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Original Article

Biological Characterization of Colorectal Cancer in Patients Undergoing Surgery and Its Correlation with Gender and Age

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ABSTRACT

Among cancer patients'colorectal carcinoma abbreviated as CRC is the one of the chief cause of death **Objective:** To study the biological characteristics and types of colorectal cancer, and its correlation with various age groups and gender. **Methods:** It was descriptive study carried out in different surgical units of LUMHS Jamshoro, Sindh for period of 2 years including 115 patients. Biopsy was performed to diagnose colorectal carcinoma after getting consent from patients and the immune histochemical analysis was performed. **Results:** The age range of patients diagnosed with colorectal cancer were above 60 years males. Majority of patients showed per rectal bleeding with positive family history. Patients were also observed to be associated with different types of colorectal carcinomas including rectal, mucinous, well differentiated, moderately differentiated and poorly differentiated. The analysis of TNM classification showed majority at in stage II, also some were in stage 1V (8.09%). The biological markers showed P53 and BCL2 the most common and cytokeratin and P53 were found significantly positive in age group of 31-45yeras and 46-60 years Additionally, HER2, P53 VEGF showed significantly (p=0.05) higher rates in males. **Conclusion:** Mucinous carcinoma was most common colorectal cancer, and biological markers P53 and BCL2 were frequently common.

INTRODUCTION

Among cancer patients' colorectal carcinoma abbreviated as CRC is the one of the chief cause of death [1]. Genetic mutations in CRC is the cause of 5% deaths [2] and its prevalence in both developed and developing countries is increasing [3] in age groups of 45 years to 65 years and also in younger population [4]. The chief risk factors of CRC include dietary, nutritionals and lifestyle-related factors, higher intakes of alcohol, processed and red meat, limited exercise and physical activity and obesity while the natural protective factors against CRC includes higher intakes of, leafy and green vegetables, dietary fiber, micronutrients like calcium and folate, found in fruits and vegetables [5]. According to [6] the survival rate of colorectal cancer is 58% to 65% if diagnosed early can be treated. Worldwide, colorectal carcinoma is becoming the leading cause of cancer-related so, researchers are focusing the development of biomarkers used to precisely diagnose and predict treatment outcomes. The TNM criteria, which has been used shows substantial over or under treatment of CRC. Therefore, it is the need of the time to develop modern, efficient and precise biomarkers to ensure significant treatment strategies leading toward precise medication [7]. This can and was previously achieved by advancing in molecular genetics of colorectal cancer (CRC) to develop specific biomarkers used as diagnostic, prognostic markers, and markers of treatment responses

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[8]. Such biomarkers arre: "Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), bcl -2 proto-oncogene", p53, Ki67 and Vascular endothelial growth factor (VEGF)". "Epidermal Growth Factor Receptor (EGFR)" is a ErbB receptor related and other tyrosine kinases includes "EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4)". The mutations cause altered EGFR activity and expression resulting in cancer [9]. EGFR signaling pathways is responsible for development as well as progression of various tumors including colorectal cancer. Additionally, EGFR pathway and its downstream components also acts as targeted molecules in cancer therapy so modulations in these pathway presents prognostic implications [10]. It has been also reported that patients with "EGFR positive CRC" are resistance to therapy of monoclonal antibodies [11,12,13]. HER2 expression also showed ambiguous outcomes in colorectal cancer as its expression varies from 0 to 84% so targeting HER2 is also a treatment option [14]. The bcl-2 proto-oncogene is the inhibitor of apoptosis allowing propagation and accumulation of cells in genetic modulations [15]. and its over expression is critical in colorectal carcinogenesis [16]. Nuclear p53 accumulation has also been associated with no survival in case of colorectal carcinoma [17]. Moreover, high expression of Ki67 is considered to be prognostic marker showing low nodal status and tumor stage [18]. "Vascular endothelial growth factor (VEGF)" is the most predominant angiogenic factor important in colorectal carcinoma progression. VEGF expression and its quantification provide significant prognostic information in CRC as it contributes toward progression and metastasis [19]. As these biomarkers are significant in CRC so this study was conducted to analyze their role in patients with colorectal cancer using immunohistochemistry technique and analyze their correlate with factors such as age and gender. Additionally, this research also emphasized the controversies and challenges withholding the clinical use of biomarkers to provide evidence based guidelines for implementation in various gastrointestinal malignancies by the personals involved in carcinomas, malignancies management.

METHODS

The study population was the patients admitted in surgical units of hospital. Inclusion/Exclusion criteria: The patients diagnosed with colorectal carcinoma by biopsy were included in the study and the patients receiving any neo-adjuvant therapy were not included in the research. The sample size was 115 patients, determined by "Openepi, epidemiological scientific calculator", as the anticipated frequency of colorectal cancer was 12%, so 90% confidence interval was used and calculated by following formula. $n = [DEFF*Np(1-p)]/[(d2/Z21-\alpha/2*(N-1)+p*(1-p)]$

Data were collected by analyzing tumor specimens by immune histochemical analysis. IBM SPSS (statistical packages for social sciences) 16.0 was used to analyze the collected data by applying descriptive statics and correlation.

RESULTS

The results of age distribution of the patients (Table 1) showed mean range to be 45+10, gender distribution showing 65(56.52%)male while 50(43.47%)female.

Variables	Frequency /%
Age (Years)	
15-30	21(18.26%)
31-45	31(26.95%)
46-60	25(21.73%)
>60	38(33.04%)
Gender	
Male	65(56.52%)
Female	50(43.47%)

Table 1: Frequency distribution of age and gender

Table 2 represents implications in CRC showing per rectal bleeding in 70(60.86%), change of bowel habits in 20(17.39%), polyp in 30(26.08%), abdominal pain in 25(21.73%) and mucus discharge in 10(8.69%) patients, risk factors of CRC in study population revealing smoking in 73(63.47%), alcohol in 25(21.73%), low dietary fibers 27(23.47%) and chronic bowel infection in 15(13.04%), positive family history in 33(28.69%), no family history in 65(56.53%).

Variables	Frequency /%
Symptoms	
Per rectal bleed	70(60.86%)
Change of bowel habits	20(17.39%)
Something coming out of anus (polyp)	30(26.08%)
Abdominal pain	25(21.73%)
Mucus discharge	10(08.69%)
Risk Factors	
Smoking	73(63.47%)
Alcohol consumption	25(21.73%)
Low dietary fibers	27(23.47%)
Chronic bowel disease	15(13.04%)
Family History	
Present	33(28.69%)
Absent	65(56.53%)
Not known	17(14.78%)

Table 2: Frequency Distribution of symptoms & risk factors

Based on predisposing factors, 17(14.78%) patients showed adenoma, 20(17.39%) revealed synchronous carcinoma, ulcerative colitis was found in 20(17.39%), 08(6.95%) showed crohn disease, 31(26.95%) had pre disposing factors Table 3 also showing the histological type of rectal carcinoma and locality of invasion of tumor.

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Variables	Frequency /%
Predisposing factors	
Adenoma	17(14.78%)
Synchronous carcinoma	20(17.39%)
Ulcerative colitis	20(17.39%)
Crohn's disease	08(6.95%)
Others	31(26.95%)
Not known	19(16.52%)
Histological type	
Adenocarcinoma	20(17.39%)
Mucinous carcinoma	50(43.47%)
Medullary carcinoma	15(13.04%)
Signet ring cell carcinoma	06(05.21%)
Anaplastic	05(04.34%)
Not specified	19(16.52%)
Predominant area	
Well differentiated	55(47.82%)
Moderate differentiated	40(34.78%)
Poorly differentiated	20(17.39%)
Local invasion of the tumorp	
To No evidence of primary tumor	00
pTis carcinoma in situ	04(03.47%)
pT1 Limited to sub mucosa	10(08.69%)
pT2 Invasion into muscularis propria	20(17.39%)
pT3 Beyond muscularis propria	22(19.13%)
pT4a Tumor invades adjacent organs	22(19.13%)
pT4b Tumor cells have breached serosa	37(32.17%)
pTx Primary tumor cannot be assessed	00
Lympho-vascular invasion	
Yes	80(69.56%)
No	35(30.43%)

Table 3: Frequency distribution of Predisposing factors, Histological type, Predominant area, Local Invasion, Tumor involvement

NM classification and biological markers are represented in table 4 while the correlation of biomarkers expression with age groups and gender is shown in table 5 and 6 respectively.

TNM classification	Frequency /%
Stage I	31(26.95%)
Stage II	55(47.82%)
Stage III	19(16.52%)
Stage IV	10(08.69%)
Biological markers	
Name	**Positive**	**Negative**
HER2	45(39.13%)	70(60.87%)
EGFR	50(43.47%)	65(56.53%)
BCL2	61(53.04%)	54(29.49%)
Cytokeratin	47(40.86%)	68(59.14%)
P53	60(52.17%)	55(47.83%)
VEGF	50(43.47%)	65(56.53%)

Table 4: Frequency distribution of TNM Classification, Biological markers

Bio markers	Age groups					p-Value
	15-30 years	31-45 years	46-60 years	>60 years	Total	
	HER2					
Positive	07	11	12	15	45	0.401
Negative	14	20	23	23	70	
	EGFR					
Positive	08	15	16	11	50	0.31
Negative	13	16	09	27	65	
	BCL2					
Positive	12	15	18	16	61	1
Negative	09	16	07	22	54	
	Cytokeratin					
Positive	06	19	17	05	47	0.04
Negative	15	12	08	33	68	
	P53					
Positive	10	24	19	07	60	0.02
Negative	11	07	06	31	55	
	VEGF					
Positive	12	10	15	13	50	0.822
Negative	09	21	10	25	65	

Table 5: Correlation of Biomarkers with age

Bio markers	Gender			p-Value
	Male	Female	Total	
	HER2			
Positive	31	14	45	.021
Negative	34	36	70	
	EGFR			
Positive	28	22	50	0.211
Negative	37	28	65	
	BCL2			
Positive	35	26	61	0.651
Negative	30	24	54	
	Cytokeratin			
Positive	27	20	47	0.41
Negative	38	30	68	
	P53			
Positive	40	20	60	0.05
Negative	25	30	55	
	VEGF			
Positive	32	18	50	0.05
Negative	33	32	65	

Table 6: Correlation of Biomarkers with gender

DISCUSSION

Colorectal carcinoma is ranked to be the third frequently occurring malignancy across the globe [1]. and second in the United States causing cancer related deaths [20]. The prevalence of CRC is higher in males with frequency of 48.3 to 72.5/100,000 people however in females its frequency is 32.3 to 56 per/100,000 per annum [21,22]. The results of this study showed 65(56.52%) of CRC patients were men and 50(43.47%) patients were women in consistent with

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the findings of [23]. who also reported the higher prevalence in males (2:1). The results of age frequency showed majority cases in older age 38(33.04%) in above 60 years followed by 21(18.26%) patients with age range of 15 years to 30 years, 31(26.95%) with 31years to 45 years, 25(21.73%) with age of 46years to 60 years. 10 colorectal carcinoma patients were in 31 years to 40 years and only 2 were below 20 years supported by the findings of [22] demonstrating CRC prevalence higher in older population. The analysis of per rectal bleeding showed frequency of 70(60.86%) while 20(17.39%) patients had altered bowel habits, 30(26.08%) had polyp, 25(21.73%) complained abdominal pain and mucis discharge was observed in 10(8.69%) identical to the study of [23] demonstrating the abdominal pain, weight loss and bleeding per rectum the major implications of CRC. Also [22] reported the bleeding per rectum to be the common symptom of CRC along with altered bowel habits and intestinal obstruction. The common risk factor was found to be the smoking found in 73(63.47%) followed by alcohol use 25(21.73%), low dietary fibers 27(23.47%) and chronic bowel infection 15(13.04%) showing the harmful effects on rectum and colon. [24] also found that smoking cause colorectal cancer deaths in 12% population because it the increase progression of cancer in colon and rectum. [25] found that carcinogens of tobacco increase adenomatous polyps' formation leading to lesions thus resulting in colorectal cancer. The use of alcohol also onset of colorectal cancer [24,26]. and acetaldehyde of alcohol disproportionate tumors in colon [27]. Family history is also the risk factor of CRC, the analysis found that 33(28.69%) patients had positive family history while 50(43.47%) patients had no family history supported by the results of [28]. showing 20% population develop CRC due to family history. Moreover, [29] also reported strong association of family history with CRC development. The results of histological evaluation of rectal carcinoma, [32] found 20(17.39%) of adenocarcinoma, 50(43.47%) with mucinous carcinoma, 15(13%) had carcinoma, 6(5.21%) showed signet ring cell carcinoma, 5(4.32%) with anaplastic carcinomas in consistent with the results of [22]. We found that 55(47.82%) patients also had well differentiated carcinoma moderately differentiated carcinoma was found in while 40(34.78%) and poorly differentiated carcinoma in 20(17.39%) patients identical to the results of [23] stating 56% with moderately differentiated carcinoma and 38% with poorly differentiated carcinoma. Likewise, [31] also reported 50% of patients of CRC showed moderately or poorly differentiated tumor. Regarding the TNM classification, stage I accounted for 31(26.95%) patients, stage II = 55(47.82%) patients, stage III = 19(16.52%) and 10(08.69%) were at stage 1V similar to results of [33]. who reported 71.2% cases at grade II, 19.2% at grade III and 9.6% at grade IV. [34] also reported the identical findings at the time of diagnosis. The determination of biological markers showed BCL2 and P53 to be the most common found in 60(52.17%) and 61(53.04%), supported by the findings of Pity IS et al129 who reported higher p53 and Bcl2 expression in CRC patients. "HER2, EGFR, Cytokeratin and VEGF" were found in 45(39.13%), 50(43.47%), 47(40.86%) and 50(43.47%) respectively (9.6%) relative to [35] research who found that HER-2/neu in 81.8% of tumors and [36] reported high HER-2/neu expression. Our study also found the significantly higher expression EGFR and VEGF of colorectal cancer tissues and paraneoplastic normal tissue supported by findings of Li [37] reporting their high expression and showing statistically insignificant difference (P>0.05).

CONCLUSIONS

After all this discussion it can be concluded that prevalence of colorectal cancer is higher in males and older ages and is becoming the major cause of deaths. The major risk factors include smoking inducing the higher expression of biological markers P53 and BCL2. P53 and Cytokeratin showed significantly higher expression in older age in both genders while HER2, P53 VEGF were overexpressed in male. There is still need of appropriate and precise biomarkers in order to diagnose and treat CRC and other types of cancer.

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