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ORIGINAL RESEARCH ARTICLE

PTEN Expression and Specific Clinicopathological Associations in Colorectal Carcinomas

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ABSTRACT

Introduction: Colorectal carcinoma (CRC) refers to any cancer that affects the colon and the rectum and it is a significant public health issue.[1] It is the third most common cancer to be diagnosed globally and the fourth most frequent reason for cancer-related mortality. The diagnosis of CRCs occurs in places with affluent economies about 60% of the time. The present study assessed phosphatase and tensin homolog (PTEN) expression in colorectal cancer and its association with tumor characteristics.

Materials and Methods: The study was carried out over the course of 18 months, from 1 February 2021 to 31 July 2022, at the SRMS IMS Bareilly Department of Pathology. The analysis included surgically removed specimens of colorectal cancer that had been obtained at the SRMS, IMS Department of Pathology. The patient's medical records provided the clinical information.

Results: Loss of PTEN expression was seen in 76.9% of CRC cases, while 23.1% of cases revealed positive expression. Maximum cases were of age>60 years and male predominance was noted. In 62.5% of cases with tumor size ≥5 cm displayed loss of PTEN expression. In 52.5% loss of PTEN tumor cases were histologically moderately differentiated, 37.5% were well differentiated, and 10% were poorly differentiated. 50% of cases with pathologic tumor stage (pT3) and 65% left-sided tumors showed loss of PTEN expression.

Conclusion: Loss of PTEN expression was observed in the majority of colorectal tumors along with its negative association with tumor size and pathologic tumor staging.

Keywords: Colorectal cancer, PTEN, Pathologic tumor stage, Tumor size.

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INTRODUCTION

Any cancer affecting the colon and the rectum is referred to as colorectal carcinoma (CRC), a significant public health issue.[1] It is the third most common cancer to be diagnosed globally and the fourth most frequent reason for cancer-related mortality. The diagnosis of CRCs occurs in places with affluent economies about 60% of the time.

CRC is a common cancer worldwide, however, there is little data on how common it isin India. CRC is not common in India; the estimated five-year prevalence is 87 per 100,000 people. The low incidence of CRC in developing countries is assumed to be caused by variations in dietary habits and lifestyles. Yet, death rates are higher in less developed nations with weak health infrastructure and sparse resources. This demonstrates the deficiencies in the routes for CRC diagnosis and care.[2]

Many different tumor types, including breast cancer, melanoma, prostate cancer, endometrial cancer, and brain tumors, such as glioblastomas and astrocytomas, have expressed PTEN gene abnormalities.[3] PTEN expression or function may be compromised at the genomic, transcriptional, post-transcriptional, and post-translational levels during the development of colorectal tumors.[4]

The current study aimed to assess PTEN expression in colorectal cancer and its association with clinicopathological parameters.

MATERIALS AND METHODS

The study was carried out at the SRMS IMS Bareilly Department of Pathology overthe course of 18 months, from 1 February 2021 to 31 July 2022. Surgically removed specimens of histologically proven CRC that were received at the SRMS, IMS pathology department were included. Small biopsies of CRC, all non-neoplastic lesions and benign tumors of the colorectum were all excluded.

Data Collection

The patient's medical records provided the clinical information. Gross details of thespecimens were checked and recorded and then were fixed in formalin for 24 hours before the standard routine processing of the

biopsy specimens and paraffin embedding. Sections of 5 μm thickness were cut to be stained with hematoxylin and eosin. Routine staining was done with hematoxylin and eosin.

Assessment of IHC

The percentage of PTEN immunostaining tumor cells was determined, and the staining results were scored using a semi-quantitative scoring system:

Score	*Percentage of tumor cells (%)*
0	<5
1	5–25
2	25–50
3	>50

For PTEN expression, scores of 0 were deemed negative and 1, 2, and 3 were deemed positive.

Data Analysis

Data were recorded in a proforma, entered into Microsoft® Excel workbook 2019, and exported into SPSS v21.0 (IBM, USA) for statistical analysis. Categorical data were expressed as frequency percentages, and compared using Chi-square test and Fischer exact test. *p-value* <0.05 was considered statistically significant.

RESULTS

Demographics Characteristics

The majority of subjects (46.2%) were over 60 years, and the least cases (3.8%) were in the 10 to 20 year age range. A total of 32 subjects (61.5%) were male, compared to 20 (38.5%) female subjects, showing that men were more prevalent. 33 (63.5%) cases were located on the left side of the colon and the remaining 19 cases (36.5%) were located on the right side. In 31 instances (59.6%) had tumor sizes equal to or larger than 5 cm, while 21 cases (40.9%) had tumor sizes smaller than 5 cm.

Adenocarcinoma NOS accounts for 80.8% of cases, with mucinous adenocarcinoma and signet ring cell carcinoma accounting for 11.5 and 7.7% of cases, respectively (Table 1).

Table 1: Demographics characteristics (N = 52)

Demographics Characteristics	*Frequency (n)*	*Percentage (%)*
Age Group(years)		
10–20	2	3.8
21–30	3	5.8
31–40	8	15.4
41–50	11	21.2
51–60	4	7.7
>60	24	46.2
Gender		
Female	20	38.5
Male	32	61.5
Tumor Site		
Right	19	36.5
Left	33	63.5
Tumor Size		
<5 cm	21	40.4
≥5 cm	31	59.6
Tumor Type		
Adenocarcinoma,NOS	42	80.8
Mucinous Adenocarcinoma	6	11.5
Signet ring cell Adenocarcinoma	4	7.7

Histological Differentiation

In our study, 20 cases had well histological differentiation, 27 had moderate differentiation, and 5 (9.6%) had poor differentiation (Table 2).

Lymph vascular Invasion

Out of 52 instances, lymph vascular invasion was found in 34 cases (65.4%) andabsent in 18 cases (34.6%).

Pathologic Tumor staging

In our study, the majority of cases (53.8%) were in the pT3 stage, followed by 32.7% in the pT4 stage, 9.6% in the pT2 stage and 3.8% in the pT1 stage.

Relationship of PTEN expression with the Tumor characteristics

PTEN expression was positive in 23.1% of colorectal carcinoma cases and negative in 76.9% of cases. PTEN expression in differentiated tumors have been shown in Figure 1. 75% positive PTEN tumor has size <5 cm. Tumor size was significantly associated with PTEN expression (*p-value* = 0.009). 41.7% of positive PTEN tumors had histologically well differentiated, 50% had moderately differentiated, and 8.3% had poorly differentiated. Histological differentiation was not significantly

Table 2: Criteria for histological grading of colorectal adenocarcinomas

Criterion	*Differentiation category*	*Numerical grade*
>95% gland formation	Well-differentiated	1
50–95% gland formation	Moderately differentiated	2
<50% gland formation	Poorly differentiated	3

Table 3: Relationship of PTEN expression with the tumor characteristics

Clinico pathological parameters	*Total Number of cases (n = 52)*	*Pten expression*		*p-value*
		Positive (%) N = 12 (23.1%)	*Negative (%) n = 40 (76.9%)*	
Site of tumor				
Right	19	41.7	35	0.674
Left	33	58.3	65	
Size of tumor				
<5 cm	22	75	32.5	0.009
≥5 cm	30	25	62.5	
Histological grade				
Well-differentiated	20	41.7	37.5	
Moderately differentiated	27	50	52.5	0.961
Poorly differentiated	05	8.3	10	
Lymphovascular invasion				
Absent	18	58.3	27.5	0.05
Present	34	41.7	72.5	
Pathological stage				
pT1	02	6.7	00	
pT2	05	8.3	10	0.019
pT3	28	66.7	50	
pT4	17	8.3	40	
Lymphnode staging				
N0	25	58.3	45	0.417
N1 + N2	27	41.7	55	

associated with PTEN expression (*p-value* = 0.961). 41.7% positive PTEN tumor had lympho-vascular invasion. Lympho-vascular invasion was also not significantly associated with PTEN expression (*p-value* = 0.05).

In 16.7% positive PTEN tumor had tumor staging pT1, 8.3% had pT2, 66.7% had pT3, and 8.3% had pT4. Tumor staging was significantly associated with PTEN expression (*p-value* = 0.019). 41.7% positive PTEN were located in the right side of the tumor and 58.3% positive PTEN tumors in the left side of the colon.

The tumor site was not significantly associated with PTEN expression (P = 0.674) (Table 3).

DISCUSSION

In the present study, most subjects (46.2%) were over 60 years, and the least (3.8%) were in the 10 to 20 year age range. In investigations conducted by Waniczek al,[5] Li *et al.*,[6] and Nassif *et al.*,[7] the mean age at diagnosis was 67.7 years (42-81), 69.16 years and 67 years, respectively, which was slightly higher than in our study. In a study done by Yazdani *et al.*,[8] comparable findings, with a higher percentage of occurrences involving patients over 50 years.

A total of 32 subjects (61.5%) were male, compared to 20 subjects (38.5%) who were female, showing male predominance with a female ratio of 1.6:1. A similar distribution was reported by Nassif *et al.*,[7] with 22 males (56.4%) and 17 females (43.6%). In a study done by Yazdani *et al.*,[8] 70 (56%) were men and 55 (44%) were women.

Cases 33 (63.5%) were located on the left side, and the remaining 19 cases (36.5%) were located on the right side of the colon. In 31 instances (59.6%) had tumor sizes equal to or larger than 5 cm, while 21 cases (40.9%) had smaller than 5 cm sizes. Right- and left-sided cancers are different in terms of clinic-pathological characteristics and molecular pathogenesis. In a study done by Spano *et al.*,[9] left-side cancers (43%) were higher as compared to the right side (24%) but contrasting to it Nassif *et al.*,[7] observed more right-sided carcinomas (56.1%) than left-sided.

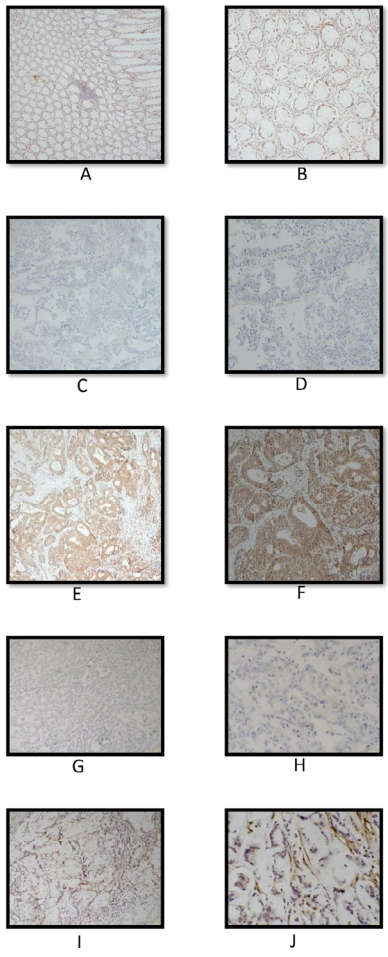

Figure 1: PTEN expression. A-B: PTEN control: Normal colonic mucosa (10X and 40X), C-D: PTEN expression- Negative in moderately differentiated adenocarcinomas of the colon (10X and 40X), E-F: PTEN expression- Positive in a case of well-differentiated adenocarcinomas of the colon (10X and 40X), G-H: Loss of PTEN expression in poorly differentiated adenocarcinoma of the colon (10X and 40X), and I-J: Loss of PTEN expression – mucinous carcinoma of colon (10X and 40X).

Adenocarcinoma NOS accounts for 80.8% of cases, with mucinous adenocarcinoma accounting for 11.5% of cases and signet ring cell carcinoma accounting for 7.7%. Similar to our study, Waniczek D *et al.*[5] also observed 23 (65.7%) cases were moderately differentiated and 08 (22.9%) cases were well differentiated, and the remaining 04 (11.4%) cases were poorly differentiated out of the total 35 cases. Ali A. *et al.*[10] and Nassif *et al.*[7] observed in their studies the maximum number of cases were of moderately differentiated cases, followed by poorly differentiated and well differentiated.

Based on tumor staging, the maximum number of cases (53.8%) were in the pT3 stage followed by 32.7% cases in the pT4 stage, 9.6% in pT2 staging, and minimum in the pT1 stage (3.8%). In the study done by Waniczek D *et al.*,[5] cases in stage pT1, pT2, pT3, and pT4 were 11.4, 28.6, 40, and 20% of patients respectively. Spano *et al.*,[9] reported 64% in T3, 23% in T4, 11% in T2, and 2% in the T1 stage.

Out of 52 cases, lymph vascular invasion was present in 34 cases (65.4%). In a study by Powell *et al.*,[11] vascular invasions were seen in 172 cases (41.8%) out of a total of 411 cases. However, in a study by Li XH *et al.*,[6] only 49 (15%) cases out of 327 subjects presented with lymph vascular invasion.

Loss of PTEN expression was seen in 76.9% and positive PTEN expression in 23.1% of colorectal carcinoma cases. 75% of positive PTEN cases had a tumor size <5 cm.

Tumor size was significantly associated with PTEN expression (*p-value* = 0.009). 41.7% of positive PTEN tumor had histologically well differentiated, 50% had moderately differentiated, and 8.3% had poorly differentiated. Histological differentiation was not significantly associated with PTEN expression (*p-value* = 0.961). 41.7% positive PTEN tumor had lympho-vascular invasion. Lympho-vascular invasion was significantly associated with PTEN expression (*p-value* = 0.048). 16.7% positive PTEN tumor had tumor staging pT1, 8.3% had pT2, 66.7% had pT3, and 8.3% had pT4.

Tumor staging was significantly associated with PTEN expression (*p-value* = 0.019). 41.7% of positive PTEN tumor had right-sided tumor site and 58.3% of positive PTEN tumor had left tumor site. Tumor site was not significantly associated with PTEN expression (p = 0.674).

Li *et al.*,[6] Hsu *et al.*,[12] and Yazdani *et al.*[8] in their studies had similar results with a non-significant relationship between PTEN expression and histological differentiation of CRC cases. Similar outcomes were seen in a study conducted by Yazdani *et al.*,[8] Hsu *et al.*[12] also reported a significant association between lower PTEN expression and advanced T3 and T4 stages. This difference was not found to be statistically significant. In a similar study done by Waniczek *et al.*,[5] Hsu *et al.*[12] also showed no such significance. However, a study done by Li *et al.*,[6] showed a significant relationship between PTEN expression and lymph node metastasis.

CONCLUSION

PTEN expression was observed to be lost in 65.4% of colorectal cancer patients. The size of the tumor and the progressing pathologic tumor stage were statistically associated with loss of nuclear PTEN expression on IHC examination.

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