strategies.

In summary of the discussion, the findings highlight the diversity within CRC cases and underscore the significance of p53 as a molecular marker associated with various clinicopathological parameters. The clinical significance of p53 expression in colorectal carcinomas remains debated, with our study suggesting its potential as a useful biomarker for identifying advanced disease. Recent studies also support the role of p53 signaling in colorectal cancer and its impact on overall survival.

In study provides valuable data on clinicopathological characteristics and p53 expression in colorectal adenocarcinoma, shedding light on potential prognostic markers and guiding further research for a comprehensive understanding of this complex disease

Conclusions

In conclusion, study includes 42 colorectal adenocarcinoma cases providing key insights. Notably, the age span (45-82 years) centers around 61-70 years, with a male-to-female ratio of 0.8:1. Carcinoma growth predominantly occurs on the left side (57%), and most cases are adenocarcinoma NOS (95.2%), with 57.1% being moderately differentiated. Tumor extension, lymph node involvement, and staging patterns exhibit diversity. P53 expression is detected in 83.3% of cases, emphasizing its significant nuclear presence. Clinical-

pathological associations highlight links with tumor characteristics but not with age, sex, site, or tumor type. Hence understanding of colorectal adenocarcinoma, with a particular focus on the prevalent expression of p53 and its clinicopathological implications. This underscores the importance of incorporating p53 status into the comprehensive management strategy for this intricate malignancy.

Future perspectives

Undoubtedly, the reactivation and restoration of p53 function hold significant promise as a novel therapeutic approach for CRC. However, it's worth noting that while several molecules have demonstrated the ability to induce cell cycle arrest and apoptosis in CRC cells, most of these findings originate from cell line and animal model studies and have not yet progressed to clinical trials. Additionally, the diverse oncogenic effects of mutant p53 remain incompletely understood, and the impact of different mutations on p53 function complicates the assessment of small molecule inhibitors targeting mutant p53 in clinical trials. This area of research warrants further exploration. Notably, addressing resistance to treatments and improving the prognosis of CRC patients with new p53 mutations will necessitate the ongoing development of agents specifically targeting these novel mutations.

Author contribution

All authors have contributed equally and read and approved the final draft of the manuscript.

Conflict of interest

The authors report no conflict of interest.

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