Colorectal Cancer Epidemiology: Incidence, Clinical, Pathological and Molecular Features

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Background: Colorectal carcinoma is the second most common cancer in the Kingdom of Bahrain, in both males and females.

Objective: To evaluate the incidence, clinical presentation, histopathologic diagnosis and molecular genetic testing for colorectal carcinoma.

Setting: Pathology Department, Salmaniya Medical Complex, Bahrain.

Design: A Retrospective Study.

Method: Ninety-seven patients who were diagnosed with colorectal cancer from January 2016 to March 2018 were included in the study. Patients' clinical information, histopathology and molecular testing results were documented.

Result: Between January 2016 to March 2018, 97 newly diagnosed cases of colorectal cancer were documented; 48 (49.5%) were males and 49 (50.5%) were females. The average age at the time of diagnosis was 60 years. Resection specimens accounted for 54 (56%) cases and the biopsy specimens were 22 (23%) cases. The remaining 21 (21%) specimens were received for second opinion or for molecular testing.

The most common clinical presentation was per rectal bleeding, 29 (30%). Eighty-one (84%) were diagnosed as moderately differentiated adenocarcinoma. The tumor was located in the distal part of the colon in 37 (38%) cases. Thirty-eight (39%) of the newly diagnosed cases were discovered at advanced pathological stages. The molecular testing revealed that 7 (7%) had Microsatellite Instability (MSI), 27 (28%) had KRAS mutation and 18 (19%) had TP53 mutation.

Conclusion: The majority of the patients were diagnosed at an advanced stage. The incidence and mortality can be decreased with an improved screening program and detecting cases at an early stage. Genetic testing plays an important role in improving patient outcome.

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Colorectal carcinoma is the most common malignancy of the gastrointestinal (GI) tract and is a major cause of morbidity and mortality worldwide[1]. It is the third most commonly diagnosed cancer worldwide (1.8 million cases, 10.2% of the total) and it is the second leading cause of death (881,000 deaths, 9.2%)[2].

In Bahrain, colorectal cancer is the second most common cancer after lung cancer in males and breast cancer in females. It accounts for 10.2% and 7% in both males and females, respectively[3].

The aim of this study is to evaluate the epidemiology of colorectal carcinoma including the incidence, clinical presentation, pathological analysis, and genetic molecular testing.

METHOD

Ninety-seven patients diagnosed with colorectal cancer between January 2016 and March 2018 were included in the study. The data collected included the following: age, gender, clinical presentation, type of specimen received, anatomical location of tumor and type, grade and pathological stage of the tumor. Molecular genetic testing, which included testing for mismatch repair (MMR), KRAS mutation, BRAF mutation and other mutation were documented. Testing of mismatch repair status was performed using MMR immunohistochemistry while the other mutations such as KRAS and BRAF were sent overseas. The compiled data has been analyzed using Microsoft Excel 2010.

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RESULT

Ninety-seven specimens for 97 patients between January 2016 and March 2018 were included in the study. Resection specimens were 54 (56%) cases and the biopsy specimens were 22 (23%) cases. The remaining 21 (21%) were received for second opinion or for molecular testing.

The age ranged from 27 to 86 years. The average age at the time of diagnosis was 60 years. Forty-six (47%) patients were aged 50-64 years, 29 (30%) were aged 65-79 and 3 (3%) were aged 80. Nineteen (20%) patients were under the age of 50, 8 (8%) of them were under 40 years, see table 1. The most common age for the diagnosis of colorectal cancer in female patients was 50-64 years and 65-79 years in male patients. The incidence is relatively equal in males and females, 48 (49.5%) compared to 49 (50.5%), see figure 1.

Table 1: New Colorectal Cancer Cases by Age

	Total	Percentage	Male	Percentage	Female	Percentage
years 0-49	19	20%	8	17%	11	23%
years 50-64	46	47%	19	39%	27	55%
years 65-79	29	30%	20	42%	9	18%
years 80=<	3	3%	1	2%	2	4%
Total	**97**	**100%**	**48**	**100%**	**49**	**100%**

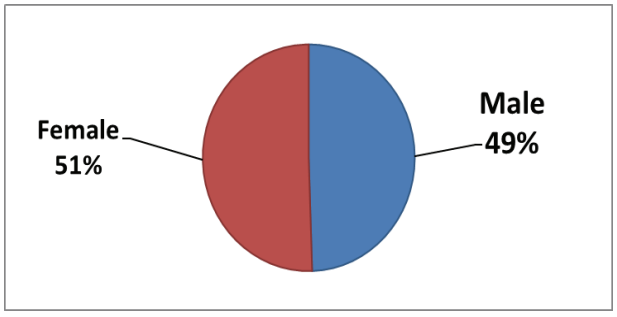

Figure 1: Colorectal Cancer Incidence in Males and Females, January 2016 to March 2018

Thirty-five (32%) were diagnosed with colorectal cancer during 2016. In 2017, the cases increased to 53 (49%). Nine (9%) cases were diagnosed in the first quarter of 2018.

The most common clinical presentations were per-rectal bleeding and anemia in 29 (30%) patients followed by constipation in 10 (10%) patients and abdominal pain in 5 (5%) patients. History of the colonic polyp was reported in 6 (6%) patients and a history of Crohn's disease was reported in 2 (2%) patients. Clinical history was not provided in 45 (47%) patients.

The tumor was located in the distal colon in 37 (38%) patients, the rectum in 20 (21%) patients, and the proximal colon in 17 (17%) patients, see table 2.

Table 2: Colorectal Cancer Subsite

	Number of Cases	Percentages
Proximal	17	17%
Distal	37	38%
Rectum	20	21%
Unknown	23	24%
Total	**97**	**100%**

Ninety-six (99%) were diagnosed as colorectal adenocarcinoma and one (1%) was diagnosed as metastatic carcinoma. Eighty-one (84%) were moderately differentiated adenocarcinoma, see figure 2. Three (3%) were well-differentiated adenocarcinoma and four (4%) were poorly differentiated adenocarcinoma. Nine (9%) were diagnosed as adenocarcinoma, not otherwise classified (ANOS).

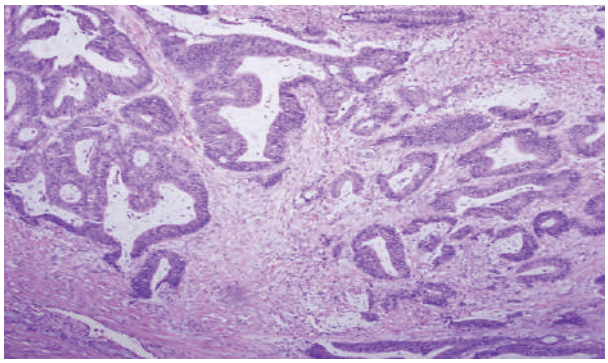

Figure 2: Moderately Differentiated Adenocarcinoma

Thirty-eight (39%) presented at an advanced stage (stage pT3 and pT4). Twenty (21%) patients had the tumor invading the subserosa or into non-peritoneal pericolic or perirectal tissues (Stage T3). Eighteen (19%) patients were diagnosed at stage 4; 9 (9%) had a tumor that perforates visceral peritoneum and the other 9 (9%) had tumor directly invading other organs or structures. In 10% of the patients, the tumor was invading muscularis propria (stage T2) and only 3 (3%) of the patients were diagnosed in early stage where the tumor invaded the submucosa only (Stage T1), see figure 3. Fifty-eight (56%) already had lymph node metastasis at the time of diagnosis.

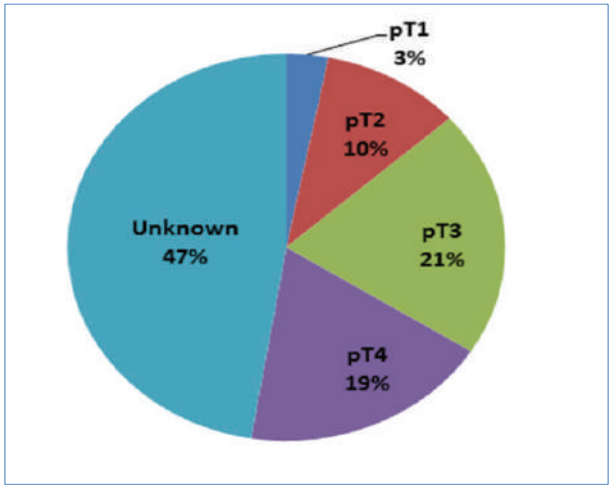

Figure 3: Colorectal Cancer Stage Distribution

Sixty-three (65%) were tested for MMR immunohistochemistry. Fifty-six (58%) had microsatellite stability (MSS) and 7 (7%) had microsatellite instability (MSI). Six (6%) of the MSI tumor showed loss of MSH6 & MLH1- gene nuclear expression and one (1%) showed loss of MSH6 & PMS2-gene nuclear expression, see figures 4 (A-D).

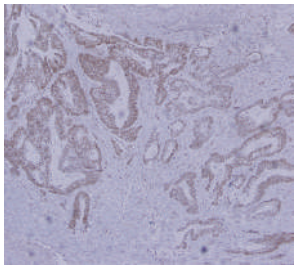

Figure 4 (A): MSH-2

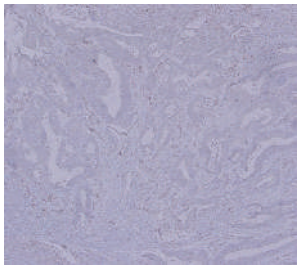

Figure 4 (B): MSH-6

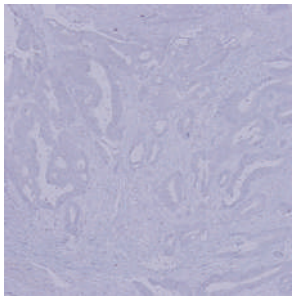

Figure 4 (C): MLH-1

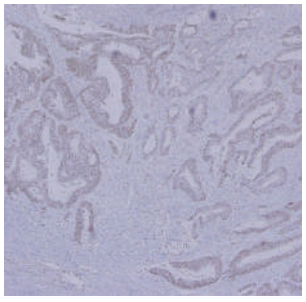

Figure 4 (D): PMS-2

Figure 4 (A-D): MSI Tumor Showing Loss of MSH-2 (B) and MLH-1 (C). Normal Expression of MSH-6 (A) and PMS-2 (D)

Sixty-five (67%) specimens were sent overseas for other mutation testing. The results revealed that 27 (28%) had KRAS mutation, 18 (19%) had TP53 mutation, 1 (1%) had NRAS, 2 (2%) had BRAF and 2 (2%) had BRAF and PTEN mutation. In 15 (15%), no genetic mutations were detected.

DISCUSSION

Colorectal cancer is the second most common cancer in both males and females in Bahrain. It is the second after breast cancer in females and lung cancer in males[3]. This differs from the United States, where colorectal cancer is the third most common cancer[4].

Age is an important factor and it has a positive relationship with colorectal cancer. The majority of cases occur in advanced age. The incidence is increasing after the age of 50, with an average age of 60 years. A study by Amersi et al reported that the average age of colorectal cancer is 64 in the United States[4].

Siegel et al found that the most common age was 65-79[5]. In our study, the most common age was 50-64, which means that colorectal cancer affects Bahraini population at a younger age.

Marley et al found 2-8% cases of colorectal cancer in patients under the age of 40 years in both the United States and European Union. A higher incidence was found in Egypt (38%), Saudi Arabia (21%) and Philippines (17%) for the same age group[6]. Our study found only 8% of cases diagnosed under the age of 40; the incidence is similar to that in the United States and European Union[6].

The youngest patient at the time of diagnosis was 27 years old and the eldest patient was 86 years old. If colorectal carcinoma is seen in younger patients, ulcerative colitis, familial adenomatous polyposis (FAP), or hereditary non-polyposis colorectal carcinoma (HNPCC) should be suspected; further investigations and family counseling are needed[7].

Females and males are almost equally affected. The incidence of colorectal cancer in the United States and worldwide is equal in males and females, which is consistent with our result[8].

Female patients are usually younger at the time of diagnosis. In this study, 78% of female patients were diagnosed under the age of 65, while only 56% of male patients were diagnosed at the same age group, which is similar to the findings of another study from Saudi Arabia, while in the United States the males are diagnosed at a younger age than females[9].

Both genders are diagnosed at the same advanced stage (stage PT3), however, women usually present with lymph node metastasis. The tumor which is located in the distal part of the colon or in the rectum will have lower mortality than a tumor located in the proximal part of the colon[10]. The most common location of colorectal cancer in our study was the distal colon, which accounted for 38% of the cases. The proximal colon and rectal cancers accounted for 17% and 21% of cases, respectively. Siegel et al found that the most common location of colorectal cancer in the United States is in the proximal colon which accounted for 41% of their cases[5].

The most common malignant tumor of the large intestine is adenocarcinoma that accounts for 98% of all large intestinal cancers worldwide[7]. All the specimens that were received were diagnosed as primary colorectal adenocarcinoma except one case which was metastatic carcinoma. Two cases were sub-classified into mucinous and papillary adenocarcinoma. Mucinous adenocarcinoma is defined as >50% of the tumor composed of extracellular mucin pools containing tumor cells[7].

According to our data, 84% of cases were moderately differentiated adenocarcinoma. Well and poorly differentiated adenocarcinomas were rare and accounted for, 3% and 4%, respectively.

According to AJCC cancer staging (8th edition), we found that the majority of our cases were diagnosed at an advanced stage[11]. Forty percent of our cases were diagnosed in stage pT3 and pT4.

The 5-year survival rate is 90% if cancer is detected at a localized stage, 70% for regional and only 10% for a patient diagnosed with distant metastasis[12].

A study by Siegel et al showed that the majority of the cases (74%) in the United States were discovered at an early localized or regional stage and only 22% discovered with distant metastasis[5].

Currently, molecular testing plays an important role in diagnosis, treatment, prognosis and family counseling of many types of cancer. The MSI tumor is resistant to 5-fluorouracil treatment[13]. MSI accounts for ~15% of all colorectal adenocarcinomas[14]. In our study, it accounted for 7% of the tested specimens while the remaining specimens showed preserved protein.

Approximately 90% of patients have mutations in either MLH1 or MSH2 gene[15,16].

Our study showed 28% of cases with KRAS mutation which is lower than the 40% found by Brink et al[17]. Meanwhile, 4% of cases with BRAF mutation were lower than the result of Davies et al, which was 10%[18].

Mutant KRAS and BRAF will be resistant to EGFR targeted therapy[19,20,21]. The patient that will receive anti-EGFR therapies should be tested for KRAS mutation as recommended by the American Society for Clinical Oncology and National Comprehensive Cancer Network.

CONCLUSION

Colorectal carcinoma is the second most common cancer in Bahrain. The incidence is equal in males and females. The average age at the time of diagnosis is 60 years. Most patients are diagnosed at an advanced stage.

Author Contribution: All authors share equal effort contribution towards (1) substantial contribution to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version should be published. Yes.

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Competing Interest: None.

Sponsorship: None.

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