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Assessment of immunohistochemical Expression of HER2\Neu and BRCA1 in Colorectal Tumors and it's Correlation with Clinicopathological Variables

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Abstract:

Background: HER2\neu and BRCA1 expression in tumors is consider as a important prognostic marker in relation to the use of adjuvant therapy specially in a patients with worse prognosis in which that result in improvement in their survival. this research was done to assess the HER2\neu and BRCA1 immunohistochemical expression in colorectal tumors in correlation with some clinicopathological parameters.

Methods: in this study(which was done retrospectively), A 44 cases include22 benign colonic lesions and 22 colonic adenocarcinoma in addition 6 normal resection (non tumors) margin were used as a control group, paraffin embedded archival materials from this cases were collected for the period between Nov 2015- July 2016.the expression of 2 markers (HER2/neu and BRCA1)were assessed and then were correlated with different clinicopathological parameters .

Results: the immunohistochemical expression of HER2\neu was (45%) of CRC, in (27%) of colorectal polyps and in (4) out of (6) non-neoplastic colonic tissues.

HER2\neu was expressed more frequently in the colon in about (46%),in female (39%), in the age group of more than 40 years (43%) , in well differentiated adenocarcinoma (67%), in non mucinous adenocarcinoma (90%), in T2 (54%) and the tumor size of more than 4 cm (66%) although the results were statistically not significant..

BRCA1 immunostaining was found in (6%) of colorectal tumor and there were (14%) positive cases of colorectal polyps, the result was statistically not significant.

BRCA1 expressed more frequently in the colon (20%), in male (8%) and age group of more than 40 years(10%) the results were statistically not significant. there was no difference in BRCA1 expression between tumor size of more or less than 4 cm .

Conclusions: In this study researchers concluded that expression of HER2\neu in colorectal tumors (benign and malignant) is not infrequent phenomena , HER2\neu expression was obviously increased in non-neoplastic tissues and adenoma, Low expression of BRCA1 in colorectal tumors and no significant correlation of BRCA1 expression in relation to the clinicopathological parameter (age, gender, tumors types, site and size).

Key words: Immunohistochemical Expression-HER2\neu , BRCA1 , Colorectal Tumors

Introduction

one of the most common malignancies worlds wide is Colorectal carcinoma (CRC) , it regarded as fifth most common form of cancer in the United States and in the Western world it consider the second leading cause of cancer-related death [1,2] in Iraq, it was noticed there was a steady rise in CRC especially over the last two decades the percentage of total cases of colorectal carcinoma was 4.45% of all malignancies for both genders and among the leading causes of death from cancer it was the seventh [3].

HER2\neu and BRCA1expression in tumors is consider as a important prognostic marker in relation to the use of adjuvant therapy specially in a patients with worse prognosis in which that result in improvement in their survival for that reason HER2\neu and BRCA1 have been studied in many tumors [4, 5].

The role of HER2\neu and BRCA1 has been recognized in breast carcinoma and is consider a routine tests for breast cancer patients especially with the introduction of effective therapy targeting HER2,Trastuzumab was the most important one, but There are only a few studies about HER2\neu and BRCA1expression in colorectal tumor. There are only few studies with great controversy and lack conclusive result regarding the HER2\neu and BRCA1 real prognostic value in colorectal tumor in addition to their location on the long arm of chromosome 17 in close proximity gave an interest in investigating these markers together. [6]

The proto-oncogene HER2\neu (C-erbB-2) has been localized to chromosome 17q and encodes a transmembrane tyrosine kinase growth factor receptor [7].

HER2/neu directed therapy:- The use of an anti-HER2 monoclonal antibody (Herceptin) treatment of the patients has been shown to augment the effects of chemotherapy ,to reduce tumor volume and to increase survival in primary and metastatic breast cancer [8].

The use of HER2/neu directed therapy in breast cancer with successful result has lead to evaluate the protein expression and gene amplification in many tumors of the body, colorectal cancer among others.it has been shown that Herceptin inhibit colony formation of the HCA-7 colon cancer cell line and HCA-7 tumor xenografts [9].

BRCA1:-It is tumor suppressor located on long arm of chromosome 17 [10], which maintains genomic integrity to prevent uncontrolled proliferation. [11], BRCA1 mutations Carriers have increased risk of developing breast cancer about 20-fold higher than the general population. Many cases of high-grade sporadic breast and ovarian cancers reported reduced BRCA1 expression that's implying the role of BRCA1 in sporadic breast and ovarian cancer as well [12]. Mutations in BRCA1 are also associated with other cancers, particularly "hormone-responsive tumor types" like the uterine, cervical, fallopian tube, testicular and others like colonic cancers. [13,14]. In the past Several studies had been reported an increased risk of colorectal cancer in patients with BRCA1 or BRCA2 germ-line mutations [5,14,15] . It has been shown that there is association between shorter survival in colorectal cancer and loss of heterozygosity at the BRCA1 gene locus [5].

This study was done to assess the immunohistochemical expression of HER2\neu and BRCA1 in colorectal tumors (carcinoma and polyps) in correlation with some clinicopathological parameters.

Patients, Material and Methods :

Tissue Sample: - In this study (retrospective study) a total of (44) cases of colorectal tumors of which (22) cases CRC and (22) cases colorectal polyps were taken .Of these (44) cases, (30) cases were colectomy and (14) cases were tissue biopsy. In addition to these cases there were (6) cases of normal (non tumorous) resection margin as a control.

A formalin fixed, paraffin-embedded tissues were retrieved from the archived files of the department" of pathology of Al-Kadhimiya teaching hospital,Al-Nasrya(Alhussain)teaching hospital and Gastrointestinal intestinal tract center for the period between Nov 2015- July 2016.From the available histological reports Clinicopathological parameters was obtained .

Three sections of 5µm thickness were taken for each case; one section was stained with (H & E), and the other was stained immunohistochemically with HER2\neu and BRCA1 tumor markers.

Immunohistochemical staining:

The streptavidin –biotin is the method has been used .

The Sections (5 µm) were cut from paraffin blocks and they were deparaffinized in xylol and rehydrated through descending alcohol series. After retrival of the slides in the retrival solution in water bath at 95o C for 40 minutes for HER2/neu and for 20 minute for BRCA1.then endogenous peroxidase was inactivated by incubating the section with 3% hydrogen peroxide for 10 minutes , The sections were incubated with primary antibody over night at 40 C .the antibodies used were monoclonal mouse antibody anti-human BRCA1 (Dako) at 1:50 dilution and the other is polyclonal rabbit antihuman HER2/neu oncoprotein (Dako) at 1:250 dilution.

Sections then were incubated for 30 minutes with biotinylated anti-mouse immunoglobulin (Dako).Then strepavidin conjugated to horseradish peroxidase was used, then washing with phosphate buffer solution .Then the section were incubated with diaminobenzidine substrate for 10 minutes . The section were rinsed with distilled water and counter stained with Mayr's haematoxyllin.

for each staining run negative and positive control slides were included .The negative control slides in the absence of primary antibody and the Positive control were invasive breast cancer for HER2\neu and the ovarian cancer for BRCA1 .

Interpretation of the results of staining characteristic:

The positive reactivity is indicated by the presence of brown reaction product of more than 10% of tumor hcells at the target antigen site.

Counter stain will be pale to dark blue coloration of the cell nuclei.

The pattern of Staining for HER\2neu: cytoplasm or membrane-cytoplasm [16] and **for BRCA1**: cytoplasm or nuclear -cytoplasm.

The quantity of the immunostaining was evaluated as follows [17,18]:

_ Less than10% of tumor cell immunostaining.

\+ 10-40% of tumor cells immunostaining.

++ 41-70%o of tumor cells immunostaining.

+++ > 70% of tumor cells immunostaining.

The positive result classified as focal and diffuse.

Focal:-in which clusters of positive cells where seen in some areas of the tumor but other region where negative

Diffuse: - in which isolated and/or clusters of positive cells where seen throughout most areas of the tumor.

Statistical analysis was done using the SPSS 10.01(statistical package for social sciences).

Two-tailed t-test, chi square distribution test and ANOVA test, were used. (P) values of ≤ 0.05, were considered statistically significant

Results:

There were (26) cases males and (18) cases females and males: females' ratio is 1.4

The mean age of the cases was 44.42 ± 2.53 years, with a range of (3-87) years.

The mean size of the cases (Mean ± SEM) was 2.59±0.54 cm with the range of (0.2-21) cm.

In table 1, the detailed data of 44 specimen are shown.

Table 1: Patients characters

Clinicopathological parameters		Benign		Malignant	
		Number	Percent %	Number	**Percent %**
Age in years	≤ 40	16/23	70	7/23	**30**
	> 40	4/21	19	17/21	**81**
Sex	Male	14/22	64	12/22	**55**
	Female	8/22	36	10/22	**45**
Tumor site	colon	14/26	54	12/26	**45**
	Rectum	8/18	44	10/18	**56**
Tumor size in cm	≤ 4	10/15	67	5/15	**33**
	> 4	8/29	2 8	21/29	**72**
Tumor type	Mucinous			3/22	**14**
	Non mucinous			19/22	**86**
Histological type	TA	8/22	36		
	TVA	2/22	9		
	VA	3/22	14		
	JRP	2/22	9		
	Hyper.P	2/22	9		
	Inf.polyp	4/22	18		
	Hamartomatous polyp	1/22	5		
	AC			22/22	**100**
Tumor grade	WD			3/22	**14**
	MD			9/22	**41**
	PD			10/22	**45**
Tumor depth	T1			5/22	**22**
	T2			13/22	**59**
	T3			**4/22**	**18**

Immunohistochemical study:

HER2\neu over expression:

HER2\neu immunostaining was clearly evident as brown membrane and cytoplasmic staining or brown cytoplasmic staining.

Positive staining was localized in the membrane and cytoplasm in (15) cases (93%) and cytoplasmic in (1) case (7%) of the cases of colorectal tumors (benign and malignant).

The quantity of the HER2\neu immunostaining was +++ in (13) cases of colorectal tumor (81%) and ++ in (3) cases (19%).

Pattern of staining was variable; it was diffuse in (15) cases (93%) and focal in (1) case (7%) of colorectal tumors (benign and malignant).

Correlation between the expression of HER2/neu and various 2 clinicopathological parameters are shown in table 2.

Table 2: correlation between HER2/neu expression and various clinicopathological parameters:

The variable		Positive HER2/neu	negative HER2/neu	P value
Groups	Normal	4/6(67%)	2/6(33%)	**0.174**
	Benign	6/22(27%)	16/22(73%)	
	Malignant	10/22(45%)	12/22(55%)	
Age	≤40	7/23(30%)	16/23(70%)	**0.174**
	>40	9/21(43%)	12/21(57%)	
Sex	Male	9/26 (35%)	17/26(65%)	**0.639**
	Female	7/18 (39%)	11/18 (61%)	
Tumor site	colon	12/26(46%)	14/26(54%)	**0.174**
	Rectum	4/18(22%)	14/18(78%)	
Tumor size in cm	≤4	6/15(40%)	9/15(60%)	**0.174**
	>4	19/29(66%)	10/29(34%)	
Tumor histology	Mucinous	1/3(33%)	23(67%)	**0.783**
	Non mucinous	9/19(47%)	1019(53%)	
Tumor depth	T1	2/5(40%)	3/5(60%)	**0.576**
	T2	7/13(54%)	6/13(46%)	
	T3	¼(25%)	¾(75%)	
Tumor grade	WD	2/3(67%)	1/3(33%)	**0.174**
	MD	5/9(56%)	4/9(44%)	
	PD	**3/10(30%)**	**7/10(70%)**	

Correlation between BRCA1 and different clinicopathological parameters:

Pattern of staining was diffuse in all the cases.

Positive staining was localized in the cytoplasm in all the cases.

The quantity of BRCA1 immunostaining was +++ in (2) cases while was ++ in (1) case.

Table 3: Correlation between BRCA1 expression and different clinicopathological parameters:

The variable		Positive BRCA1	negative BRCA1	P value
Groups	Normal	0	6(100%)	**0.073**
	Benign	3/22(14%)	19/22(86%)	
	Malignant	0	22(100%)	
Age	≥40	1/23(4%)	22/23(96%)	**0.557**
	<40	2/21(10%)	19/21(90%)	
Sex	Male	2/26(8%)	24/26(92%)	**1.000**
	Female	1/18(6%)	17/18(94%)	
Tumor site	colon	2/26(8%)	24/26(92%)	**0.687**
	Rectum	1/18(6%)	17/18(94%)	
Tumor size in cm	≥4	1/15(7%)	14/15(93%)	
	<4	**2/29(7%)**	**27/29(93%)**	

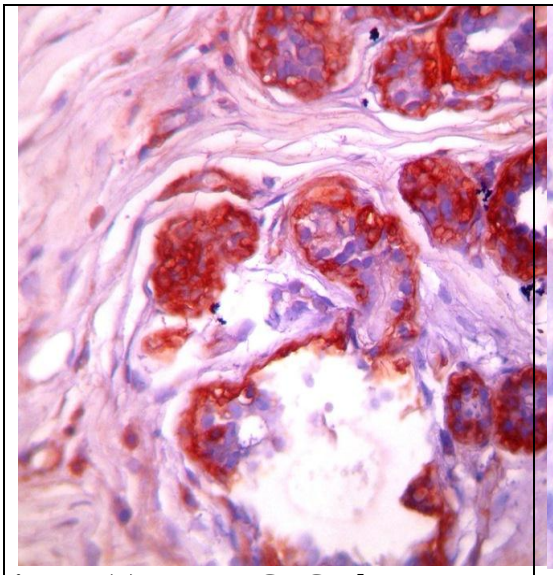

Figure (1): M D CRC show strong positive HER2\neu expression membrane and cytoplasm (arrow) (IHC staining) x40

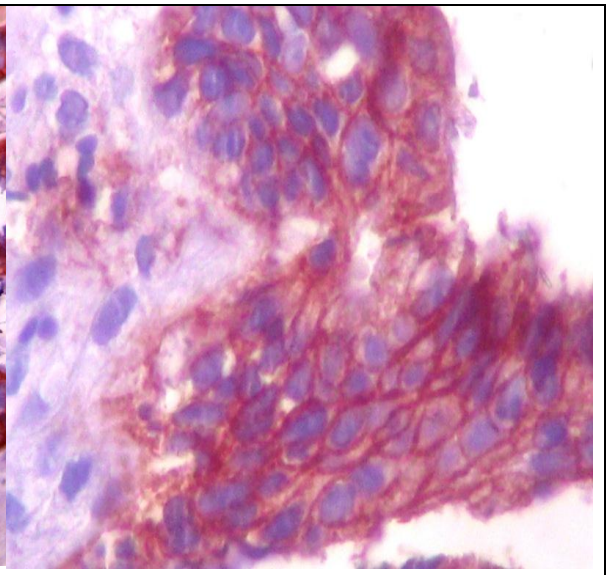

Figure (2): Well to M D CRC show strong positive HER2\neu expression membrane and cytoplasm (arrow) (IHC staining) x40.

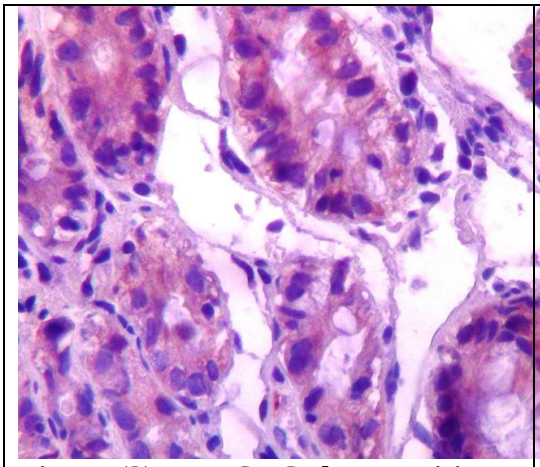

Figure (3): P D CRC show positive HER2\neu expression membrane and cytoplasm (arrow) (IHC staining) x40

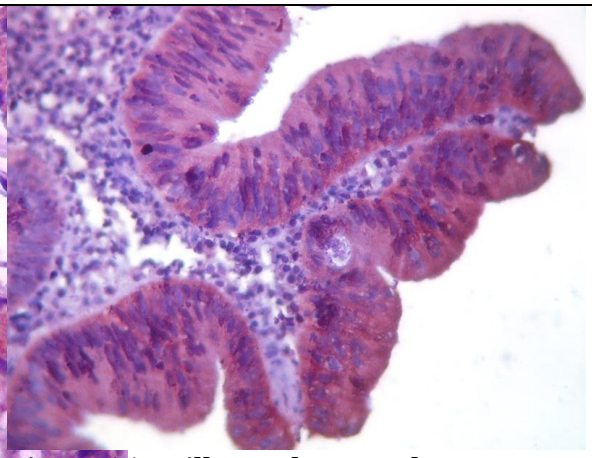

Figure (4): Villous adenoma show strong positive HER2\neu expression membrane and cytoplasm (arrow) (IHC staining) x40

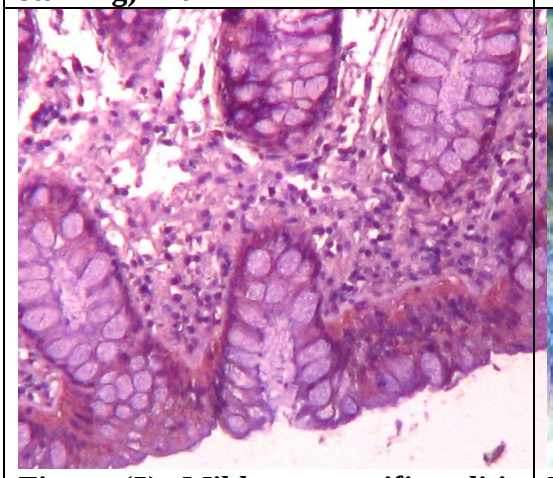

Figure (5): Mild non specific colitis (biopsy) tissue show positive HER2\neu expression membrane and cytoplasm (arrow) (IHC staining) x40.

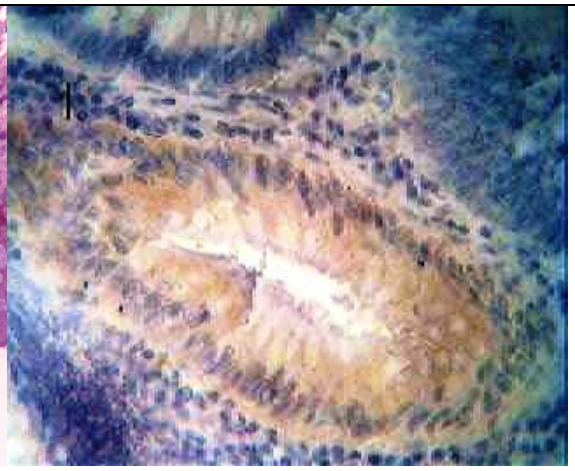

Figure (6): Tubular adenoma show positive BRCA1 cytoplasmic expression (arrow) (IHC staining) x40.

Discussion:

Clinicopathological Aspects:

The findings of the present study was revealed that high incidence of colorectal tumors in male (male :female ratio was1.4:1) These results were in accordance with data from other Iraqi studies [19,20,21].The sex ratio in other series in Iraq and Arab countries also reported high male ratio [22,23,24] while male to female ratio in west countries is (1:0.9) [25].This finding represent difference in sex ratio between Arab and west population, although it may be a function of referral focus.

Regarding the mean age of cases in the present study was 44.42 ± 2.53 years for both sexes. This result was in accordance with data of Al-Bahrani, 2003 [19] in which the average age was 49.8 years for colonic and 43.4 years for rectal cancers.

Regarding the site of colorectal tumors, the colon was the most common site for colorectal tumors (26 cases) most of them (20 case) in the sigmoid, while in the rectum there were (18) cases of colorectal tumors this was in agreement with other studies [17, 19, 20] in which the colon was the most common site.

To compare our results concerning the tumor grade, most of the cases were of poorly differentiated adenocarcinoma this was in agreement with some studies [26] while disagree with others [19,20,22,23,24,27,28], where the moderately differentiated grade consisted most of the cases this different due to small sample size in the present study .

HER2\neu immunoreactivity:

The pattern of staining is one of the important features of HER2 expression in colon cancer in the present study. Although there is high percent of positive staining (36% of colorectal tumors), there is no pure membranous staining. This means that other mutations for HER2\neu must be responsible in colon carcinoma. In the present study, HER2\neu expression was membranous (predominant) and cytoplasm staining in most of the cases and pure cytoplasmic staining in one case .There was no case with pure membranous staining, This result matches the observations of others [17,29,30] who showed cytoplasmic staining or membrane and cytoplasm but no pure membrane staining while others considered only membranous staining as HER2\neu over expression (according to guidelines for breast cancer) [31, 32].

The percentage of the HER2\neu expression increased in order of adenoma (27%) to adenocarcinoma (45%) although the result was statistically not significant. This was in agreement with other studies [33,34] who showed that the over expression of HER2\neu in colon polyps (adenoma) was lower than in cancer group.

HER2\neu was expressed in (45%) of CRC. Eliane C et al, 2005[35] showed that HER2\neu over expression was (51%) of CRC, the expression of HER2\neu in Irena et al, 2000 (36) study was (54%), in Ghaffarzadegan et al,2006(17) study showed (59%), in J A McKay et al,2002 [37] study (81.8%)of CRC, in Schuell B et al,2006 [38] study (30%) of CRC , in Nathanson et al,2005[39] study only in (3.6%) of the cases and in Park et al,2004[40]) study found that HER2\neu over expression in (12.5%) of patients, these differences were due to difference in sample size in each study and different staining pattern in the last two studies.

HER2\neu was over expressed in(27%) of colonic polyps Marek et al, 2009 [34] was showed that HER2\neu over expression was found in (43%) of colorectal polyps and Irena et al, 2000[36] was showed that HER2\neu over expression in (87%) of colonic polyps.

Regarding the site of colorectal tumors,HER2\neu was more frequently expressed in the colon (46%) while its expression in rectal tumors was (22%).The result was statistically not significant . This result was in agreement with other studies [17,37].

Regarding the age and sex of patients , HER2\neu expression was found to be more frequently among females (39%) and patients of an age group more than 40 years (43%) although the result was statistically not significant. This was in agreement with other studies [17,37.38,41], HER2\neu was more frequently Expressed in well differentiated adenocarcinoma (67%).This result was in agreement with other studies [17,37,38,39.41]

Regarding HER2\neu expression in colorectal polyps in the present study, it was expressed most frequently in tubulovillous adenomatous polyps (50%). This is in agreement with the result of some studies [36] but not with others [41] which showed that there is no HER2\neu expression in colorectal polyps.

HER2\neu was expressed highly in non-mucinous type (47%) as compared with the mucinous type of CRC (33%). This

was in agreement with other studies [17, 41].

HER2\neu expression was higher in tumors size of more than 4 cm. The result was statistically not significant. This result was in agreement with others [37, 38, 41].

HER2\neu expression was observe in (4) out of (6) non neoplastic colonic tissue which were cases of mild non specific colitis. Galandiuk s, 1993[42] showed that there was high HER2\neu expression in non neoplastic colonic tissues (normal colonic tissues, non specific colitis, Crohn's colitis and ulcerative colitis) and J A McKay et al,2002 [37]showed that HER2\neu expression in normal colonic tissue was in high percent , Wen Jin et al,2004 [43] show that the levels of HER2\neu were obviously increased in normal colonic tissue and adenoma.

In addition to other studies, Ross et al, 2001[44] studied the HER2\neu oncogene in tumors of the gastrointestinal tract. They found wide range of HER2/neu expression in Esophageal, gastric and colon carcinoma. They concluded that either HER2protein overexpression or gene amplifications associated with one – forth of all gastrointestinal malignancies and strategies designed to employ the marker in therapy selection appear warranted [44].

BRCA1 immunoreactivity:-

BRCA1 expression was found in (6%) of the cases of colorectal tumors (benign and malignant), there were (14%) positive cases of colorectal polyps. There was non significant correlation between BRCA1expression and types of tumors (benign or malignant).

Garcia-Pati et al, 1998[63] showed that BRCA1 was expressed in (49%) of colorectal tumor this difference may be explained by small sample size in the present study.

BRCA1 expression was more frequently in males patients (8%) than in females patients (6%) although the results were statistically not significant. This was in agreement with others [18,46]

BRCA1expression was more in age group more than 40 years old (10%) although the result was statistically not significant. This in agreement with other studies, [18, 46].

There was no difference in BRCA1 expression between tumors with size of more than or less than 4 cm. This result was in agreement with other studies [18, 46] that also showed no significant correlation of BRCA1 expression with tumors size.

BRCA1expression was more frequently observed in the colon (20%) than in the rectum (8%) although the result was statistically not significant.This was in agreement with other[18].

BRCA1 expressed in (1) out of (2) tubulovillous adenomatous polyps, in (1) out of (3) villous adenoma and in (1) out of (8) tubular adenoma. Ishiguro K et al, 2006 [47] showed that there was BRCA1 expression in 13% of colorectal tubular adenomas, 53% of villous adenomas so they reached to conclusion from this study that the presence of genetic alterations in stroma form an early stage of carcinogenesis, accompanied by stepwise increasing genetic instability of epithelia with progression to cancer. Thus microenvironmental changes due to genetic alteration in Chr17 markers in stromal cells may play an important role in colon adenoma and adenocarcinoma development, BRCA1 genes on chromosome 17(Chr17) my play an important role in adenoma carcinoma sequence.

There was no BRCA1 expression in colorectal adenocarcinoma in the present study while Heike Grabsch et al, 2006[18] showed that BRCA1 was expressed in (86%) of colorectal adenocarcinoma. This difference between this study and the present study may be explained by small sample size in the present study .

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استظهار عامل HER2 \ NEU و BRCA1 في أورام القولون والمستقيم وعلاقته بالخصائص المرضية \ دراسة مرضية سريرية

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الخلاصة

خلفية البحث: يعد سرطان القولون من السرطانات الشائعة وخاصة في العراق .لقد اضهرت نسبة كبيرة من أورام القولون تعبير مناعي نسيجي كيميائي عالي ل HER2\NEU.
لقد أثبتت دراسات كثيرة أن التغيرات الوراثية تلعب دور في سرطان القولون والمستقيم كما أثبتت أيضا زيادة خطر الإصابة بسرطان القولون والمستقيم في الأشخاص الذين يحملون تغيرات وراثية ل BRCA1.
لقد كان الهدف الباحثون هو دراسة التغير المناعي النسيجي ل HER2\NEUوBRCA1في أورام القولون والمستقيم(الحميدة والخبيثة) ومدى علاقتها بالعوامل السريرية والمرضية.

المواد وطرق العمل: تمت هذه الدراسة باختيار خمسون مقطع شمعي نسيجي (٢٢ حالة ورم حميد،٢٢ حالة ورم خبيث و٦ حالة خالية من الورم).تم اختيار هذه الحالات للفترة مابين تشرين الثاني ٢٠١٥لغاية تموز ٢٠١٦.
تم تقطيع هذه المقاطع الشمعية وصبغها بصبغة الهيماتوكسلين والايوسين ثم استعمالها لمعرفة نوع الورم وتصنيف المرض ودرجة التمايز وأخرى تم صبغها بالصبغة المناعية النسيجية الكيميائية ل HER2\NEU وBRCA1.
لقد كان التعبير المناعي لHER2\NEU ظاهرا في الغلاف الخلوي او السايتو بلازم أو كالاهما بينما التعبير المناعي لBRCA1 فقد كان في السايتوبلزم او النواة والسايتوبلازم و تم فحص المقاطع المصبوغة بهذه الصبغات المناعية كونها سالبة أو موجبة.

النتائج: من بين أل(٤٤)حالة من أورام القولون والمستقيم ٣٦%أظهرت تعبير مناعي لHER2\NEU وكانت تشمل ٤٥ % في الأورام الخبيثة و ٢٧% في الأورام الحميدة وكان هذا التعبير أكثر في الذكور.
أما بالنسبة للتعبير المناعي BRCA1 فقد ضهر في ٦% فقط من أورام القولون والمستقيم (الحميدة والخبيثة) وكان أكثر في الذكور٠

الاستنتاجات: أن تعبير ألHER2\NEU في أورام القولون والمستقيم ليس بقليل ٣٦% من أورام القولون والمستقيم اظهر التعبير بينما كان تعبير BRCA1 في أورام القولون والمستقيم قليلا ٦% فقط اظهر التعبير.