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P53 Gene and Ki 67 Proliferative Index in Colorectal Adenomas- A Clinico-pathological Study

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ABSTRACT

Aim: To study *p53*gene expression and Ki-67 proliferative index in colorectal adenomas and its relation to variable clinicopathological parameters.

Method: A retrospective study of 100 formalin-fixed and paraffin-embedded samples from 84 patients with adenomatous polyps was selected from the files of the histopathological department at Rizgary Teaching Hospital and some of the private histopathological laboratories in Erbil city during the period from January 2014-January 2018 who underwent elective colonoscopy and subsequently polyp removal. *P53* and Ki-67 expression were studied by immunohistochemistry using the monoclonal mouse anti-human p53 protein (clone DO-7)and monoclonal mouse anti-humanantibody (Clone MIB-1) respectively, by the standard streptavidin-biotin immunoperoxidase method. The expression of p53 and ki67were correlated with the clinicopathologic parametersand statistically analyzed by SPSS version 22.

Results: Overexpression of *p53* and Ki-67 were seen in 94% and 79% of cases respectively. A strong significant relationship was observed between *p53* expression and degree of dysplasia (p=0.004), advanced adenomas (p=0.001) and size of the adenomas (p=0.001). A significant relationship was observed between Ki-67PI and the gender of the patients (p=0.03). There is a strong significant statistical relationship between the type of adenomas and the degree of dysplasia (p= 0.005). There isa strong significant statistical relationship between p53 expression and Ki-67 PI (p=0.001). There was immune-expression of p53 and Ki-67 and clinicopathological parameter differences between synchronous adenomas from the same patients.

Conclusion: *P53* expression is a frequent finding in large-sized, high-grade dysplasia and advanced adenoma. The Ki-67 expression in relation to clinicopathological parameters was significant in relation to the sex, and Ki-67 increases with size, type of adenoma, high-grade dysplasia and advanced adenomas. The high-grade dysplasia is seen more in villous adenomas. Increasing *p53*expression in colorectal adenomas is correlated with an increasing ki-67 activity index.

Key words: Colorectal Adenoma, P53, Ki-67

INTRODUCTION

Colorectal polyps are benign neoplasms that arise from the mucus-secreting colonic epithelial cells forming tumors that project into the lumen of the gut, friction on the mass may create a stalked polyp or the polyp may be sessile without a definable stalk[1].

Adenomatous polyps are common, particularly in western countries population, accounting in the United States 20–40% of screening colonoscopies in people older than 50 years of age, and overall they are present in approximately 50% of adults over the age of 50 years[2].

Adenomas are the precursors of adenocarcinomas. Therefore, a greater knowledge of the predominance of adenomas in the general population would assist define the efficacy of a colorectal cancer screening program[3], and they are classified according to the World Health Organization as tubular, tubulovillous, and villous adenomas, depending on the bearing and amount of villous content[4,5].

Adenocarcinomas of the colon do not arise de novo from normal colonic epithelium, somewhat, within a set of genetic mutations that activate proto-oncogenes and impair tumor suppressor genes, thus normal colonic epithelium gives way to pre-cancerous polyp formation and eventually frank carcinoma[6]. Approximately 85% of colorectal cancers are thought to evolve from conventional adenomas through a median of approximately 60 mutations per tumor that go beyond the genes that are major drivers; this process is referred to as the adenoma-carcinoma sequence[7].

P53 is encoded by the *TP53* gene located on 17p13. Its expression is abnormal in more than 50% of human tumors. Mutation or loss of p53 usually occurs at the time of the transition from adenoma to cancer in the adenoma-carcinoma sequence. Loss of *p53*tumor suppressor gene is seen in 70-80% of colon cancers, yet comparable losses are uncommon in adenomas, implying that mutations in *P53* occur late in colorectal carcinogenesis[8]. The biochemical function of *P53* as a sequence-specific DNA-binding protein and transcription factor controlling the expression of a large number of genes[4].*P53* has been marked the 'guardian of the genome' because of its capability to prevent cell proliferation in the presence of DNA damage, to stimulate DNA repairing and to promote apoptotic cell death if repair is inadequate. Loss of *p53* function, therefore, gives to the proliferation of damaged DNA to daughter cells and, compatible with this, mutation of *p53* has been shown to lead aneuploidy clonal divergence[9].

Ki67 is a non-histone nuclear protein strictly correlated with proliferating cells and the expression of the Ki67 protein in humans is strictly linked with cell proliferation, and this is recognized during the cell-cycle

phases G1, S, G2 and mitosis, and out in the G0 phase. Thus Ki-67 is a unique marker for proliferating cells[10,11].

MATERIALS AND METHODS

A retrospective study of a total of 100 formalin-fixed paraffin-embedded samples from 84 patients with adenomatous polyps was selected from the files of the histopathological department at Rizgary Teaching Hospital and some of the private histopathological laboratories in Erbil City during the period from January 2014-January 2018 who underwent elective colonoscopy and subsequently polyp removal.The inclusion criteria for the current study were electively resected colorectal adenomas based on histopathological results of endoscopically resected polyp specimens and no history of adenomatous polyposis coli or lynch syndrome. Three samples were excluded because of the insufficiency of materials.

All blocks were examined and the one which represented the best diagnosis (no necrosis, no hemorrhage) was selected for the study and new sections were made and stained by Hematoxylin and Eosin (H&E) for histological evaluation.All tissue samples submitted forimmune staining for evaluation of*p53*and Ki67.

The tissue cuts were prepared in 4 µm thick and placed on special salinized slides. Then the samples were deparaffinized and put into a buffer solution for 20 min at 95-99°C, cooled in room temperature for 20 min. The method used was Dako Cytomation EnVision + System - horseradish peroxidase (HRP) - which is a two-level IHC staining method.Then ready-to-use Anti-p53(monoclonal mouse anti-human p53 protein, clone DO-7)and Anti-Ki67 (monoclonal mouse anti-human antibody, MIB-1) solutions were applied for staining the prepared tissue samples by special IHC methods. The endogenous peroxidase activity was inhibited by incubation of slices inside peroxidase inhibitor for 10 min. The slices were incubated inside the primary diluted antibody for 30 min and then on labeled polymers for another 30 min. After staining, the slices were put in 3,3-diaminobenzidine (DAB) + substrate chromogen which detects the antigen in brown color. Then, the stained samples were reviewed under a light microscope and labeled cells were counted in both pathological and normal tissues for 100 cells in the microscopic field. The rate of positivity of tissues according to p53 and Ki67 was registered as the percent of labeled cells. Then, the scoring was performed.A section of Colon adenocarcinoma known to stain positive for p53 and Ki-67 was included in each run as positive control and N- Universal negative control mouse (Dako) which does not recognize p53 protein as a negative control.All cells labeled by p53 and Ki-67 antibodies show a nuclear staining pattern of brown color. The evaluation was conducted using a semi-quantitative scoring method by determining the proportion of positive cells over the total number of cells.Positive cells were determined by counting 1000 cells. All significantly stained cells were considered positive and divided by 10 to acquire the percentage. At least 10 HPFs were measured for each case for the purpose of scoring.For p53 expression, the density (number of cells which were stained) and intensity (the intensity of staining) were evaluated at the same time. The density was measured by the percentage of stained cells and the intensity was measured by qualitative measurement. Then the numbers of density and intensity multiplied by each other and gave a number range from 0 to 4. The range again categorized as (0) for negative expression, 1 and 2 for weak expression, and 3 and 4 for strong expression.For the Ki-67 expression, the density (number of cells that were stained) was evaluated. The density was measured by the percentage of stained cells as less than 5% for negative expression, 5 to 10% for weak expression, and more than 10% for strong expression.

Data have been recorded on a specially designed questionnaire, collected and entered in the computer and then analyzed usingStatistical Package for Social Sciences (SPSS) version 22 and the results compared between patients with different variables, with a statistical significance level of < 0.05. The results are presented as rates, ratio, frequencies, percentages in tables and figures and analyzed using the Chi-square test.

RESULTS

A total of 100 formalin-fixed, paraffin-embedded blocks of endoscopically resected polyps from patients with colorectal adenomas, were included in this study. There were 59 (59%) males and 41 (41%) females. Patient's age ranged from 21-85 years with a mean age of (53.3±15) years. Thirty percent of cases were less than 1 cm, 41% were ranged between 1-2 cm and 29% were more than 2 cm. The smallest adenomas were 0.3 cm and the larger one measured 7 cm. Eighty-one percent of adenomas were removed from the left colon including rectum while 19% were in the right-side colon including the cecum, ascending colon and two-third of the transverse colon. Tubular adenoma constituted 22% of cases, while 66% of the cases were tubule-villous adenoma, and 12% of adenomas were diagnosed with villous adenomas. The degree of dysplasia was enrolled as low grade and high- grade dysplasia, 57% of cases were with low-grade dysplasia whereas 43% of cases were with high-grade dysplasia. Thirty-six percent of the cases were diagnosed as advanced adenoma, 64% were non-advanced adenomas (Table 1).

The relationship between *p53* expression and clinicopathological variables is shown in table 2. The overall frequency of adenomas with positive *p53* expression was 94%. A strong significant relationship was observed between *p53* expression and degree of dysplasia (p=0.004), advanced adenomas (p=0.001) and size of the adenomas (p=0.001); but there was no significant relationship between *p53* expression and other clinicopathological parameters in term of gender, age, site of biopsy and type of polyps (p>0.05).

The relationship between the Ki-67proliferating index (PI)and clinicopathological variables is shown in table 3. The overall frequency of adenomas with positive Ki-67PI was 79%. A significant relationship was observed between Ki-67PI and gender of the patients (p=0.03); but there was no significant relationship between Ki-67PI and other clinicopathological parameters in term of age, site of biopsy and type of polyps, degree of dysplasia, advanced adenomas and size of adenomas (p>0.05).

It was observed as shown in table 4 that villous adenomas were with higher percentages of high- grade

dysplasia and followed by tubule-villous then by tubular adenomas. There is a strong significant statistical relationship between the type of adenomas and the degree of dysplasia (p= 0.005).

In a correlation between p53 expression and Ki-67 PI as shown in table 5, it was observed that most of the adenomas with strong p53 expression showed strong Ki-67 PI. There is a strong significant statistical relationship between p53 expression and Ki-67 PI (p=0.001).

A total of 14 patients with synchronous adenomas are included, 12 with 2 polyps and 2 with 3 polyps. 13 patients with left colon and 1 with the right colon.11 patients had the same type of adenomas while 3 of them had different types of adenoma. The size of all adenomas was different ranging from 0.5-5 cm.12 of patients showed the same degree of dysplasia while 2 patients showed different degrees of dysplasia between their adenomas. 4 of the patients had different expressions of p53 and 10 of them showed the same expression. 7 patients had different Ki-67 proliferative index and 7 had the same activity of Ki-67 (table 6).

Table 1: Clinico-pathological parameters of the colorectal adenoma cases

Variables	**Categories**	**Number (%)**
Gender	Male	59 (59%)
	Female	41 (41%)
Age	20-29 years	4 (4%)
	30-39 years	18 (18%)
	≥ 40 years	78 (78%)
Site of biopsy	Right colon	19 (19%)
	Left colon	81 (81%)
Size	< 1cm	30 (30%)
	1-2 cm	41 (41%)
	≥ 2 cm	29 (29%)
Type of polyp	Tubular	22 (22%)
	Tubulo-villous	66 (66%)
	Villous	12 (12%)
Dysplasia	High grade	43 (43%)
	Low grade	57 (57%)
Advanced adenoma	Yes	36 (36%)
	No	64 (64%)
Total		100 (100%)

Table 2: Clinicopathological parameters and their correlation with P53 expression.

Clinicopathological Parameters	**Variables**	**P53 expression**				***P* value**
		Negative expression n%	**Weak expression n%**	**Strong expression n%**	**Total**	
Gender	Male	4 (6.8)	20 (33.9)	35 (59.3)	59%	0.83
	Female	2 (4.9)	16 (39)	23 (56.1)	41%	
Age (years)	20-29	0 (0)	2 (50.0)	2 (50.0)	4%	0.67
	30-39	1 (5.6)	4 (22.2)	13 (72.2)	18%	
	≥40	5 (6.4)	30 (38.5)	43 (55.1)	78%	
Site of biopsy	Right colon	1 (5.3)	9 (47.4)	9 (47.4)	19%	0.51
	Left colon	5 (6.2)	27 (33.3)	49 (60.5)	81%	
Size of the polyp	< 1cm	2 (6.7)	20 (66.7)	8 (26.7)	30%	0.001**
	1-2 cm	3 (7.3)	9 (22.0)	29 (70.7)	41%	
	≥2 cm	1 (3.4)	7 (24.1)	21 (72.4)	29%	
Type of polyp	Tubular	2 (9.1)	13 (59.1)	7 (31.8)	22%	0.08
	Tubulovillous	3 (4.5)	20 (30.3)	43 (65.2)	66%	
	Villous	1 (8.3)	3 (25.0)	8 (66.7)	12%	
Degree of dysplasia	Low grade	4 (7.0)	28 (49.1)	25 (43.9)	57%	0.004*
	High grade	2 (4.7)	8 (18.6)	33 (76.7)	43%	
Advanced adenoma	No	4 (6.3)	33 (51.6)	27 (42.2)	64%	0.001**
	Yes	2 (5.6)	3 (8.3)	31 (86.1)	36%	
Total		6 (6%)	36 (36%)	58 (58%)	100%	

Table 3: Clinicopathological parameters and their correlation with Ki-67 proliferative index.

Clinicopatho-logical Parameters	**Variables**	**Ki-67 expression**				***P* Value**
		Negative expression n%	**Weak expression n%**	**Strong expression n%**	**Total**	
Gender	Male	14 (23.7)	18 (30.5)	27 (45.8)	59 (%)	**0.03***
	Female	7 (17.1)	23 (56.1)	11 (26.8)	41 (%)	
Age (years)	20-29	0 (0)	2 (50.0)	2 (50.0)	4 (%)	0.58
	30-39	2 (11.1)	9 (50.0)	7 (38.9)	18 (%)	
	≥40	19 (24.4)	30 (38.5)	29 (37.2)	78 (%)	
Site of biopsy	Right colon	5 (26.3)	7 (36.8)	7 (36.8)	19 (%)	0.80
	Left colon	16 (19.8)	34 (42.0)	31 (38.3)	81 (%)	
Size of the polyp	< 1cm	9 (30.0)	12 (40.0)	9 (30.0)	30 (%)	0.07
	1-2 cm	9 (21.9)	20 (48.8)	12 (29.3)	41 (%)	
	≥2 cm	3 (10.4)	9 (31.0)	17 (58.6)	29 (%)	
Type of polyp	Tubular	5 (22.7)	7 (31.8)	10 (45.5)	22 (%)	0.69
	Tubulovillous	14 (21.2)	30 (45.5)	22 (33.3)	66 (%)	
	Villous	2 (16.7)	4 (33.3)	6 (50.0)	12 (%)	

Degree of dysplasia	Low grade	15 (26.3)	23 (40.4)	19 (33.3)	57 (%)	0.27
	High grade	6 (14.0)	18 (41.9)	19 (44.2)	43 (%)	
Advanced adenoma	No	16 (25.0)	26 (40.6)	22 (34.4)	64 (%)	0.37
	Yes	5 (13.9)	15 (41.7)	1 (44.4)	36 (%)	
Total		21	41	38	100%	

Table 4: Association between the type of polyp and degree dysplasia (p= 0.005)

Type of poyp	Dysplasia		Total
	Low grade	High grade	
Tubular	18	4	22
	81.8%	18.2%	100%
Tubulo-villous	36	30	66
	54.5%	45.5%	100%
Villous	3	9	12
	25%	75%	100%
Total	57	43	100
	57%	43%	100%

Table (5): Relationship between P 53 scoring and Ki-67 scoring (p 0.001).

P 53 scoring	Ki-67 scoring			Total
	Negative	Weak	Strong	
Negative	5	0	1	6
	83.3%	0%	16.7%	
Weak	11	15	10	36
	30.6%	41.7%	27.8%	
Strong	5	26	27	58
	8.6%	44.8%	46.6%	
Total	21	41	38	100
	21%	41%	38%	100%

Table 6: Patients with synchronous polyps and differences in parameters

Case no.	No. of polyps/patient	Polyp no.	Site	Type	Size	Dysplasia	P53 expr.	Ki-67 exp.
1	2	A	LC	TV	1	HGD	2	1
		B	LC	TV	2.5	HGD	2	1
2	2	A	LC	TV	1.5	HGD	2	1
		B	LC	TV	2	HGD	1	1
3	2	A	LC	TV	2.5	HGD	2	2
		B	LC	TV	1.5	HGD	2	1
4	2	A	LC	TV	5	HGD	2	2
		B	LC	TV	5	HGD	2	2
5	2	A	RC	TV	0.5	LGD	2	0
		B	RC	V	1.5	HGD	2	2
6	2	A	LC	V	0.5	HGD	2	1
		B	LC	V	0.5	HGD	2	2
7	2	A	LC	T	0.5	LGD	0	0
		B	LC	TV	1	LGD	2	0
8	2	A	LC	TV	1.5	LGD	2	0
		B	LC	TV	1.5	LGD	1	1
9	2	A	LC	TV	2.5	HGD	2	1
		B	LC	T	1	LGD	2	1
10	2	A	LC	V	2	LGD	2	2
		B	LC	V	1	LGD	2	1
11	2	A	LC	TV	1	HGD	2	0
		B	LC	TV	2	HGD	2	0
12	2	A	LC	TV	2	LGD	2	2
		B	LC	TV	0.7	LGD	2	0
13	3	A	LC	TV	3	HGD	2	2
		B	LC	TV	4	HGD	2	2
		C	LC	TV	7	HGD	2	2
14	3	A	LC	TV	1	LGD	2	1
		B	LC	TV	2	LGD	2	1
		C	LC	TV	2.5	LGD	0	2

LC: Left colon, RC: Right colon, T:Tubular adenoma, TV: Tubulovillous adenoma, V: Villous adenoma, HGD: High-grade dysplasia, LGD: Low-grade dysplasia

DISCUSSION

Colorectal polyps are common lesions in the general population and colonoscopy permits direct visualizationof the entire colon, as well as the removal of a large part of polyps observed. The common reason for polypectomy is that colorectal polyps, even if it is of a benign clinical appearance, can show, at histology, a potential or actual features of malignancy[12]. They are common, especial
y in western countries, accounting in the United States 20–40% of screening colonoscopies in people older than 50 years of age, and in general they are present in nearly 50% of adults by the age of 50 years[2]. Approximately 85% of colorectal cancers are thought to evolve from conventional adenomas through a median of approximately 60 mutations per tumor that go beyond the genes that are major drivers; this process is referred to as the adenoma-to-carcinoma sequence, variously called the *APC/β-catenin* pathway or the chromosome instability pathway. It is characterized by chromosomal instability linked with the stepwise accumulation of mutations in various oncogenes, and tumor suppressor genes[7,13]. The *p53* tumor-suppressor

gene is critical in maintaining genomic integrity through cell cycle arrest, DNA repair, and apoptosis, while its mutation results in the aberrant accumulation of mutant p53 protein[14,15]. Ki-67 is a non-histone nuclear protein closely associated with proliferating cells. The adverse prognostic value of Ki- 67 overexpression has been studied in different malignancies[16,17,18]. This study was designed to evaluate the immunoexpression of *p53* and Ki-67 PI in formalin-fixed, paraffin-embedded tissue sections of colorectal adenomas.

The *p53* immunoexpression was highly significant in adenomas with high-grade dysplasia, advanced adenomas, and adenomas with larger sizes (p<0.004). These findings are in a direct relationship. The adenomas with high-grade dysplasia showed more *p53* expression and similar findings are found worldwide by other authors worked on adenomas and serrated adenomas[2,11,19-21.]. Among advanced adenomas, more than 86% of them had strong *p53* expression while non-advanced adenomas showed a weaker expression. The reason why advanced adenomas show more *p53* expression is that advanced adenomas are premalignant tumors with higher potentials for cancerous transformation, they have passed all sequences of adenoma-carcinoma and they are in the late stage of this sequence. A similar association was found by another author[22]. In our study adenomas smaller than 1 cm showed 66.7 % weak *p53* expression while adenomas ranging between 1-2 cm and larger than 2 cm showed 70.2 % and 72.4% strong *p53* expression respectively. A strong correlation between the size of adenomas and *p53* expression was observed (*P*-value 0.001) and similar significant statistical results were found by others[2,23] while others found opposite results[11,14]. In our study, we did not find any significant correlation between *p53* expression and other variables such as sex, age, site of biopsy and type of adenomas that our finding agrees with others[2,11,23-26]..

The Ki-67 immunoexpression in our study was significantly correlated to the sex of the patients. Among males, strong expression was prevalent while week expression was prevalent among females. On the other hand, no significant correlation found between Ki-67 PI and other parameters such as age, site of biopsy in agreement with others (2,11,20).Although the Ki-67 expression was higher is larger adenomas, in adenomas with villous content, adenomas with high-grade dysplasia, and advanced adenomas these findings agree with findings of other authors (2,11,19–21,27,28).

The adenomas with villous content had higher grades of dysplasia(75%)than tubular adenomas that possess a lower grade of dysplasia (81.8%). On the other hand, the degree of dysplasia is increased with increasing villous content. 75% of the villous adenomas have high-grade dysplasia while 45.5% of tubule-villous adenomas had high-grade dysplasia. This correlation was highly significant (*P*=0.005) and this indicates that the degree of dysplasia is correlated with an increase of the villous content and the villous content is a precursor of adenocarcinoma of the colon, a similar result was found by Giuliani *et al*[12].

A highly significant correlation was found in studying the relationship between *p53* and ki-67 activity index (*P*-value 0.001). The loss of function of p53 and its suppressive activity leads to uncontrolled proliferative activity and eventually a higher Ki-67 activity index. In our study, we were successful to show this relation which indicating that adenomas with strong p53 expression have a strong ki-67 proliferative index which is similar to the results of Nussrat *et al*. (2)that indicates a positive correlation but not statistically significant results. But other authors showed no correlation between p53 and Ki-67 expression[11,19,20].

Colorectal adenomas which are discovered simultaneously or 6 months after the diagnosis of primary adenoma or colorectal cancer (CRC) is called synchronous adenomas. The presence of synchronous adenomas increases the probability of adenomas with severe dysplasia as well as CRC[29].From a total of 84 patients who were included in our study, 16.6% of them had synchronous polyps. 14.2% of them had two and 2.4% had 3 polyps. A study done by Sousa *et al* found similar percentages of synchronous polyps with two and three polyps[11]. The main site for synchronous adenomas was found to be left colon including rectum with the same results found by Radovanoović-Dinić*et al*, 2010[29]. The villous component is the predominant pattern with similar results approved by[30]. In our study 30 synchronous adenomas taken form, 14 patients were involved and immunohistochemical studies of *p53* and Ki-67 immunoexpression are done for all. Among these patients, 12 of them had 2 adenomas and 2 of them had 3 adenomas. The *p53* and Ki-67 expression, site of biopsy, size of adenomas, type of adenomas and degree of dysplasia of these adenomas are compared to corresponding adenomas from the same patients. Although such studies are less done by other authors, we were successful to show some differences between different adenomas from the same patients. All adenomas were taken from the same site either LC or RC. Among all synchronous adenomas, adenomas of 3 patients showed different types. Two patients showed TV and T adenomas and one patient diagnosed with TV and V adenoma. Regarding the size of synchronous adenomas, all adenomas had different sizes. Among patients with two adenomas, two of them showed different degrees of dysplasia. One adenoma with HGD and one with LGD. These findings are in parallel to the finding of Bomme *et al* who worked to determine cytogenetic alteration in synchronous colorectal adenomas. They found that synchronous colorectal adenomas have a different type, size, site of biopsy and degree of dysplasia[31].Among these patients with 2 adenomas, 3 cases showed different *p53* expression. First, two cases had one strong and one weak *p53* expression while the third case had one adenoma with negative and one with strong p53 expression. Among patients with 3 adenomas, one patient had different *p53* expression. Two of three adenomas of this patient showed strong *p53* expression while the third adenomas showed no expression.For Ki-67 differences in synchronous polyps, 6 patients of two adenomas and 1 patient of 3 adenomas showed different Ki-67 expression. Three patients showed one strong and one weak Ki-67 expression. Two patients showed one strong and one negative Ki-67 expression. One patient showed one weak and one negative expression. In a patient with 3 adenomas, two adenomas showed weak while third adenomas showed strong Ki-67 expression. Although there were differences in 28.5% of *p53* expression and 42.8% of Ki-67 immune expression

among our synchronous adenomas, but still most of them showed the same expression of both genes with similar results done by[32] who showed that multiple synchronous colorectal lesions show nonoverlapping mutational signatures highlighting the degree of heterogeneity between multiple specimens in the same patient.

CONCLUSION

P53 and Ki-67 potentially contribute to the multistep carcinogenesis process in colorectal oncogenesis. P53 plays an important role in malignant transformation and more likely to be expressed in advanced, large sized, higher degree of dysplasia and with villous morphology.
These markers can be used as an ancillary marker for the risk of transformation and as a target for chemo-preventive drugs.

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