CLINICOPATHOLOGICAL CHARACTERISTICS OF COLON CANCER IN LIBYA

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ABSTRACT

The study describes demographic and clincopathological features of colorectal cancer in the middle region of Libya. The study was conducted on 229 patients with colon cancer, admitted to the Misurata Cancer Centre, during the years 2010-2014. The clincopathological features were collected from pathology reports and hospital files of the patients. The mean age of colon cancer patients in Libya was 56.06 years, which in men is much higher than in women (p=0.02). The histological types of the colon cancer in Libyan populations showed that the adenocarcinoma was the predominant type followed by mucinous carcinoma. Among Libyan patients the systemic and LN involvement, higher stage tumors, and more tumor extension were strongly associated with poor survival. Although, the men patients had shorter life span than women did, this survival difference was not statistically significant. The histological types and other histopathological risk features show similar importance in respect to survival as the data from European colon cancer. In Libya, the colon cancer is slightly more common in female than in male. Libyan mucinous colon cancer is dominantly seen in younger adult and displays unfavorable features such as high histological grade and stage, large size, and frequent systemic involvement.

KEY WORDS: Colorectal cancer, Libya, North Africa, Europe, Demography, Duke's, Histopathology, Survival, clinicopathological features .

INTRODUCTION

Colorectal cancer is one of the most common pathological problems in the world particularly in the western countries. More than one million new cases worldwide. Colorectal cancer (CRC) is contributing to 13% of all cancers[1,2,3].It is well known that the colon cancer more frequently in male than female patients, and its prevalence increases with age in both gender. Over thirty percent of patients with CRC are over the age of 70 years in the Western world[1,4,5,6]. In several countries, colon cancer mortality is figured of nearly half of new cases and accounts for 10-13% of all cancer deaths. It is the second leading cause of female cancer death and the third common cause of male cancer mortality[3,7]. It is well known that, in countries where rates were initially very high, gradual falls in mortality have been noted with time[1]. Because in developed countries the colorectal cancer screen is well established which might diagnosed CRCs in their early, more curable stages by using faecal occult blood test (FOBT) and colonoscopy, no such screening test exist in developing countries[8]. Majority of colon tumor patients' complain of polypoid lesions that may cause intestinal obstruction and bleeding per rectum[1,2]. Globally, the incidence of CRC varies ten-folds, with the highest incidence rates in North America, Australia, and northern and western Europe. Some recently developed countries particularly Malaysia, Korea and developing countries of Africa and Asia have lower rates[2,9]. These geographic differences appear to be attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility[3].

In general, colon cancer incidence is increasing worldwide in the recent 3 decades, but it varies from area to area[6]. For example, in the USA, the incidence has been increasing steadily by about 20% during the period from 1973 through 1987 and remained relatively constant[2, 8]. Contrast with Japan and Korea the incidence is rising rapidly[2,9].

In the African and Arabic countries, the studies are not fully covering. In North Africa, colon cancer incidence is about 16.0 new patients per 100.000 persons[3,10]. The background of Arabic colon cancer incidences may be more related to other African colon cancer incidences than to European colon cancer incidences.

Most colorectal carcinomas are located in the sigmoid colon and rectum, but there is evidence of changing distribution in recent years, with an increasing proportion of more proximal carcinomas[11] which tend to grow as exophytic masses and are usually circumscribed with about 20% are mucinous[12]. Proximal colon cancers tend to have high levels of microsatellite instability (MSI-H) or ras proto-oncogene mutations[12,13,14]. In this study, we would like to characterize some demographic and clincopathological features that associated with colon cancer in Libya. To the best of our knowledge, such results on Libyan database have not been published previously.

MATERIALS AND METHODS

Patients and Methods: A retrospective pathological study was conducted on 229 patients (table 2). All

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were followed-up at the Misurata Cancer Center, Libya during the years 2010-2014. The pathological features were collected from pathology reports and patients hospital files. The estimated clinical or pathological characteristics included sex, age, body mass index, presenting complain, clinical stage; TNM staging system including (location and extension of tumor, LN status, systemic metastasis), Duke's stage, histological grade, histological type, and follow-up of the patient. Patients were followed-up until they died or to the end of the observation period in the end of 2014. Some patients were lost during follow-up prior to 2014. For these patients, the last date of contact was defined as the date for the end of follow-up. The follow-up period ranged from 1 to 60 months with an average of 13.0 months. The patients' files show that the number of readmissions during the study period varied between patients. Many patients seem to have entered the hospital for a preliminary diagnosis, after which they negotiated with their families and decided about the treatment. Many patients stayed until the histopathological diagnosis, usually after the primary surgery was carried out, and decided about further action thereafter; 46 patients were completely lost of follow up post to the surgery. Some patients started therapy at the Misurata Cancer Center, but interrupted it and were also lost from the follow up. Finally, around half of the patients were diagnosed, treated, followed up, and subjected to further therapy at the center. The lost patients were generally treated elsewhere (other Libyan hospitals, or abroad).

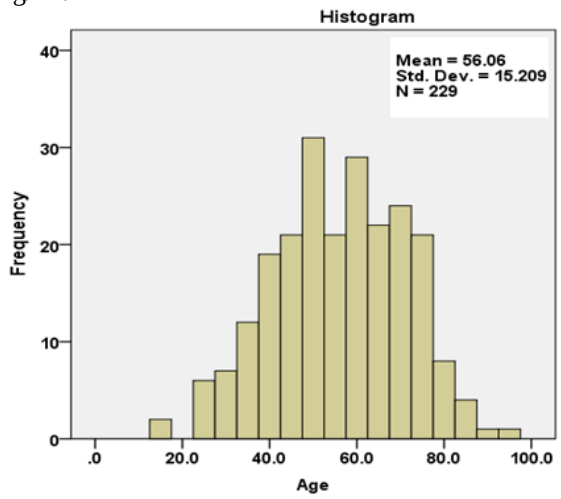
Statistical analysis:

The variables of the Libyan patients were grouped and descriptive statistics calculated for the continuous variables by using SPSS software packages for Windows, versions 21.0 (SPSS, Inc., Chicago, USA). For survival analysis, Kaplan- Meier curves were plotted, and differences between the curves analyzed using the log-rank test. Pearson and Spearman's correlation tests were used for comparison between two variables. P-values below 0.05 were regarded as significant. Comparison of numerical data was done by the chi-square test. Student t-tests and ANOVA were also used to test differences between the groups. Microsoft Excel 2007 was used to draw graphs and to evaluate relationships between variables.

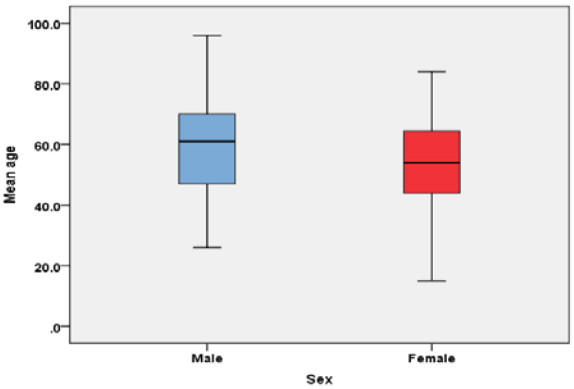
RESULTS

Age, sex and body mass index at presentation. The study shows 116 females of mean age 53.78±14.65 years (range 15-84 years) and 113 males of mean age 58.39±15.47 years (range 26-96 years) who had colon cancers (figure 1).

Mucinous carcinoma had lower mean age than ordinary adenocarcinoma cancers (table 1). Male patients usually have higher age than female (figure 2). The difference between the mean ages of men and women patients is statistically significant (p value = 0.02).The mean weight of our patients is 68.6kg; 23% of them have body mass index (BMI) >27 kg/m².



(Figure 1) Age distribution at diagnosis of histologically verified colon cancer patients in the middle region of Libya in 2010-2014. The graph is based on 229 patients.



(Figure 2) Shows Mean patients age ±2SD in histological section of colorectal cancer of Libyan patients in male and female patients. Clearly, the mean age is increased with the male gender (P (T-test) = 0.021)

(Table 1) Pathological type of colon carcinoma, along with their clincopathological characteristics and their relative 5-year survival.

(Table 1) Pathological type of colon carcinoma

Histological Type	Frequency (%)	Mean age (year)	Tumor extension to muscle layer (%)	Nodal involvement (%)	Systemic disease (%)	5 years survival (%)
Adenocarcinoma	95.2	56.5	97.2	63.3	8.7	65.1
Mucinous carcinoma	4.4	43.9	100.0	60.0	10.0	57.1
Adenosquemous carcinoma	0.4	70.0	100.0	0.0	0.0	100.0

Describes pathological features in colon cancers

Histological type:

The histological type's distribution in Libya are shown in (table1) with relation to clinicopathological features.

Histological grade:

In this study 56% of Libyan colorectal cancer patients have high grade while 44% have low grade.

Tumour extension:

The majority of colon cancer in both female and male Libyan patients are extended to muscle layer; only 6 patients (2.6%) had tumour localized to mucosa and submucosal tissues with size of 2cm or less (T1). Present study shows the average tumor extension of high grade carcinoma was deeper than the average of low grade carcinoma.

(Table 2) The frequency of different stages among 229 colorectal cancer cases listed based on the TNM classification of 2006. The majority of Libyan colorectal cancer patients belong to stages B and C (combined 79.1% of all patients).

(Table 2) The frequency of different stages among 229 colorectal cancer cases listed based on the TNM classification of 2006

Clinical Stage	Duck's stage	Corresponding TNM categories	Frequency	%
0	0	Tis N0M0	0	0
1	A	T1N0M0	5	2.2
	B1	T2N0M0	18	10.0
2	B2	T3N0M0	57	24.8
		T4N0M0	5	2.2
3	C1	T(1/2)N(1/2)M0	45	19.7
	C2	T(3/4)N(1/2)M0	79	34.5
4	D	T(0-4)N(0-2)M1	20	8.7
Total			229	100.0

Lymph node status and distant metastases:

Proximately 63% of Libyan colon cancer patients had regional lymph node involvement at the time of surgery (table 2). Distant metastases (to one or multi-organ including bone, lung and liver) were present in 8.7% of our patients. In current study, systemic metastases were significantly more common in mucinous than in Adenocarcinoma (table 1).

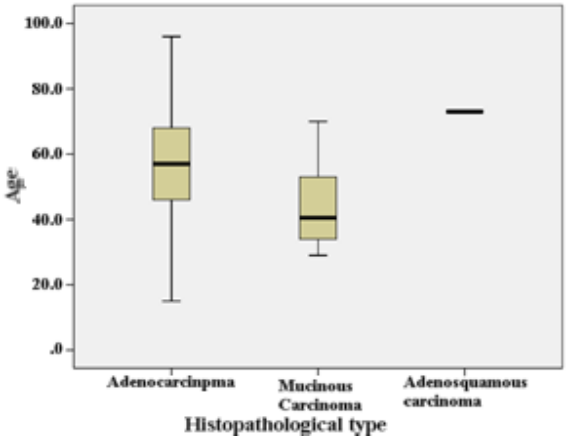
Stage: More than 60% of Libyan patients were seen in stage 3 and 4. While 85 colon cancer patients had early stage at the time of surgery (23 stage 1 and 62 stage 2).

Location site:

The most frequent colorectal cancer sites were the left side has (80.7%) particularly, rectosigmoidal region. The right side colon involved by (19.3%).

Survival analysis:

By the end of follow-up, 41 patients were known to have died, Mean survival for the whole series of 229 patients was 13 months (range 1-60 months).



(Figure 3) Mean patients age of different histological types of colorectal cancer in Libyan patients. Clearly there are significant difference among different histological types (P (ANOVA-test) = 0.01)

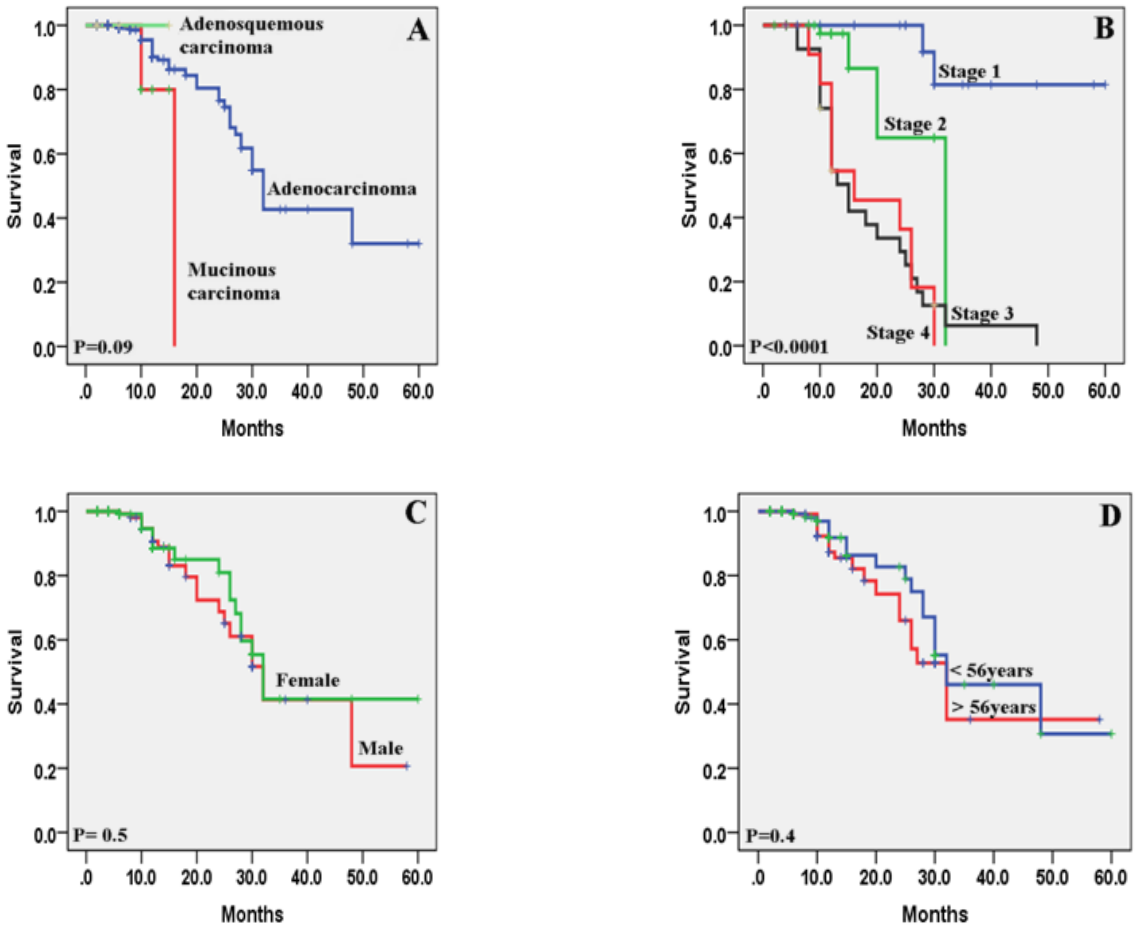
Clincopathological features:

Among Libyan patients the gender, tumour grade and age of patient did not seem to influence survival. However, systemic involvement, advanced stage of tumor were strongly associated with shortened survival rate. The group of patients with stage 1 had the best 5-year survival ($p < 0.0001$), (Figure 4-B). The mucinous histological type of tumor also associated with shortened survival rate but with only trend to be significance (Kaplan-Meier and log rank ($p = 0.09$), (figure 4-A).

DISCUSSION

Age at presentation:

The occurrence of colon cancer in Libyan population is age related with nearly 65.0% of cases arising inpatient who are 50 years or older. In contrast to European countries; colon cancer is a rare diagnosis before the age of 40, with 90 % of cases occurring after age 50 years[15,16]. Recent reports show that, in the USA, it was the most frequent form of cancer among persons aged 75 years and older[6,8]. In New Zealand the incidence of colorectal cancer has continued to rise in older age group of population, but has fallen in age group below 50 years[17]. In this study, 61.0% of male colon cancers aged more than 50 years. On contrast with female colon cancer, we found that in females aged older than 50 years there is about 54.0% of female colon cancers (figure 2). In low-risk (developing) areas and new developed countries such as Korean the colon cancer was the most common cancer in middle-aged females, whereas, in industrial countries such as Italy, colon cancer is usually presents in the seventh decade[6,8]. Currently study, shows statistical difference in the mean age at diagnosis between female and male patients [43.6 and 56.2 respectively] with p-value = 0.024. The younger age female have more risk for colon cancer, this might partly be related to estrogen factor.



(Figure 4) Overall survivals of patients according to the histopathological type of colon cancer, patients with mucinous carcinoma type have trend to be more worse survival than other type (p = 0.09). B. Survival curves of Libyan colon cancer patients in different clinical stages. The group of patients with stage 1 had the best 5-year survival (p < 0.0001).
C and D. Survival curves associated with patients' sex and age are not show any significant

Gender:

In Libya, nearly 50.7% of colon cancer patients were women, which left 49.3% for men patients. Although, it is well known that the male gender has colorectal cancer incidence slightly greater than in the female. Unlike rectal cancer the colon cancer is more common in women with age of 55 and below but thereafter becomes slightly more common in men[16]. In Europe and United States colon cancer, the men are affected about 20% more than female[3,17]. In Japan colon cancers reveals about 40% more frequent in males than females, affect (39.5/100.000) of male population and (24.6/100.000) of female population with ratio nearly 2:1[3], the cause of this decreased incidence of colon cancer in Japanese women still is unclear. However, in Central American, the colon cancer incidence in males is almost equal that is seen in females. The latter is true especially in Mexico where the incidence in Mexican male and female population was 10.8 and 10.4 per 100,000, respectively[8].

Obesity status and hyperlipidemia roles:

The fraction of obese patient is rare in current study. However, approximately 50% of Americans between 20 and 75 years of age are overweight with BMI >27 kg/m². It was clearly that Libyan patients had lower obesity; about 20% lower in respect to the developed countries population who had a higher average weight in related to same age group as well as higher animal fat consumption[18,19]. Which might be an additional factor that has resulted in an decreasing of obesity in Libyan patients decrease the mutagenic effect of lipid related factors. That may responsible for the low incidence of colon cancer in Libyan patients.

Tumour extension:

Libyan colon cancer patients like other North African had higher tumor size extension than developed countries patients. This data from developed countries suggests the efficiency of more sophisticated and advanced diagnostic facilities in detect smaller lesions in that population[2]. This suggests that the start of fecal occult blood test (FOBT) as stool screening test associated with advanced endoscopic diagnostic facilities should be considered in Libya.
Present study shows the average tumor extension of high grade carcinoma was deeper than the average of low grade carcinoma.

Lymph node status and distant metastases:
The significant increasing of systemic and regional lymph nodes metastases in Libyan patients may suggest a delay in diagnosis in developing countries, and lack or inefficacy of advanced diagnostic facilities. However, the aggressiveness of biological features in African colon cancer should also be considered.

Histological grade:
Colorectal adenocarcinoma can be graded according the degree of differentiation to well differentiated (grade I), moderately-differentiated (grade II) and poorly differentiated (grade III) carcinomas, or into low-grade (encompassing well and moderately differentiated adenocarcinoma) and high-grade (including poorly differentiated adenocarcinoma and undifferentiated carcinomas). Poorly differentiated adenocarcinoma should have at least some mucin and gland like formation; tubules are typically irregularly folded, deformed, and distorted. When a carcinoma has variability in differentiation, grading should be based on the least differentiated component, not including the border of invasion. Small foci of apparent poor differentiation are common found at the advancing edges of tumours, but this feature is inadequate to classify the tumour as poorly differentiated[20]. In general, the percentage of the tumour showing formation of gland-like structures can be used to define the grade. Well differentiated (grade 1) lesions exhibit glandular structures in > 95% of the tumour; moderately differentiated (grade 2) adenocarcinoma has 50-95% glands; poorly differentiated (grade 3) adenocarcinoma has 5-50%; and undifferentiated (grade 4) carcinoma has < 5%. Mucinous adenocarcinoma and signet-ring cell carcinoma are considered poorly differentiated (grade 3). Medullary carcinoma with MSI-H appears undifferentiated. Additional studies of the biological behavior of MSI-H cancers are needed to relate the morphological grade and molecular subtypes of mucinous, signet ring cell and medullary carcinoma to outcome since MSI-H carcinomas have an improved stage-specific survival[21,22]. In this study more than 50% of Libyan colorectal cancer patients have high grade. Libyan patients had more aggressive colorectal cancer than European patients, however, their age is lower than in European cancer patients (figure 3). African results are in line with the results on African American patients[1,2,3,8,23]. One explanation for grade differences may just because the younger patients group in African population have more active proliferation tumours.

Stage:
The staging system currently in use for colon cancer is based on the extension of primary tumour, degree of spread to lymph nodes and presence of systemic metastasis. The Libyan colon cancer staging in our study is based on the TNM classification of 2006[24]. The large fraction of patients in advanced stages (table 2) because early-stage CRC may be asymptomatic or produce vague, nonspecific symptoms, many cases are diagnosed at later stages, when regional nodal or systemic metastasis is more likely[25]. However, it may reflects delayed presentation and late diagnosis, which was also obvious in the study of Ermiah et al 2012 on Libyan material[26]. On other hand, screening through colonoscopy and other facilities (such as CT virtual colonoscopy) has been quit not practiced in Libya[27].

Location site:
The most frequent Libyan colorectal cancer located at rectosigmoidal region. This is in line with other previous studies which show about 40% of all large bowel cancers occur in the rectum and rectosigmoid area. The sigmoid colon accounts for a further 25%. Of the remaining bowel, the ascending colon is a site of predilection and it would appear that the incidence of cancer in the right colon is increasing[2, 27], especially in high-risk areas for colorectal cancer. However, this could be in part an age-related phenomenon compounded by the greater use of flexible endoscopy in elderly subjects. Most cancers of the colon and rectum are ulcerating tumours with raised everted edges.

The relation of histological type to clincopathological features:
The frequencies for each of histological types of colon cancer were found in the present study is in line with other studies. Adenocarcinoma is the most common colon cancers worldwide. In the current study, adenocarcinoma was the predominant type (95.2%) among both men and women, These figures in line with international fraction range which are (95-98%)[19]. Mucinous carcinoma is common in our populations (4.4%) , however, it still lower than in West of Europe (10%) which might be related to younger age patient's presentation[2,28,29]. Mucinous adenocarcinoma occurs with increased frequency in HNPCC but is more obviously over-represented and likely to be poorly differentiated amongst sporadic MSI-H cancers[30,31].

Prognostic value of clinicohistopathological features in Libyan colon cancer:
The Libyan and other North African colon cancer patients have slight worse prognosis than that recognized by studies in European patients. However, in respect to progressive pathological indicators, the North African colon cancer behaves as the European colon cancer as shown by current study (figure 4). For example, early clinical stage associated with very significant better survival rate while patients have high stage with LN involvement, systemic involvement and tumor extended to muscle layer were strongly associated with shortened survival rate (Kaplan-Meier and log rank) ($p < 0.0001$). However, the Adenosquemous carcinoma and well differentiated adenocarcinoma show only tendency to signifi-

cant better survival (Kaplan-Meier and log rank) (p = 0.09). This online with other studies that stated the patients with larger size tumors (T3 or more), lymph node involvement and distant stage tumors were associated with local recurrence, and poorer survival among both men and women. The presence of lymph node metastases is greatly worsens prognosis. More than 83.0% of patients without lymph node metastases disease (i.e. Dukes A and B cases) survived 5 years but the figures markedly drop to 32.0% for lymph node-positive patients (higher stages)[32]. It well known that approximately 30% of colorectal cancers will die with blood-borne metastases. The current study and other studies found that the liver is by far the most frequently involved organ (>60%), followed by the lungs, bones and brain in respectively of order of frequency[33]. Some authors have found that grading system associated with colon cancer has significant independent prognostic influence, particularly if staging is performed suboptimally[34,35]. However, several studies stated that the microacinar morphology and mucinous differentiation are associated with a poor prognosis but does not appear to be an independent prognosticators[20,36]. One cause for the above discrepancies may be associated with studies methodological variability in the use of different other prognosticators. Several authors provide that WDTC particularly adenocarcinoma stage 2 or below is the most common colon cancer that can be treated by only surgical intervention, and usually associated with an excellent prognosis with overall survival more than 90 %[2,16]. On other hand, among Libyan patients the histological type, gender, and age of patient did not seem to considerably influence patients' survival. These results are in line with the results of other studies[16].

CONCLUSION

Libyan colon cancer is affect women like men and is dominantly seen in older age group , it displays unfavorable features such as high histological grade and stage, deeper extension and frequent lymph node involvement, and systemic metastases were strongly associated with poor outcome. The adenocarcinoma was the most common type of colon cancer followed by mucinous carcinoma then other rare types. Finally, in our hospital setting, the results of this study could be used as a baseline data for further research studies. Furthermore, to increase the health education and raising awareness about cancers and widespread implementation of screening programme which can lead to early detection and significantly improve the outcome.

AUTHOR'S CONTRIBUTIONS

This work was carried out in collaboration between all authors. Author ABF participate in the design and preparation of the manuscript and performed the statistical analysis. Author RM, AF and AR provided the clinical data, and participated in the organizing the clinical data. Author AW conceived of the study, and participated in the organizing the pathological data. Author BMJ participate in the design and coordinate the research and drafted the manuscript. All authors read and approved the final manuscript.

CONSENT

The proposed study has been examined and approved by the Research Council of Misurata Cancer Center

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