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ANALYSIS OF THE PROGNOSTIC SIGNIFICANCE OF P53 IN COLORECTAL CARCINOMAS

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ABSTRACT

Colorectal carcinoma, which is rather a common cancer, constitutes a significant proportion of the global burden of cancer morbidity and mortality. Tumour extent, lymph node status, tumour grade and the assessment of lymphatic and venous invasion are still the most important morphological prognostic factors. P53 is one of the most frequently mutated genes in human cancers & mutation of p53 is a late event in colorectal carcinogenesis. In our study we have evaluated p53 expression in 50 cases of colorectal adenocarcinomas and found a statistically significant (P value = 0.027) correlation between p53 over expression & advanced stage of the tumour but not the grade of the tumour. Mucinous carcinomas had a lower level of expression of p53. Hence p53 can be used as a prognostic marker in conventional adenocarcinomas and it may help to assess the responsiveness of the patients to standard chemotherapy regime.

KEY WORDS: colorectal carcinoma, p53, prognosis, mucinous carcinoma

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with an estimated 1, 30,000 new patients diagnosed each year. Colorectal adenocarcinoma accounts for over 90% of the malignant tumors of the large bowel.[1] It is the second leading cause of death because of cancer (approximately 55,000 people annually).[2] About 60% of all patients diagnosed with colorectal carcinoma will present with locally advanced disease.[3] Appropriate therapeutic decision making for these individuals depends primarily on the depth of penetration of the primary tumor and metastatic disease in the regional lymph nodes.[4] Unfortunately, despite improvements in medical and surgical provision, there has been comparatively little change in mortality due to colorectal cancer during the past 40 years and the overall five year survival is only around 40%.[5] There are a number of genetic mutations involved in colorectal carcinogenesis. These can be assessed by immunohistochemistry. Mutations in p53 have been found to occur in 70% to 80% of patients with colon cancer.[2] This p53 mutation was proposed as a late event in the transition from adenoma to carcinoma. Preclinical investigations have demonstrated that mutant p53 renders malignant cells less sensitive to most chemotherapeutic agents.[6] The purpose of this study is to analyse the level of expression of p53 in colorectal adenocarcinomas and correlate this with the histological grade and stage.

MATERIALS AND METHODS

This study is a prospective study undertaken in the department of pathology over a period of 3 years. A total of 120 colectomy specimens received were analysed.

(i) Plan

The patients who were included in this study were screened with predetermined inclusion and exclusion criteria. Selected patients underwent through consent protocols. Brief clinical history and examination findings were collected with predetermined proforma.This study was approved by our institutional ethical committee.

(ii) Inclusion criteria

All cases proved to be adenocarcinomas of colorectal region by histopathology irrespective of age and sex was included for the study.

(iii) Exclusion criteria

All malignancies of the colorectal region other than adenocarcinomas and those cases with poor clinical data were excluded from the study.

(iv) Method of data collection

All the cases enrolled in the study according to the above criteria were evaluated. Of the 120 cases, adenocarcinomas found in 115 cases. Among the 115 cases, 100 cases had adequate clinical and investigatory data. Among these cases, 7 were of mucinous subtype. Adequate samples were taken from the growths in these specimens. Histopathological appearance and extent of the malignancies were studied. The adenocarcinomas found have been categorized into well differentiated (grade I), moderately differentiated (grade II) and poorly differentiated (grade III).[7] The number of cases in each category were tabulated. The staging of the malignancy was done according to the American Joint Committee on Cancer (AJCC) staging system[8] and the results were tabulated. P53 expression was studied by immunohistochemistry in various stages and grades of the tumour in 50 randomly selected cases which included 6 mucinous carcinomas.

(v) Method of scoring for p53

With reference to the study by Martin Kruschewski et al,[9] the p53 immunohistochemical staining was scored based on the percentage of positive tumour cells as follows:

Score	% of positive tumour cells
0	0%
1	1%-10%
2	11%-25%
3	>25%

P53 expression was scored as 0 to 3 according to the percentage of cells showing nuclear positivity irrespective of the staining intensity. Results were tabulated and analyzed. For the purpose of statistical analysis stages I and II were categorized as low stage and stages III and IV were categorized as high stage. Similarly grade III and mucinous carcinomas were classified as high grade and Grades I and II were classified as low grade.

RESULTS

A total of 100 cases were studied. Histopathological examination and AJCC staging was done which showed the following results.

	NO. OF CASES
Adenocarcinomas	- 100
(i) Stage	
I	- 32
II	- 25
III	- 18
IV	- 25
(ii) Grade	
I	- 41
II	- 32
III	- 20
Mucinous carcinoma	- 07

Age of patients with colorectal adenocarcinoma was ranging from 24 to 76 years and it was more common in males. In those above 60 years of age high stage tumors were common (52.6%). In this study low grade tumours (Figure 1) predominated in both the sexes and the higher grade tumours were more common in males. Mucinous carcinomas (Figure 2) showed slight female preponderance. However, the statistical analysis using Chi-Square test revealed no significant correlation (p value = 0.247) between sex and the grade/histological type of the tumour. Most common clinical presentations of colorectal adenocarcinomas were bleeding per rectum and altered bowel habits (52% and 39% respectively).Most of the colorectal adenocarcinomas exhibited an ulceroproliferative growth pattern grossly (78%) (Figure 3). Rectum was the commonest site for colorectal adenocarcinomas in both the sexes and in all the age groups

Figure 1
Grade I adenocarcinoma – 100X

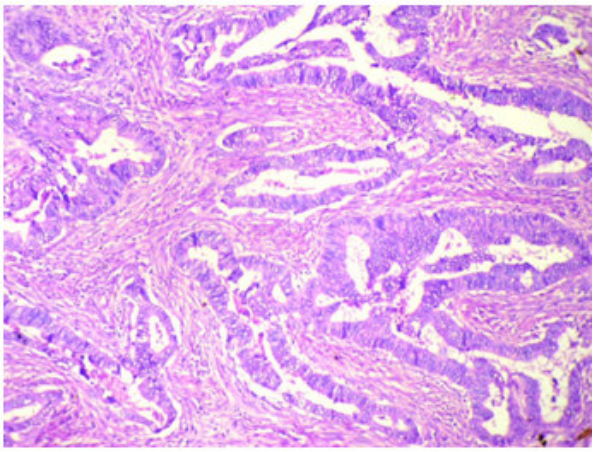
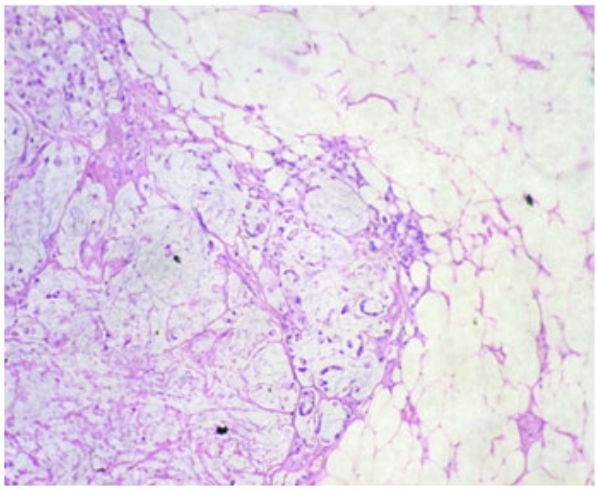
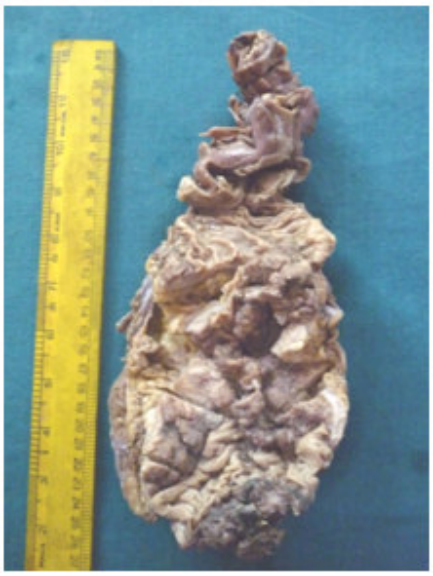


Figure 2
Mucinous carcinoma – 100X



Size of the tumours was ranging from 3 to 13 cm in maximum dimension. All those tumours which presented as luminal narrowing were present in rectum (n = 8). 67% of the larger tumours (>10 cm) were situated in the caecum

Figure 3
Ulceroproliferative growth - rectum



In our study 78% of the colorectal adenocarcinomas revealed p53 positivity (Table 1) (Figure 4, Figure 5, Figure 6, Figure 7 & Figure 8). The mucinous carcinomas showed a lower rate of p53 positivity. (Table 2) (Figure 9)

Figure 4
Grade I adenocarcinoma – score 3

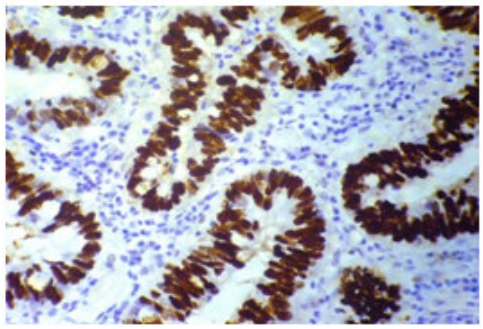
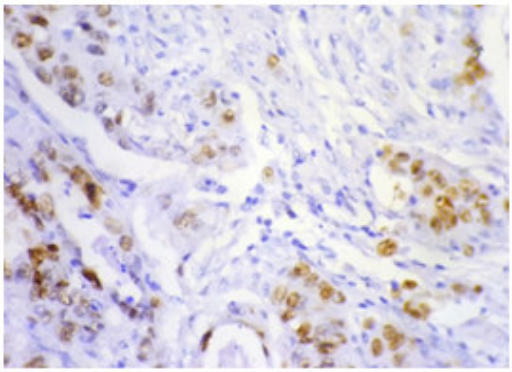


Figure 5
Grade II adenocarcinoma – score 2



There was a progressive increase in p53 score as the stage of colorectal adenocarcinoma increases (Table 3). Statistical analysis using Chi-Square test was done which revealed a P value of 0.027 which is statistically significant.

Figure 6
Grade II adenocarcinoma–score 3

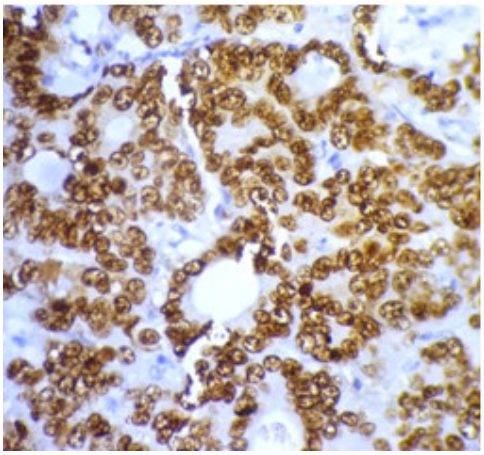


Figure 7
Grade III adenocarcinoma–score 1

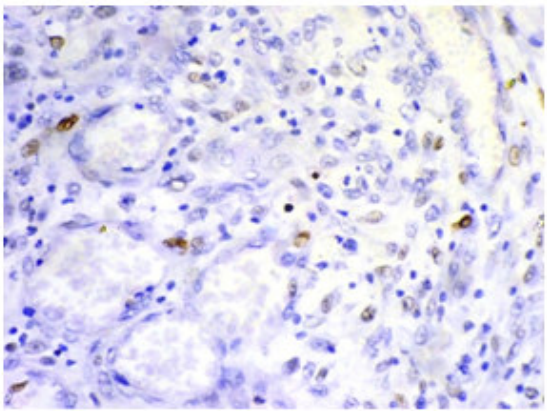


Figure 8
Grade III adenocarcinoma –score 3

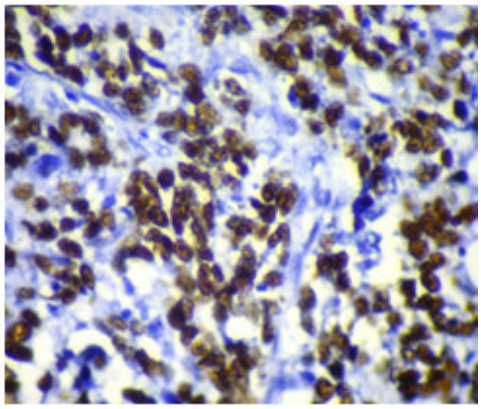
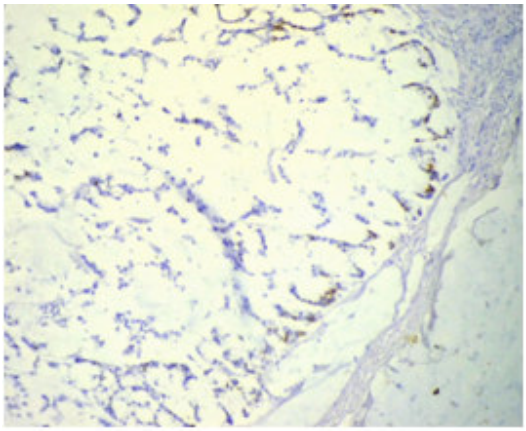


Figure 9
Mucinous carcinoma –score 1



Most of the mucinous carcinomas were in low stage and showed lower p53 scores (Table 4). P value could not be determined due to smaller sample size. In different grades of the tumour p53 score was ranging from 0 to 3(Figure 4, Figure 5, Figure 6, Figure 7 & Figure 8). Grade III tumours commonly had high scores and most mucinous tumours had low scores (Table 5) (Figure 9)

Table 1
P53 expression in colorectal adenocarcinomas

P53 expression	Positive	Negative	Total
Conventional	36	8	44
Mucinous	3	3	6

Table 2
p53 score in relation to subtypes

Adenocarcinomas	P53 score				Total
	0	1	2	3	
Conventional	8	6	14	16	44
Mucinous	3	2	0	1	6
Total	11	8	14	17	50

Table 3
P53 score in conventional adenocarcinomas in relation to stage (AJCC)

Stage (AJCC)	P53 Score				Total	%
	0	1	2	3		
I	5	4	1	2	12	27.27%
II	2	1	3	2	8	18.18%
III	1	1	4	3	9	20.45%
IV	0	0	6	9	15	34.1%

Table 4
p53 score in mucinous carcinomas in relation to stage (AJCC)

Stage (AJCC)	**P53 score**				**Total**
	0	**1**	**2**	**3**	
I	**1**	**0**	**0**	**0**	**1**
II	**1**	**1**	**0**	**1**	**3**
III	**1**	**1**	**0**	**0**	**2**
IV	**0**	**0**	**0**	**0**	**0**
Total	**3**	**2**	**0**	**1**	**6**

Table 5
p53 score in relation to histological grade

	P53 score				Total	%
Histological grade	0	1	2	3		
I	5	4	8	8	25	50%
II	2	1	3	4	10	20%
III	1	1	3	4	9	18%
Mucinous carcinoma	3	2	0	1	6	12%
Total	11	8	14	17	50	100%

High p53 scores were obtained predominantly in left sided tumours. However statistical analysis did not prove this association (p value = 0.541).

DISCUSSION

Colorectal carcinoma is a major cause of mortality and morbidity worldwide.[1] colorectal carcinoma is by far the most common and most curable cancer of the gastrointestinal tract. More than ninety percent of the cancers of the colorectal region are adenocarcinomas. In this study the age group for colorectal adenocarcinoma was ranging from 24 to 76 years and peak incidence was at 40 to 70 years with a male preponderance. In our study rectum was the commonest site for colorectal adenocarcinoma in all the age groups. Most of the larger tumours (>10 cm) were situated in the caecum which may probably be due to the larger luminal diameter and late presentation. In general the degree of gland formation is widely regarded as the most important feature in grading. Despite the lack of standardization and documented interobserver variation in the assessment the histological grade has been shown repeatedly by multivariate analysis to be a stage-independent prognostic factor. Colorectal mucinous carcinoma is one of the subsets of colorectal adenocarcinoma which is defined according to the World Health Organisation (WHO) as an adenocarcinoma in which a substantial amount of mucin (>50% of the tumour) is retained within the tumour.[7] The 5 year survival rate is 43.1% when compared to non mucinous type (79.4%) in stage II and stage III.[8] In our study most of the mucinous carcinomas were in low stage but the sample size was too low to get a statistically significant correlation. In colorectal carcinogenesis two distinct pathways are involved. APC(adenomatous polyposis coli) / beta-catenin pathway is associated with classical adenoma-carcinoma sequence and p53 mutation occurs in late stages of tumour progression. Second pathway is microsatellite instability pathway in which the tumours often have mucinous differentiation and are frequently located in the right colon. Hence, the mucinous carcinomas are reported to have a lower frequency of p53 mutation.[9] This study has shown p53 positivity in 78% of colorectal adenocarcinomas. George E. Theodoropoulos et al[10] reported nuclear positivity for p53 in 63.4% of colorectal adenocarcinomas. Yamaguchi et al[11] found the immunoreactivity for p53 in 61% of colorectal carcinomas. These differences may be due to the use of different scoring systems and interobserver variability. J Walker et al[12] in his study concluded that the stage is the most accurate prognostic factor for survival and recurrence. In our study statistically significant correlation was obtained for p53 over expression and advanced stage (P value = 0.027) but not for grade of the tumour. This is in accordance with the studies by Flamini et al[13], Heide et al[14] and George E. Theodoropoulos.[10] The present study showed no significant association for increasing grade of the tumour with the p53 over expression which correlates well with the results of the studies by Yamaguchi A et al[11] Soong R et al, [15] Yuan-Tzu Lan[16] and C.Hanski et al[17]. But high scores were found commonly in well to moderately differentiated tumours (70.6%) than poorly differentiated tumours (29.4%). This is in concordance with the study by Yuan-Tzu Lan[16] who found p53 over expression in 60% of well to moderately differentiated versus 40% of poorly differentiated tumours. This may be due to the fact that p53 expression may be reduced as the cells become less differentiated. So the p53 can serve as a differentiation marker in colorectal adenocarcinomas. The present study revealed a lower rate of p53 positivity in mucinous tumours with most of the tumours being negative for p53.Among the positive cases most had a score of 1 but significant correlation could not be obtained due to smaller sample size. This is in concordance with the study by C.Hanski et al[17] who found that only 36% of mucinous carcinomas have shown p53 positivity by immunohistochemistry but 76% of the non-mucinous adenocarcinomas showed p53 positivity suggesting that mucinous tumours develop by a different pathway. Satoshi Ikeda et al[18] also has observed similar findings in their study. P53 nuclear positivity in this study was found commonly in left sided tumours (56.4%) with the rectum predominating among them (46.15%). Similar results were found in the study by Antonio Russo[19] and Yuan-Tzu Lan.[16] The p53 over expression plays an important role in the progression of colorectal cancer since it correlates strongly with the advanced stage of the tumour and might therefore represent an useful marker of poor prognosis.

CONCLUSION

Since p53 expression has shown a significant association with the stage of the disease and since the stage is a proven prognostic factor in colorectal adenocarcinomas p53 over expression can be used as a poor prognostic marker. Inherited genetics of p53 pathway components could be utilized to further define patient populations in

their abilities to induce p53 activity in response to either DNA damaging or p53-targeted therapies.

CONFLICT OF INTEREST

Conflict of interest declared none.

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