HISTOPATHOLOGICALEVALUATION OF COLORECTAL CARCINOMA

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ABSTRACT

Background: Colorectal cancer is the most common gastrointestinal tract cancer worldwide. In Iraq, colorectal cancer was the seventh top cancers, whereas in Kurdistan, it was the fourth most common cancer for both males and females. Although the methods of the diagnosis and therapy have been improved, only about 50% of the patients who resected the tumor died from disease within 5 years, due to distant metastasis. The study was carried out to determine the frequency of histopathological types of colorectal cancer, and to evaluate the correlation between colorectal cancer regarding the grade, stage, with different histological finding which include desmoplastic reaction, lymphocytic infiltration, foamy macrophages, necrosis, intraglandular necrosis, and calcification.

Subject and Methods: This study includes (108) patients diagnosed with colorectal cancer. Cases were collected during the period January 2015 - December 2017 from the histopathological department at Central Public Health Laboratory and other private labs in Duhok city. Clinical information were obtained from the available histopathological reports. Paraffin embedded blocks were sectioned and stained with immunohistochemistry markers; Ki67 and VEGF then processed automatically according to protocols supplied by the antibody manufacturer.

Results: Patients age ranged from18-83 years with a mean of 54.42 years. The peak ages of the patients were between 60-69 years. Male: female ratio was 1.5:1. The commonest tumor location was (recto-sigmoidal region); rectum was (42.6 %) and sigmoid colon was(22.2%).Conventional adenocarcinoma was the predominant type 86(79.6%), majority of cases were moderately differentiated adenocarcinoma constituting85.2%. Stage III was the highest stage constituting 56(51.9%), followed by stage II which constitute 37(34.3%).The local invasion of the mucosa and other layers of colonic wall were associated with desmoplasia and collagen fiber remodeling. Infiltration of foamy macrophages decreased in number in relation to higher grade. Intraglandular necrosis showed significant correlation with tumor invasiveness, lymph node metastasis and grade. The frequency of both markers Ki67 and VEGF were 77 and 75 respectively. Ki67 immunoreactivity revealed significant relationship with tumor grade (P=0.014), whereas VEGF had significant relationship with TNM stage (P = 0.019), as well as the local invasion to the colorectal wall (P 0.009).

Conclusions: Moderate differentiated adenocarcinoma (85.2%) and stage III (51.9%) were the most frequent diagnosed cases with colorectal cancer. Macrophages infiltration was conversely related with grading of colorectal cancer. Histopathological changes like desmoplastic reaction and intraglandular necrosis were common findings in colorectal cancer and they were in concordance correlation with stage and grade.Ki67 had relationship with tumor grade, whereas VEGF correlate with tumor invasion.

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Keywords: Colorectal, adenocarcinoma, desmoplastic reaction, intraglandular necrosis, Ki67, VEGF.

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Colorectal Cancer (CRC) is the third most frequent malignancy world-wide in both men and women[1]. The disease estimation of the new cases is currently 1.4 million people and 693,900 are dying from the diseaseannually[2]. In Iraq, the colorectal cancer was the seventh cancers disease list with percentage 5.36 [3].

In Kurdistan region, the CRC ranks the fourth after lymphomas, lung and hematological malignances in males. In female, it is also ranks the fourth after lymphomas, hematological malignances and breast cancer. The percentage of CRC was estimated as 7.3% and 5.62 % for both male and female respectively [4].

Adeno carcinoma of the colon and rectum was graded predominantly on the basis of glandular appearanceas well, moderately and poorly differentiated or "other", according to the WHO histopathological classification of tumors of the colon and rectum [5].

The most widely staging system that have been used among clinicians is the TNM system that maintained by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC). This system codes the extent of the primary tumor (T), regional lymph nodes (N), and distant metastases (M) and provides a ''stage grouping'' based on T, N, and M[6].

Although the methods of the diagnosis and therapy have been improved, about 50% of the patients whose tumors were resected, they died from the cancer disease during 5 years, the main cause of death was attributed to spread of the disease and metastasize to the other tissues of the patient's body [7,8]. In the same way the early stages of the cancer can also undergo metastasis[9].

The tumor stroma represented by vascular connective tissue which is an important part in feeding the proliferative, neoplastic cells. Fibroblasts, endothelial cells, and inflammatory cells are the main component of the tumor stroma which promote the progression of the disease[10,11]. The interaction between these certain elements of the stroma and the neoplastic cells will produce biologically active compounds[12].

The dynamic variation in the cancer-associated stroma have the same events can occur in the wound-healing reaction[13], this is termeda desmoplastic reaction. Tumor infiltrating lymphocytes (TIL) may have an increase effect on the growth and spread of the cancer and it may contribute to immunosuppression associated with malignant disease[14].

Tumor associated macrophages (TAMs) are the most marked constituents of the inflammatory infiltrates in the neoplastic tissues. They are derived from circulating monocytes that secret monocyte chemotactic protein chemokines for recruiting more numbers of the TAMs. The dual roles of the TAMs in neoplasms represented by terminating neoplastic cells following activation by IL-2, interferon and IL-12[15,16], and production of mediators that have potential role in neoplastic progression such as angiogenic and lymphangiogenic growth factors, cytokines and proteases[17].

Necrosis is an unregulated and an accidental form of cellular death. Incorrect path is the overlapping of the process of the cell death and the changes that happen to cells and the body tissues after the cells die. It is represent by 'noreturn' process in cell life[18].In general, the tumor necrosis (TN) is attributed to rapid

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growth of tumor which results in chronic ischemic injury. However, inadequate tumor vascularization and tumor cell hypoxia are the main causing factors of TN that remains controversial[19].

Pathological calcification appears in soft tissues when calcium salts, especially calcium phosphate, are precipitated in an unregulated manner in these soft tissues[20]. In the tumor cells, the calcification is either resulted from the tumor itself or represented by dystrophic calcification secondary to hemorrhagic and/or necrostic conditions within the tumor during or before chemotherapy[21].

Ki67 is a nuclear antigen, which is expressed in proliferating cells from G1 to M-phase of the cell cycle[22]. Many studies have shown a predictive role of Ki67 in a wide range of human malignancies, including gastrointestinal stromal tumors[23]. However, only few studies exist on the prognostic role of Ki67 in CRC, and have partially shown contradictory results [24, 25].

Vascular endothelial growth factor (VEGF) is a pro-angiogenic factor regulates angiogenesis in gastrointestinal cancer[26] and participates in CRC angiogenesis[27]. Vascular endothelial growth factor A (VEGF-A) is a member of the VEGF family, it is a heparin-binding glycoprotein characterized by a potent mediator for angiogenesis, and promotes vascular permeability specific for endothelial cells[28].

MATERIALS AND METHODS

This study include (108) patients who were diagnosed with colorectal cancer in the Central public health laboratory and other private labs in Duhok Governorate where the patient underwent colectomy. The cancer cases were collected from the period of January 2015 - December 2017. Patients who underwent preoperative radiotherapy were excluded in this study. Clinical information was obtained from the available histopathological reports included the: age, gender, site of the tumor, histopathological subtype, including presence of mucinous component, pTstage, pN stage, pM stage, tumor grade and angiolymphatic invasion. Haematoxylin and Eosin stained for each case representative section were re-examined for detection of lymphocytic infiltration, foamy macrophages, desmoplastic reaction and the presence of necrosis (intraglandular and extaglandular necrosis) as well as calcification.

All cases of the colorectal cancer were diagnosed as adenocarcinomas originating from epithelial cells of the colorectal mucosa except for two of them were diagnosed as neuroendocrinal tumor with the aid of using neuroendocrine marker chromogranin A.

Formalin fixed, paraffin-embedded histological sections (4 mm in thickness) were immunostained for (Ki67 & VEGF). Ki67 was used as a proliferative index, and VEGF as angiogenic growth factor. The analysis was performed with anti-Ki67 (FLEX Monoclonal Mouse Anti-Human Ki67 Antigen) (clone MIB-1, dilution 1/75; Dako, USA) and anti-VEGF (clone JH121, Monoclonal Mouse Antibody, dilution 1/50; Thermo Fisher Scientific, France) antibodies. Pre-treatment with heat-induced epitope retrieval (HIER), this step was done using EnVision FLEX Target Retrieval Solution, low pH and Dako PT Link (Code PT100/PT101).

EnVision FLEX Peroxidase Blocking reagent, 3, 30-Diaminobenzidine, primary then secondary antibody, DAB+ chromogen then hematoxylin. The staining steps and incubation

times were pre-programmed into the Autostainer Link software.

After the staining procedure has been completed, the slides were dehydrated, cleared then mounted. The immunoreactive evaluation for each marker was assessed. Tumor cells that show nuclear staining pattern were positive for Ki67. The presence of a brown cytoplasmic reaction indicated positive reaction for VEGF marker, otherwise the reaction was considered negative.

Scoring

Tumor regions containing Ki67 and VEGF positive cells were identified with low power (100×) microscopy. The scoring of Ki-67 immunohistochemistry was assessed as the percentage of positive tumor cells in several representative visual fields of each tumor.

A cutoff was selected at the median value, dividing the samples in low (<40% positive tumor cells) or high nuclear Ki-67 expression (≥40%). This cutoff was done and supported by[24,29].

Expression of VEGF was based on the intensity of staining of the malignant epithelial cells only. Endothelial cell, fibroblastic or other stromal cells staining were not considered during the assessment. Smooth muscle cells were used as positive internal controls for VEGF immunoreactivity[30].

The degree of VEGF expression was categorized into three groups, according to the percentage of immuno-reactive cells (positive staining cells) over the total number of counted cells, as follow; score 0: malignant epithelial cells were stained less intensely than the normal smooth muscle; score 1: <30% of malignant epithelial cells were stained, or carcinoma cells staining intensity was similar to that of the normal smooth muscle, and score 2: >30% of carcinoma cells were stained more intensely than the normal smooth muscle. The last two scores were considered positive[30,31].

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS program version 16. Pearson Correlation (2-tailed) was used to correlate between variables in this study.Chi square or Fisher's exact probability test was used to find the association of Ki67 & VEGF expression with clinicopathological parameters. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Age and sex distribution of colorectal cancer

A total 108 cases with CRC were included in this study. The patient's age ranging of the collected cases ranged from (18-83) years with a mean age of 54.42 years. The commonest age group was among 60-69 constituting (25.9%) and includes 28 cases. The elderly group (> 80) were 7 cases (6.5%), whereas the younger age group (<20) were 2 cases (1.9%) (Table1).

Gender distribution; 65 (60.2%) were males and 43 (39.8%) were females (Figure 1), the male to female ratio was 1.5:1. Figure 2 shows the correlation of gender with age group, the figure reveals that there was no significant difference between CRC patient's age group and sex, the highest percentage was in 6th decade (25.9%) (15 male and 13 female), while the lowest percentage that include 2 cases were in 2nddecade (6.3%). Age grouped > 80 had 7 cases (5 male and 2 female).

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Table 1: Frequency and Percentage of the Patient Age Range

Range of Age	Frequency	Percent %
< 20	2	1.9
20-29	7	6.5
30-39	9	8.3
40-49	21	19.4
50-59	20	18.5
60-69	28	25.9
70-79	14	13.0
≥ 80	7	6.5
Total	108	100.0

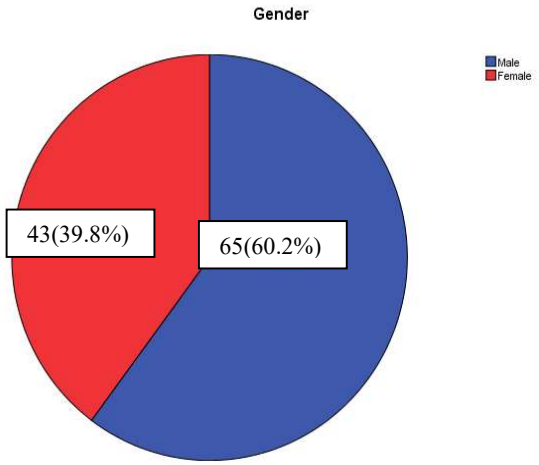

Figure 1: Frequency and Percentage of the Patients' Gender

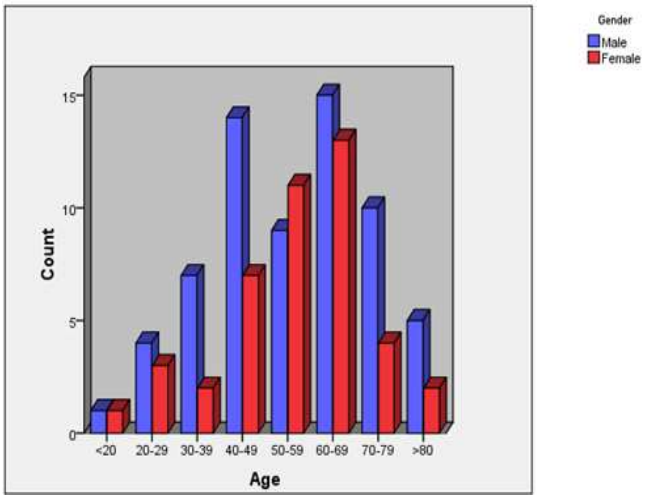

Figure 2: Correlation of Gender with Age Group for CRC Patients

Site of tumor

Regarding the anatomical locations of CRC, patients with rectal cancer demonstrated the most frequent site with (42.6 %), followed by sigmoid colon with (22.2%); this means that the left side of the colon is more susceptible to the disease than right side. The least affect site was the transverse colon with a percentage of 4.6 (Figure 3).

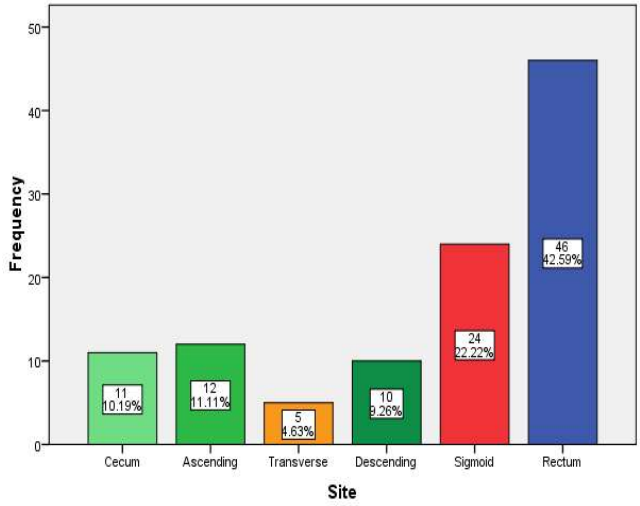

Figure 3: Frequency and Percentage of the Tumor Location

Histological types and other findings

Conventional adenocarcinoma was the most common 86(79.6%) histological type of CRC whereas the others; mucinous & signet ring cell adenocarcinoma; were the less common types 15(13.9%), 5(4.6%) consequently (Table 2). Two cases were neuro endocrinal tumor proved by chromogranin A, a stain that have been used for the demonstration of neuro endocrinal tumors (Figure 4).

Regarding the grading of the tumor, 92 cases of CRC were moderately differentiated adenocarcinoma representing 85.2%, while well

and poorly differentiated adenocarcinomas (Figure 5) were less common (Table 2).

Patients with stage III were the highest frequent group56 (51.9%).Invasion beyond the serosa into the visceral peritoneum or direct invasion into adjacent structures or the organs (T4) was less frequent 8(7.4%). Regional lymph nodes involvement N1&N2 comprised 55.6% which were higher than the cases without regional lymph node metastasis. In spite of lympho-vascular invasion had higher percentage of 77.8%, only 4 cases (3.7%) revealed distant metastasis, the majority of cases persist locally (Table 2).

Table 2: Frequency and percentage of the histological types of CRC& other findings

Parameters	Findings	Frequency	Percent %
Histological Types	Conventional	86	79.6
	Mucinous	15	13.9
	Signet ring cell	5	4.6
	Neuroendocrine Tumor	2	1.9
Grade	Well dif*	3	2.8
	Moderatedif*	92	85.2
	Poordif*	13	12.0
TNM Stage	I	11	10.2
	II	37	34.3
	III	56	51.9
	IV	4	3.7
Local Invasive Depth	T2	14	13.0
	T3	86	79.6
	T4	8	7.4
Lymph Nodes	N0	48	44.4
	N1	31	28.7
	N2	29	26.9
Distant Metastasis	M0	104	96.3
	M1	4	3.7
Lymphovascular Invasion	Negative	24	22.2
	Positive	84	77.8

dif*: differentiated

Table 3: Frequency and the Percentage of the Histopathological Changes Observed During Microscopical Examination

Parameters	Findings	Frequency	Percent %
Desmoplastic Reaction	Mild	27	25.0
	Moderate	61	56.5
	Sever	20	18.5
Lymphocytic Infiltration	Negative	63	58.3
	Positive	45	41.7
Foamy Macrophages	Negative	93	86.1
	Positive	15	13.9
Necrosis	Negative	36	33.3
	Positive	72	66.7
IGN	Negative	19	17.6
	Positive	89	82.4
Calcification	Negative	100	92.6
	Positive	8	7.4

Other histopathological findings

Many other histopathological features were observed during microscopical examination (Table 3); such as lymphocytic infiltration within the tumor area and the presence of the foamy macrophages (Figure 6 A, B&C); these showed less percentage represented by 41.7% and 13.9% respectively. Conversely75% of the colorectal cancer demonstrated moderate to severe desmoplastic reaction (Figure 6 D, E&F) of the matrix according to study done by Vermeulen et al., (2001) and Nyström et al., (2012)[32,33].

Regarding the tumor necrosis &intraglandular necrosis (IGN) (Figure 7 A, B & C) were observed during the histological examination with high percentage of 66.7 & 82.4 consequently; whereas the appearance of calcification (Figure 7 D & E) was found in 8 cases only (7.4%).

Table 4, revealed statistical correlation between grades, stage of CRC with the other parameters

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in **Table 3**, there was no significant correlation between grade and stage of the disease with lymphocytic infiltration, necrosis and calcification. While the desmoplastic reaction showed significant correlation. Increasing of the local invasive of the mucosa is induced by the desmoplasia and collagen fiber remodeling. Regarding foamy macrophages was only significant with grade of CRC. Foamy macrophages are declined in the number when grade system of CRC became higher. Also the IGN showed significant difference with each of the stage and grade.

Table 4: Correlation Between Histopathological Changes with Grade and TNM Stage

		Desmoplastic reaction	Lymphocytic infiltration	Foamy macrophage	Necro-sis	IGN	Calcific-ation
Morphological variants	Pearson Correlation Sig. (2-tailed)	.022 .819	-.027 .782	-.097 .320	-.020 .833	-.516** .000	.039 .689
Grade	Pearson Correlation Sig. (2-tailed)	.100 .303	-.059 .547	-.243* .011	.070 .471	-.406** .000	.025 .801
Local Invasive Depth	Pearson Correlation Sig. (2-tailed)	.212* .028	-.047 .632	-.002 .986	.030 .758	-.236* .014	-.120 .216
Lymph Nodes	Pearson Correlation Sig. (2-tailed)	.081 .402	.044 .654	-.077 .431	.040 .684	-.216* .025	-.111 .253
Metastasis	Pearson Correlation Sig. (2-tailed)	.169 .081	.133 .171	.063 .517	.035 .722	.091 .351	-.055 .569

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

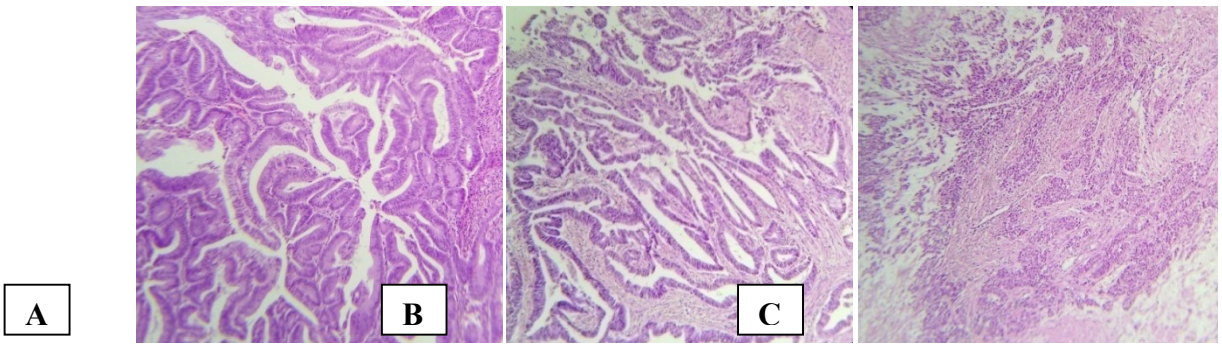

Figure 5: Grades of Colorectal Adenocarcinoma (A) Well (B) Moderate (C) Poor Differentiated AD H& E 100X.

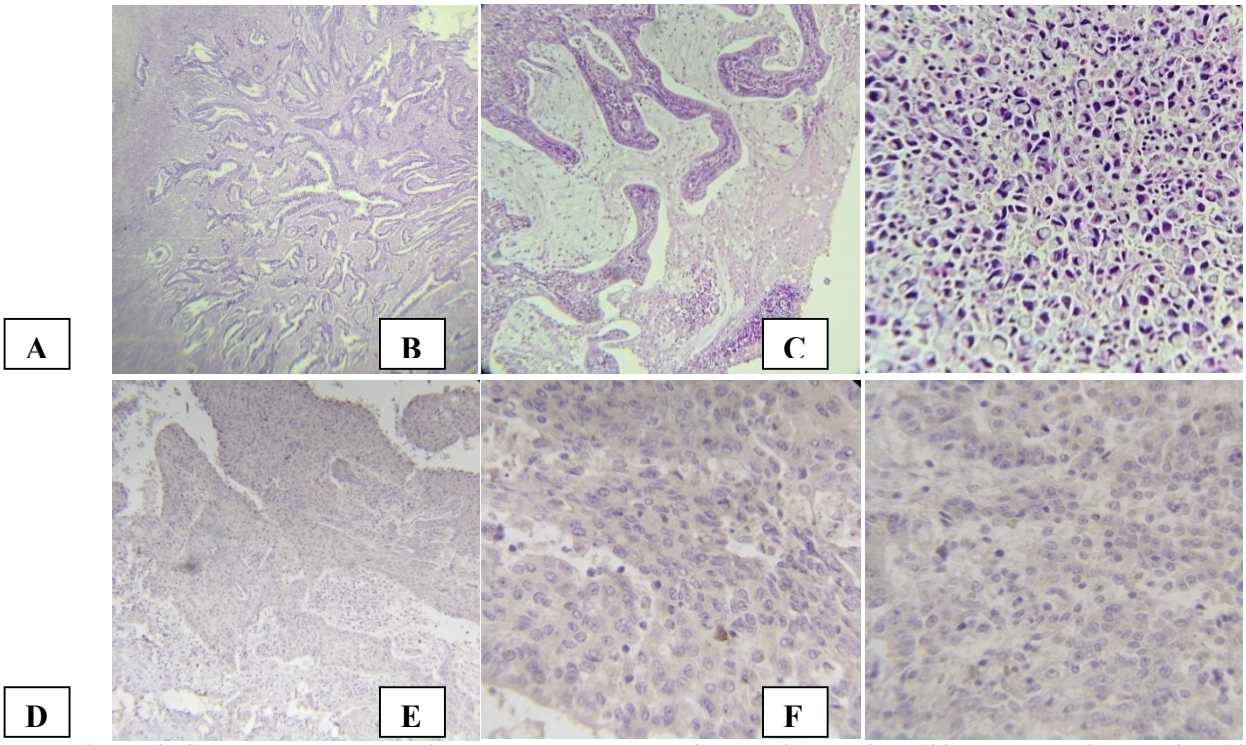

Figure 4: Colorectal Adenocarcinoma (AD) Types (A) ConventionalH& E 100X (B) MucinousH& E 100X (C) Signet Ring Cell H& E 100X (D) Neuroendocrinal Tumor Stained with Chromogranin A100X (E&F) Neuroendocrinal Tumor Stained with Chromogranin A 400X.

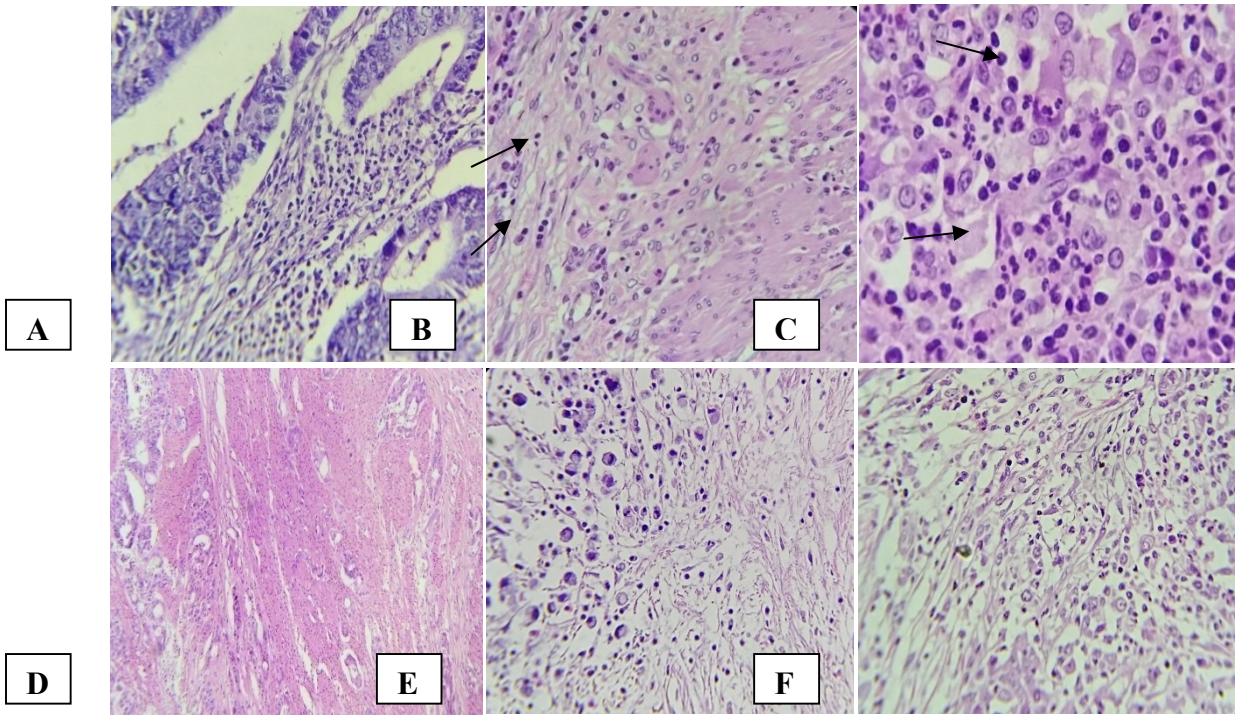

Figure 6: Colorectal Adenocarcinoma with (A) Lymphocytic Infiltration H& E 100X (B&C) Foamy Macrophages (arrow) H& E 100X,400X. (D) Desmoplastic Reaction H& E100X (E&F) Desmoplasia in Signet Ring Cell ADH&E 400X.

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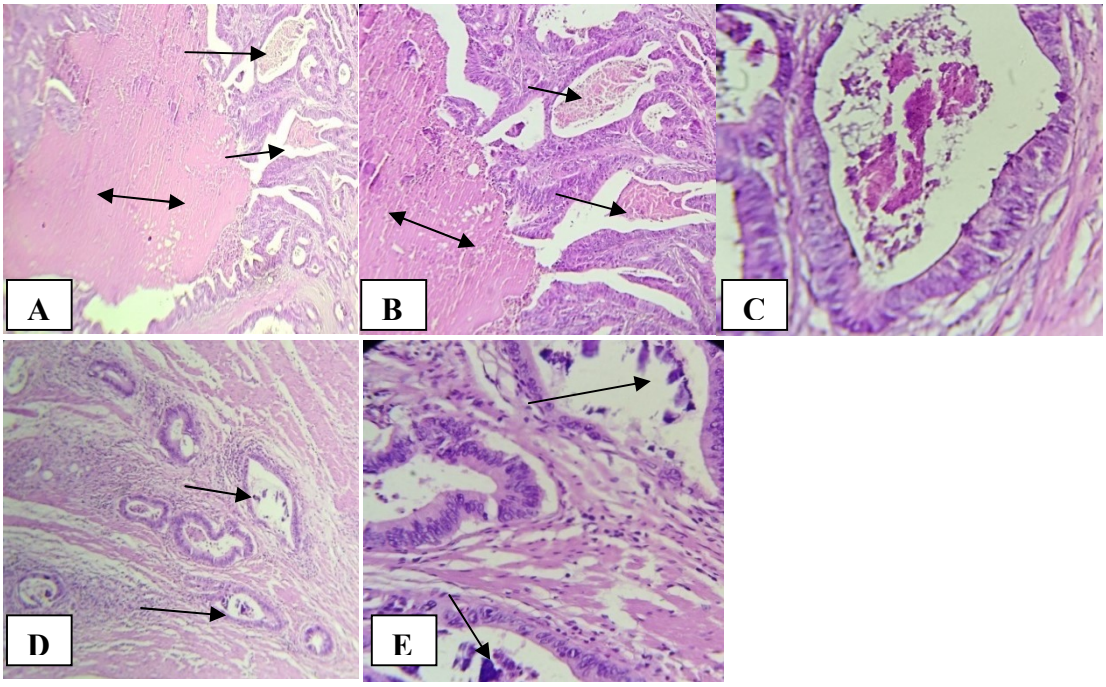

Figure 7: Colorectal Adenocarcinoma with (A) Necrosis (double head arrow) and IGN (single head arrow) H& E40X(B) Necrosis (double head arrow) and IGN (single head arrow) H& E100X (C)IGN H& E400X. (D&E) Calcification (arrow) H&E100X,400X.

Immunohistochemistry findings (Ki67 & VEGF):

From the total number of patients, 31 cases (28.7%) had low expression of Ki67, whereas 77 cases were found with high expression of Ki67 with the percentage of (71.3%) (Figure 8). Regarding VEGF expression, 33 cases (30.6%) were stained score 0 and 1 respectively, and 42 cases (38.9%) had score 2 (Figure 9), (Table 5).

Table 5: Frequency and Percentage of Ki67 and VEGF Expression

IHC marker	Expression	Frequency	Percent %
Ki67	Low	31	28.7
	High	77	71.3
VEGF	Score 0	33	30.6
	Score 1	33	30.6
	Score 2	42	38.9
	Total	108	100.0

The clinicopathological findings association with Ki67 expression is demonstrated in **Table 6.** With the exception of tumor grade, none of the gender, age, tumor site and other clinicopathological parameters has a relationship with Ki67 expression. Grade of tumor shows a significant effect (P=0.014), this means a dramatic increase of Ki67 expression with tumor grade. Although the TNM stage reveals increase in the expression of Ki67, but this increase is statistically not significant.

Table 7 illustrates the relationship between clinicopathological findings and VEGF expression. Also the majority of clinicopathological parameters don't have significant effect. All cases of signet ring cell (5 cases, 6.7%) had revealed positive VEGF

expression. Nearly about two third of mucinous cases (11 from the total 15) had positive expression for the angiogenic marker.

Conventional type also found as two third (59 from 86 cases) to express positive VEGE, while the two cases of neuroendocrine tumor didn't express VEGE immunoreactivity.

Expression of VEGF showed great relationship with TNM stage, it increased toward the progression of tumor stage (P = 0.019), as well as the local invasion to the colorectal wall (P=0.009). Tumors with positive angiolymphatic also shows high angiogenic growth factor expression (59 from 84 cases), but does not have any statistical significant.

Table 6: Association Between Clinicopathological Findings and Ki67 Expression in CRC

Histopathological Finding		Ki67 expression				P-value
		Low(<40)		High(≥40)		
		No.	%	No.	%	
Gender	Male	18	58.1	47	61.0	0.775*
	Female	13	41.9	30	39.0	
Age	<60	15	48.4	44	57.1	0.408*
	≥60	16	51.6	33	42.9	
Tumor site	Colon	19	61.3	43	55.8	0.60*
	Rectum	12	38.7	34	44.2	
Histological Types	Conventional	22	71.0	64	83.1	0.25**
	Mucinous	7	22.6	8	10.4	
	Signet ring cell	2	6.5	3	3.9	
	Neuroendocrine Tumor	0	0	2	2.6	
Grade	Well	1	3.2	2	2.6	0.014**
	Moderate	22	71.0	70	90.9	
	Poor	8	25.8	5	6.5	
TNM Stage	I	2	6.5	9	11.7	0.859**
	II	10	32.3	27	35.1	
	III	18	58.1	38	49.4	
	IV	1	3.2	3	3.9	
Local Invasive Depth	T2	2	6.5	12	15.6	0.227**
	T3	25	80.6	61	79.2	
	T4	4	12.9	4	5.2	
Lymph Nodes	Non involved	12	38.7	36	46.8	0.447*
	Involved	19	61.3	41	53.2	
Distant Metastasis	M0	30	96.8	74	96.1	1.000**
	M1	1	3.2	3	3.9	
Angiolymphatic invasion	Neg.	5	16.1	19	24.7	0.334*
	Pos.	26	83.9	58	75.3	
Total		31	100	77	100	

*** Chi square, **Fisher exact test**

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Table 7: Association Between Clinicopathological Findings and VEGF Expression in CRC

Histopathological Finding		VEGF				P-value
		Neg.		Pos.		
		No.	%	No.	%	
Gender	Male	20	60.6	45	60.0	0.953*
	Female	13	39.4	30	40.0	
Age	<60	17	51.5	42	56.0	0.666*
	≥60	16	48.5	33	44.0	
Tumor site	Colon	17	51.5	45	60.0	0.41*
	Rectum	16	48.5	30	40.0	
Histological Types	Conventional	27	81.8	59	78.7	0.11**
	Mucinous	4	12.1	11	14.7	
	Signet ring cell	0	0	5	6.7	
	Neuroendocrine Tumor	2	6.1	0	0	
Grade	Well	0	0	3	4.0	0.619**
	Moderate	30	90.9	62	82.7	
	Poor	3	9.1	10	13.3	
TNM Stage	I	8	24.2	3	4.0	0.019**
	II	9	27.3	28	37.3	
	III	15	45.5	41	54.7	
	IV	1	3.0	3	4.0	
Local Invasive Depth	T2	9	27.3	5	6.7	0.009**
	T3	21	63.6	65	79.6	
	T4	3	9.1	5	6.7	
Lymph Nodes	Non involved	17	51.5	31	41.3	0.327*
	Involved	16	48.5	44	58.7	
Distant Metastasis	M0	32	97.0	72	96.0	1.000**
	M1	1	3.0	3	4.0	
Angiolymphatic invasion	Neg.	8	24.2	16	21.3	0.739*
	Pos.	25	75.8	59	78.7	
Total		33	100	75	100	

* Chi square, **Fisher exact test

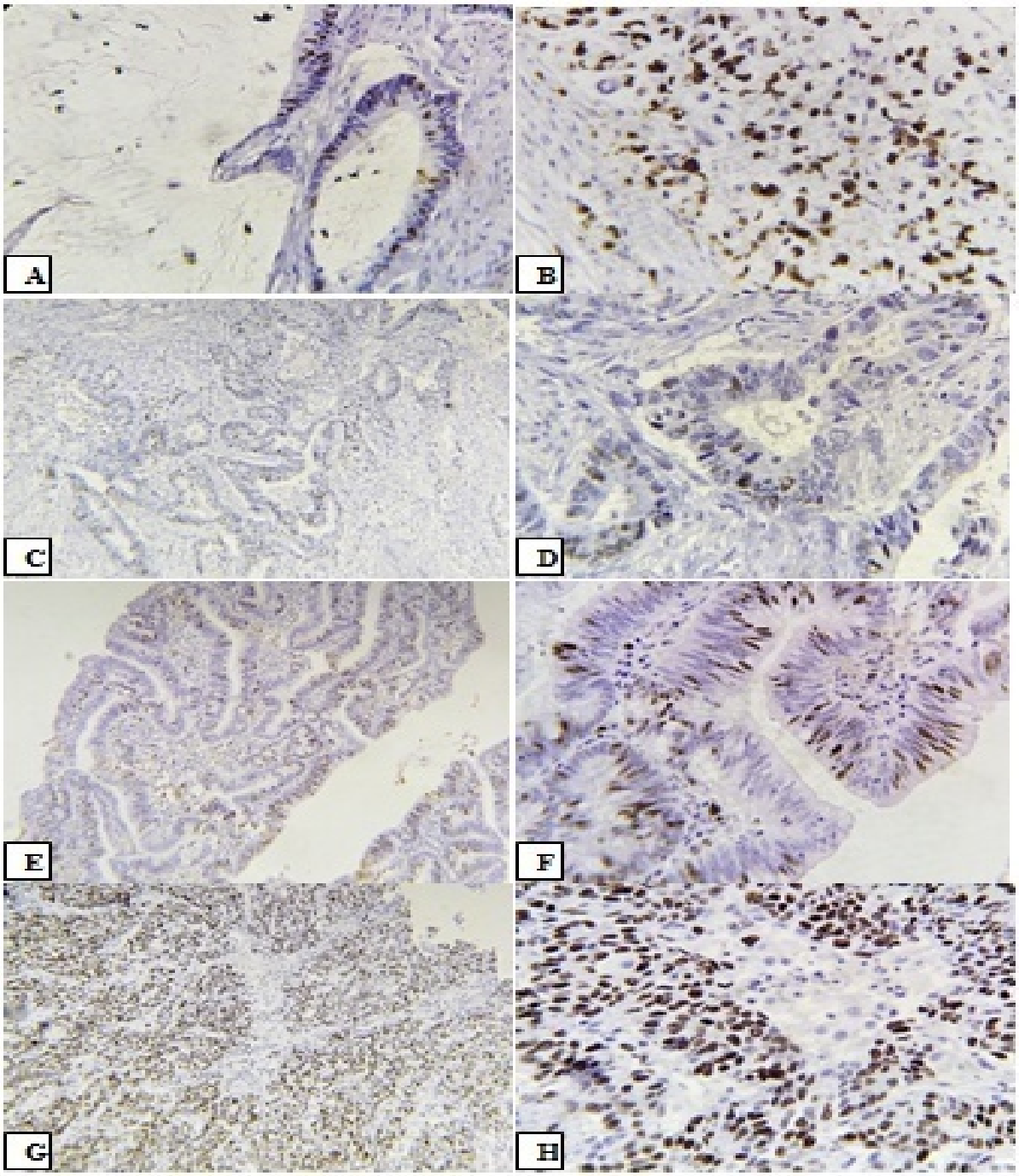

Figure 8: CRC with Ki67 expression in: Mucinous AD 400X(A), Signet Ring AD 400X(B), Conventional AD(C 100X & D 400X) Low Expression, Conventional AD (E 100X&F 400X) High Expression, Conventional AD(G 100X & H400X) High Expression. Negative Ki67 in Mucinous and Conventional AD(A, C). Positive Expression of Ki67 in B, F and H

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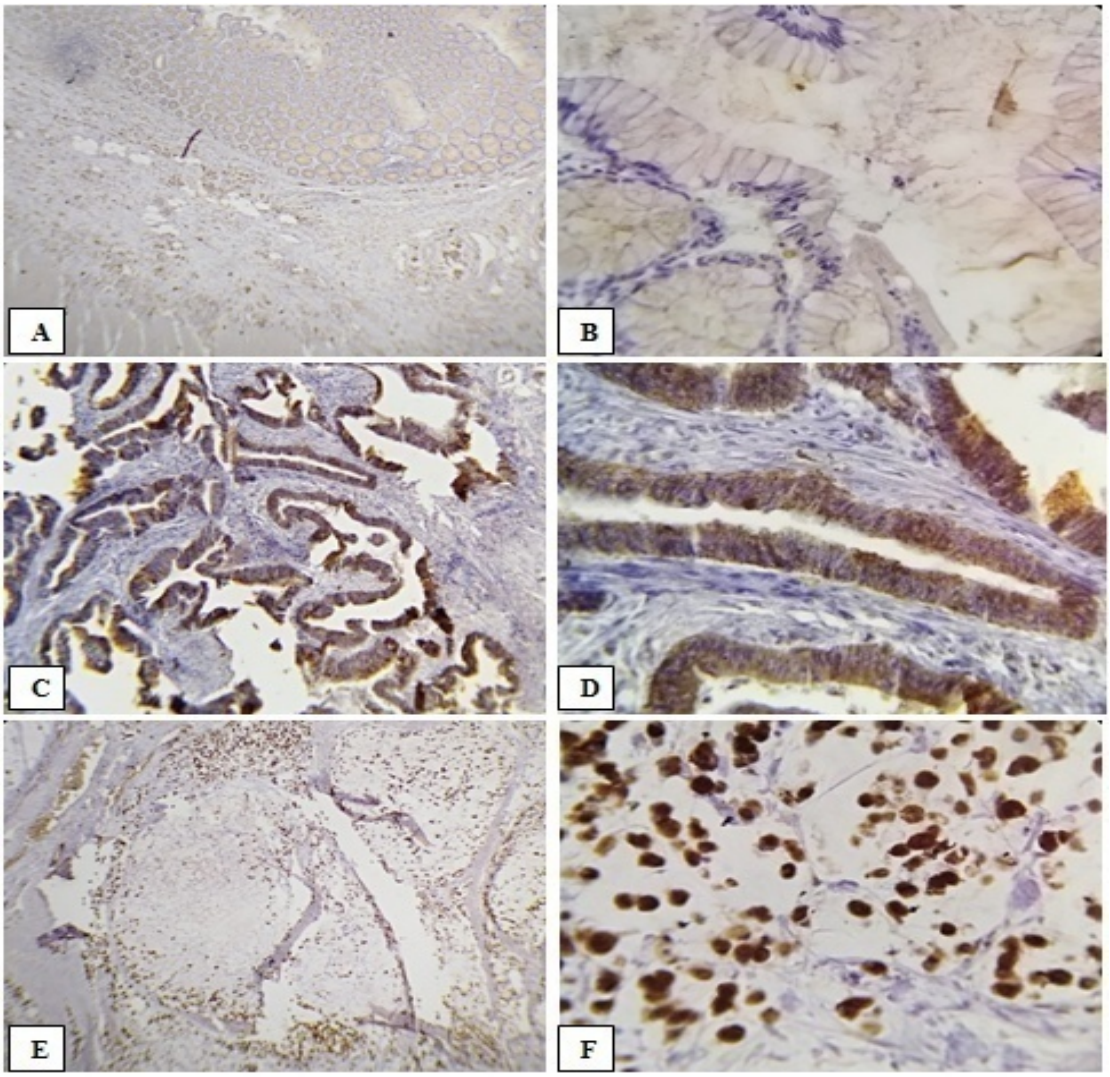

Figure 9: VEGF in CRC: Normal Colonic Mucosa Associated with CRC had Negative Expression (A&B) (100X & 400X), Conventional AD with Strong Expression (C&D) 100X & 400X, Positive Expression in Mucinous AD Containing few Signet Ring Cells (E) Low Magnification Power100X, Signet Ring Cells AD with Strong Expression (F) High Magnification Power 400X.

DISCUSSION

Colorectal cancer continues to be the most common cancer in the gastrointestinal tract worldwide[34].

A study in Turkish[35] and Saudi Arabia[36] found that CRC patients also have the same ranking with that of the Iraqi cancer patients. The neighbor countries might share nearly the same cultural and life style habits in addition they have the same environmental exposure agents leading to colorectal cancer.

The disease ranking in this study unlike the results cited by the same country and even the neighbor countries, the reason is attributed to the variation in the colorectal cancer epidemiology in different geographical regions[37].

The peak incidence of patients' groups was among 60-69 years and, the same results were recorded by some authors[34,38]. Vogelstein et al., (1988)[39] revealed that CRC occurs due to multiple genetic mutation that accumulate, like activation of certain oncogenes, such as *ras*, and mutation of tumor suppressor genes, such as *p53,* and the accumulation of the genetic alterations over the time leads to the progression from colonic adenoma to invasive carcinoma which related to multi-hit theory[40].

Despite of that the colorectal cancer is consider a disease of older patients, this study reveal that 16.7% of the patients included were under the age of 40 years, this is higher than many other studies carried out worldwide like (Smith & Butter,1989)[41] who reported 4.8%. In Iraq, Majid et al.,(2009)[34]and Rahman, (2000)[42] had been reported that 35.5%& 17.5% respectively; patients were younger than 40 years.

The increasing incidence of CRC and the change in age distribution is due to several factors like exposure to the carcinogenic substances during the wars carried on for several years in Iraq, consuming unhealthy food and lack of high quality of diagnostic procedures[43].

The male to female ratio in this study was (1.5:1) results are very close to the results mentioned by (Rahman, 2000; Pahlavan & Kanthan 2006; Azadeh et al. 2008)[42,44,45] this could be due to hormonal factors in female patients[46].

The rectosigmoid is the most common site (64.8%) to be affected with CRC. Undoubtedly, most studies demonstrated that the left side of the colon is more susceptible tumor. The mentioned percentage have somewhat near the percent that have been recorded by (Al-Bayati and Jasim, 2017; Majid, 2009)[47,34] they found that the following percentage respectively 66.67% , and 60% of the tumors were in the rectosigmoid, the same finding were found in studies carried out by many authors[48,49,50,51].

The tumor distribution throughout the large intestine depends on genetics and environmental factors involved in colorectal carcinogenesis[52, 53, 54, 55].

Conventional adenocarcinoma is the majority of tumor type found in diagnostic cases is adenocarcinoma which is quite the same resist with textbook data.Al-Bayati and Jasim (2017)[47]; Bosman et al.,(2010)[5] cited that more than 90% of colorectal carcinomas are adenocarcinomas originating from epithelial cells of the colorectal mucosa.

Doubtlessly, moderately differentiated adenocarcinoma has the highest percentage 85.2% from all cases of CRC. Poorly differentiated adenocarcinoma however is less common among CRC cases. Studies done by many researchers[49, 50, 56] indicated that the almost grading type is moderately differentiated. Histological tumor grading is basically depending on the percentage of glandular formation in conventional adenocarcinoma. Bosman et al., (2010)[5] &Compton et al.,(2000)[57] revealed that during practice, most colorectal adenocarcinomas (~70%) are diagnosed as

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moderately differentiated . Well and poorly differentiated carcinomas account for 10% and 20%, respectively.

Controversially, results recorded by(Azadeh et al., 2008)[45] found that well differentiated carcinoma was the most common between males and females, whereas(Malehi and Rahim 2016)[58] found the poorly differentiated is the common cases of the disease. In this study, well differentiated adenocarcinoma have the less percentage of 2.8%, this can be attributed to the patients' uncomplaining, late symptoms of the disease , absence of screening program or lack of knowledge about the symptoms, or even if they were, they seek a medical consult after a long period of time. These patients in many cases did not have a colonoscopy check up to determine if they have tumor to be removed or have an intense medical treatment. The late diagnosis of the disease will leads to appearing the disease with low grade and also in late stages.

Diagnosis of patients revealed that stage III (51.9%) & stage II (34.3%) appear more than other stages. Results in the present study agrees with the results found by Malehi and Rahim (2016)[58], but theycontradicts with what has been found and published by(Aykan et al., 2015)[51] where they found the majority of patients were diagnosed with stage III and IV in Turkey of 35.9% and 29.7%, respectively.

The mucosal invasion was observed and extended through muscular rispropria(T3) which shows the highest frequency number with percentage of 80.6. Invasion beyond the serosa into the visceral peritoneum or into adjacent structures or organs (T4) is the less frequent 6.5%. Regional lymph nodes involvement N1&N2 comprised 55.6% which appears as a higher percentage than cases don't reached the regional lymph nodes 44.4%. Only four cases (3.7%) show metastasis to other tissue and organs.

Azadeh et al.,(2008)[45] also demonstrated that mucosal invasion of patients were also diagnosed through the muscularispropria more than other layers. Patients behaving distant metastasis to other tissues and organs are less common. But lymph node involvements are less. These results were recorded probably due to cases that have been examined were with high grade differentiated.

Three quarter of the colorectal cancer demonstrated desmoplastic reaction. Increasing of the local invasive depth of the mucosa is induced by the desmoplasia and collagen fiber remodeling; this was increased significantly with the increase of the desmoplasia. Desmoplastic reaction (DR) represents the histological remodeling of the extracellular matrix (ECM) formed by cancer-associated fibroblasts[59], which leads to matrix turnover dys-regulation accompanied by degradation of the basement membrane rich by collagen type IV and accumulation of collagen type I which is a fibrillar collagens[60, 61].

Foamy macrophages were recorded low in number 13.9%, significantly with higher grade. Väyrynen et al., (2013)[62], found that stromal macrophages; reduced with stage progression. Mantovani et al., (2002)[63]disclosed that tumor-associated macrophages (TAMs) may have contribution to antigen presentation and phagocytosis of the cancer cell. Lymphocytic infiltration within the tumor area showed low expression also 41.7%. The reduction of immune responses have association with pronounced desmoplastic reaction and it is

apparent that the tumor progression is induced by tumor stroma remodeling[11].

Necrosis & IGN were observed during histological examination with high percentage of 66.7 & 82.4 consequently. General necrosis which appears outside of the gland in CRC tissues didn't have any effect with the grade and the stage of colorectal cancer, whereas IGN shows significant difference with each of the morphological variants, grade & stage of tumor. The IGN increasing with all these variants happens in controversial direction. Higher grade will reduce the gland formation proportion according to the World Health Organization (WHO) criteria[5]. In histopathological examination, CRC appear with huge central necrosis occupying within gland[64].

The appearance of calcification was found in 8 cases only (7.4%). The calcification in CRC tissues demonstrated that there was no significant difference with grade and TNM stage of colorectal cancer.

In the present study, the associations of Ki67 expression with tumor grade was significant (P=0.01), whereas the other clinicopathological parameter as; gender, age, tumor site and TNM stage didn't have a relationship. These finding were consistent with results demonstrated by Saleh et al., (1999)[65] they concluded that Ki-67 proliferative indexappeared to increase with decreasing degree of differentiation of colorectal carcinoma, while Salminen, et al., (2005)[24], revealed significant association with stage of tumor. Many other authors[29, 66, 67] found that there was no relationship between Ki-67 immunoreactivity and various clinicopathological and prognostic findings in colorectal carcinomas.

Several explanations are interacted for these discrepancies like difference in epitope preservation, staining procedures, methods of evaluation and quantification of Ki-67 immunoreactivity staining as well as to study population. Investigators have suggested that the lack of correlation is due to the considerable heterogencity in colorectal carcinomas[68].

Vascular endothelial growth factor was positive in 69.5 % in this study. ELLIS et al., (2000)[69], Akagi et al., (2000)[70] and Zlobec et al. (2005)(71) found that 43%, 55%, 47% had positive expression of VEGF in colorectal cancer respectively. High expression of VEGF 94.7% was recorded by Kamel et al., (2016)[72] in colorectal carcinoma.

Relationship of VEGF had significant correlation with TNM stage (P = 0.019), as well as the local invasion to the colorectal wall (P 0.009), so it increased toward the progression of tumor stage. The other clinicopathological factors do not show any effects. This situation is identical to what some publishers have reached[72, 73].

Vascular endothelial growth factor has been expressed with high percentages in several types of tumors including colorectal cancer. It plays a key role in tumor angiogenesis and considered as a positive regulator of angiogenesis[74].

Moderately differentiated adenocarcinoma and stage III, were the most frequent diagnosed cases with CRC in Duhok Governorate. Macrophages infiltration is conversely related with grading of CRC. Histopathological changes like desmoplastic reaction and intraglandular necrosis were common findings in CRC and they were in concordance correlation with stage and grade.Ki67 has relationship with tumor

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grade, whereas VEGF has significant relationship with TNM stage as well as the local invasion to the colorectal wall.

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پوختە

هەلسەنگاندنا شانەیی یا نەخۆشیێ بو شێرپەنجەیا کۆلۆنی و ریکای

پاشینە و ئارمانجێن ڤەکولینێ: شێرپەنجەیاکۆلۆنی وریکا، ئەوشێرپەنجەیا کۆئەندامێ هەرسێیەکو یا بەربەلاڤەل سەرانسەری جیهانێ و ل عیراقێ ، شێرپەنجەیاکۆلۆنی و ریکای ژ گرنگترینشێرپەنجەیا ب پلەیاحەفتێ دهێت.هەرچەندەرێزبەندیاوێ ل کوردستانێ یا چواریێیە ژ شێرپەنجە یێنپتر بەربەلاڤدناف نێر و مێیاندالی ڕێکێن دەستنیشانکرن و چارەکرنێ باشترلێ هاتن. بەلێ نێزیکی 50 ٪ ژوان نەخۆشێن وەرم بو هاتیە هەلکێشان دماوێ (5)سالاندا ژبەر وێ نەخۆشیێ گیانێ خو ژ دەستدان.ئەوژی چنکو وەرەم گەهشتە شانە یێندویرتر.ئەڤ ڤەکولینە هاتە کرنۆدبەست نیشانکرنا لدویفئێك هاتنا جۆرێن شانەیی یا شێرپەنجەیا کۆلۆن و ریکای و هەلسەنگاندنا پەیوەندیێ دناڤبەرا شێرپەنجەیا کۆلۆن و ریکای لدور ئەوا پەیوەندیدار ب پولینکرنێو قۆناغانەخۆشیێ و دگەل ئەنجامێن شانەیی یێنهەمجۆر کو کارلێکرنا پێکهاتن ئێلیا ریشالی، و تێچوونا لیمفی، خانەیێن قورگی یێن لینج، رزین، دناف رژێنێن وەرەمتنێ، و رەقبوونێ.

ڕێکێن ڤەکولینێ: ئەڤی ڤەکولینێ (108)نەخۆش بخوڤە گرتنکوب شێرپەنجەیا کۆلۆنێ و ریکایێ هاتبوونە دەستنیشانکرن. هەمی حالەت هاتنە کۆمکرن ژ کانونا دووێ 2015هەتا کانونا ئێکێ 2017ێ پشکا شانە یێن نەخۆشیێ ل تاقیگەها ساخلەمیێ یا مەڵبەندیا گشتی و تاقیگەهێن شانەیێن نەخۆشیێ یێن تایبەت ل باژێرێ دهۆکێپێزانین ژێنتەختەبەندی ژ ڕاپۆرتێن شانەیێن نەخۆشیی ڤیێنبەردەستبدەستڤە هاتن. بلوکێن دناڤ پارافێنێ دا هەلگەرتێ هاتنەپارچە پارچەکرن و ب هەردوو مارکەرێن ئیمیونوهستوکێمیایێیێن VEGFوKi67 هاتنە بۆیاغکرن و پاشی ب شێوەیەکی ئوتوماتیکی ل دوڤ پرۆتوکولێن کومپانیا دروستەکەرا دڕەتەنێن کارگەهێ هاتنە خواندن.

ئەنجام: تەمەنێ نەخۆشان دناڤبەرا 18– 83 سالیێدابوون.ئانکو ب ناڤنجیا 54,42 سالان. تەمەنێ 60 – 69 سالی، بلندترین تەمەنێ نەخۆشان بوورێژەیارەگەزێ نێر بو رەگەزێ مێ 1,5 ؛ 1 جهێ وەرمتنێ یی ڤپترببەربەلاڤدەڤەرا ریکایبوو (42,6 ٪) و کۆلۆناسینی (22,2 ٪) جۆرێشێرپەنجەیارێناوەرەمێ یا ئاسایی، جۆرێبەربەلاڤەبوو 86 (79,6 ٪)پترياحالەتێنشێرپەنجەیا کۆلۆن و ریکای ژ پلەیاناوەندبوون و ڕێژەیاوێ 85,2 ٪لێرێژەیانەخۆشێنقۆناغادووێ و سێیێهەی37 (34,3 ٪) و 56 (51,9 ٪) لدویفئێك و گەلەکدووبارەوەکقۆناغادەست نیشانکرنانەخۆشیێ. بەلاڤەبوونا جهێ نەخۆشیێدناڤتەخێندیواریکۆلۆنێگرێدابووب زێدەبوونارێژەیاریشالبوونێ و جارەکادیچێبوونا ریشالێن کولاجین.خرڤەبوناخانەیێنقورگێیێن لینج کێمتر لێهات ئەوژی ب زێدەبوناپلەیاتوشبوونێ ب شێرپەنجەیێ. رزینێدناڤرژێنێنوەرەمێئنجامێنگرنگدیارکرن د پەیوەندیکرنێدگەلبسەرداگرتناوەرەمێ، بەلاڤەبوناوەرەمێ بو گرێیێنلیمفاوی و پۆلینکرناپلەیاتوشبوونێ ب شێرپەنجەیێ.

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بەربەلاڤەبوونا هەردوو مارکەرینKi67وVEGFبریتێ بوو ژ 77 و 75 حالەتان ل دووڤ یەک. مارکەرێKi6 دیارکر کو پەیوەندیەکا ئاشکەرا و مەزن دگەل پلەیشێرپەنجەیێ هەیە (P=0,014) لێمارکەرێVEGFپەیوەندیەکا مەزن دگەل قوناغا TNMهەبوو (P=0,019)، زێدەباری تێکچوونا نافخویێیا دیواری ڕێکە و قولونێ (P=0,009).

دەرئەنجامپلەیا توشبوونێ ب شێرپەنجێ یێن خودان پلەیا ناوەند (85,2 ٪)و ژ قۆناغا سێیێ (51,9 ٪)حالەتێن پتر بەربەلاڤ دگەل شێرپەنجە یا کۆلۆن و ریکتۆخرڤەبوونا خانەیێن قورگێیێن لینج پەیوەندیەکا بەرەڤاژی هەبوو دگەل پۆلینکرنا پلەیا شێرپەنجەیا کۆلۆن و ریکتۆورانکار یێن نەخۆشیێ یێن شانەیی وەککارلێکرنا چێبوونا شانەیا ریشالی د رزیبوون دناڤ رژێنێن وەرەمێ. ئەنجامێن دیاربوون ل شێرپەنجەیا کۆلۆن و ریکتۆ د نێزیکی ئێکبوون دگەل پلە و قۆناغا نەخۆشیێ. مارکەرێ Ki67پەیوەندی دگەل پلەیا وەرەمێهەبوو لێ مارکەرێ VEGFپەیوەندی دگەل بەلاڤبوونا وەرەمێهەبوو.

الخلاصة

التقييم النسيجي المرضي لسرطان القولون والمستقيم

خلفية واهداف البحث: سرطان القولون والمستقيم هو سرطان الجهاز الهضمي الأكثر شيوعا في جميع أنحاء العالم. في العراق ، احتل سرطان القولون والمستقيم المرتبةالسابعة من بين أهم السرطانات ، في حين كان تسلسلهفي كردستان الرابع من بين السرطانات الأكثر شيوعًا لكل من الذكور والإناث. على الرغم من أن طرق التشخيص والعلاج قد تحسنت ، إلا أن حوالي 50٪ من المرضى الذين أستاصلوا الورم ماتوا بسبب المرض في غضون 5 سنوات ، بسبب غزوالورم الى انسجة اخرى بعيدة. أجريت الدراسة لتحديد تواتر الأنواع النسيجية لسرطان القولون والمستقيم ، وتقييم العلاقة بين سرطان القولون والمستقيم فيما يتعلق بدرجة التصنيف والمرحلة المرضية، مع نتائج نسيجيةمختلفة والتي تتضمن تفاعل تكون النسيج الليفي ، والتسلل الليمفاوي ، خلايا البلاعم الرغوية ، النخر ، النخر داخل الغدد الورمية ، والتكلس.

طرق البحث: شملت هذه الدراسة (108) من المرضى الذين تم تشخيصهم بسرطان القولون والمستقيم. تم جمع الحالات خلال الفترة من كانون الثاني 2015 الى كانون الاول 2017 من قسم الأنسجة المرضية في المختبر الصحة المركزي العام ومختبرات الأنسجة المرضية الخاصة الأخرى في مدينة دهوك. تم الحصول على المعلومات السريرية من تقارير الأنسجة المرضية المتاحة. تم تقطيعالعينات المطمورة بالبارافين وتصبيغها بالمعلمات النسيجية المناعية لكل من Ki67 و VEGFوتمت المعالجة بصورة اوتوماتيكية وفقًاللبروتوكولاتالمقدمةمنالشركةالمصنعةللجسمالمضاد.

النتائج: تراوحت أعمار المرضى من 18-83 عامًا بمتوسط 54.42 عامًا. كانت الفئة العمرية 60-69 سنة هي ذروة عمر الفئات العمرية للمرضى. نسبة الذكور: الإناث كانت 1.5: 1. كان موقع الورم الأكثر شيوعًا منطقة المستقيم (42.6٪) والقولون السيني (22.2٪) ، وكان نوع سرطان الغدد الورمية التقليدية هي النوع السائد 86 (79.6٪) ، وكانت أغلبية الحالات لسرطان القولون والمستقيم من الدرجةالمعتدلة وتمثلت بنسبة 85.2٪. يشغل المرضى الذين لديهم المرحلة الثانية والمرحلة الثالثة 37 (34.3٪) و 56 (51.9٪) على التوالي الاعلى تكرارا كمرحلة تشخيص المرض . ارتبط الانتشار الموضعي للمرض داخل طبقات جدار القولون بزيادة نسبة التليف وإعادة تشكيل ألياف الكولاجين. انخفض تجمع خلايا البلاعم الرغوية بازدياد درجة الاصابة بالسرطان. وأظهر التنخر داخل الغدد الورمية نتائج مهمة في الارتباط مع غزو الورم ، انتشار الورم الى العقد الليمفاوية وتصنيف درجة الاصابة بالسرطان. كان تردد كل من المعلمات المناعية النسيجية (Ki67 & VEGF) (75&77%) على التوالي. اظهر التفاعل المناعي Ki67 علاقة معنوية مع درجة تصنيف الورم (P=0,014). في حين VEGF كان له تاثير معنوي مع مرحلة المرض (P=0,019) بالاضافة الى غزو النسيج الموضعي (P=0,009) الى جدران نسيج سرطان القولون والمستقيم فهي تزداد باتجاه تقدم مرحلة الورم.

الاستنتاج: كانت درجة الاصابة بالسرطان ذو الدرجة المعتدلة (85.2 ٪) ومن المرحلة الثالثة (51.9 ٪) الحالات الأكثر شيوعا مع سرطان القولون والمستقيم. ارتبط تجمعخلايا البلاعم الرغوية عكسيا مع تصنيف درجة سرطان القولون والمستقيم. التغيرات المرضية النسيجية مثلتفاعل تكون النسيج الليفي والنخر داخل الغدد الورمية كانت نتائج شائعة في سرطان القولون والمستقيم وكانا متقاربين مع درجة ومرحلة المرض. Ki67 كانت لها علاقة مع درجة تصنيف الورم في حين VEGF كانت مرتبطة مع غزو وانتشار الورم.

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