LIBYAN INTERNATIONAL JOURNAL OF ONCOLOGY

Original article

Correlations of Sociodemographic and Clinicopathological Features with Survival Outcome of Colorectal Cancer: A Retrospective Study from A Libyan Cohort

Mussa Alragig*[1], Mohamed Elfagieh[1], Mamduh Gaber[2], Abdulah Jebri[2], Monsef Algouti[1], Fatma Belgasem[1], Abdusalam Sohoub[1], Abdsalam Rabie[1], Eramah Ermiah[3]

[1] Department of Surgery, National Cancer Institute, Misurata, Libya
[2] Department of Medical Oncology, National Cancer Institute, Misurata, Libya
[3] Medical Research Unit, National Cancer Institute, Misurata, and Department of Medical Oncology, National Cancer Institute, Sabratha, Libya.
***Correspondence**: Alragiglibya@gamial.com

Citation. Alragig M, Elfagieh M, Gaber M, Jebri A, Algouti M, Belgasem F, et al. Correlations of Sociodemographic and Clinicopathological Features with Survival Outcome of Colorectal Cancer: A Retrospective Study from A Libyan Cohort. Libyan Int J Oncol. 2023;2(2):82-95.

Received: 10-09-2023
Accepted: 12-11-2023
Published: 30-12-2023

***Funding**: This research received no external funding.*

***Conflicts** of Interest: The authors declare no conflict of interest.*

Abstract

***Aims**. To study the correlations of sociodemographic and clinicopathological variables of patients with colorectal cancer (CRC) and the association of these variables with patients' outcome. **Methods**. A retrospective analysis of 466 patients with CRC were diagnosed and treated at the National Cancer Institute (NCI), Misurata, Libya during the 2008-2017 period. Data for sociodemographic, clinicopathological, biological variables, presentation, treatment, and survival related data were collected from the patients' records. **Results**. The mean age of patient was 53.2 years (range 22-90 years) and most of patients (60.9%) were aged > 50 years. For gender distribution, CRC was nearly the same frequent among males and females (50.2% and 48.9%, respectively). Intestinal obstruction was the most frequent presentation (41.6%) followed by bleeding per rectum (34.1%). Colon cancer was more common than those located in the rectum, (60.1% vs. 39.9%), %), left sided tumours (35.4%) was more frequent than right colon (24.7%). Most tumours were adenocarcinoma (82.0%) and most of patients had moderate differentiated tumours (60.5%). In term to the AJCC staging system, the distribution of stages was as follows: 4.9% stage I, 25.4% stage II, 40.3% stage III, and 29.4% stage IV. Liver was the most common metastatic site (70.5%). In the overall population (median follow-up 46 months), patients with <50 years of age, with an advanced stage and with a high-grade tumour had shorter survival times than those with ≥50 of age, early stage and low-grade tumour (p <0.0001, p <0.0001 and p <0.0001, respectively). Disease-free survival (DFS) was better in patients with old age (p <0.0001), early stage (p <0.0001) and low-grade tumour (p <0.0001). In a Cox multivariate analysis, clinical stage (p<0.0001) and age at diagnosis (p =0.017) were independent predictors of overall survival, and clinical stage (p <0.0001) and age at diagnosis (p =0.019) also proved to be independent predictors of DFS. **Conclusion**. The present Libyan cohort of CRC shows that the mean age at diagnosis was 52.3 years with equal gender distribution. Colon cancer was more frequent than rectum cancer. Most patients had tumours that were adenocarcinoma, moderate grade and most presented with stage III. Liver was the commonest metastatic site. Clinical stage was powerful independent predicators of patients' outcome and DFS.*

***Keywords:** Colorectal Cancer, Libya, Prognosis.*

Introduction

Worldwide, more than 1 million people presented with colorectal (CRC) cancer every year resulting in more than 700,000 deaths as of 2010 up from 490,000 in 1990 [1,2]. CRC is the second most common cause of cancer in women and the third most common in men [3]. It is more common in developed than developing countries with geographical variations, highest incidence rates in Europe, Australia and the United Status and lowest rates in Africa and South-Central Asia [4,5]. For a long time, CRC was considered the disease of the elderly. Albeit the incidence of early-onset CRC has appallingly increased in several countries over the past decade, mainly in European and western countries [6,7].

Diet, obesity, smoking, and lack of physical activity are considered as risk factors for CRC [8]. Inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis are

another risk factors for CRC [8]. The inherited genetic disorders such as familial adenomatous polyposis and hereditary non polyposis CRC as risk factors, represent <5% of cases [8]. Screening is effective for reducing the mortality from CRC and its recommended starting from the age of 45 to 75 [9].
Standard treatments for CRC may include some combination of surgery, radiotherapy, chemotherapy, and targeted therapy [10]. In metastasis setting, cancer is usually not curable, with management being directed towards improving quality of life and symptoms [10].
CRC is a group of heterogeneous diseases with different genetic and biological behaviour that explain diverse tumour characteristics and prognosis [11]. The patient's outcome with CRC different greatly between the patients, and survival rates ranging from 5% to 90% based on disease stage and other variables [12].
This study was conducted to investigate the correlations of sociodemographic and clinicopathological variables of patients with CRC and patients' outcome.

Methods

Study population.

The study included 466 patients with CRC were diagnosed and treated at the National Cancer Institute, Misurata, Libya during the period from 2008 to 2017. According to medical records, there were 690 patients with CRC received during 2008-2017.Two-hundred and thirty among them were excluded for incomplete follow-up or incomplete document record. Complete sociodemographic, genetic, biological variables, tumour characteristics, risk factors, treatment and follow up related-data were collected including age, gender, marital status, address, occupation, blood group, body mass index, past medical history, family history, clinical presentations, tumour location and size, lymph node status, histological grade, stage, serum levels of carcinoembryonic antigen (CEA), type of treatment and follow-up data. These data were collected from the patients' files and summarized Table 1 and 2. The mean age of the patients (n-466) with CRC was 53.2 years (range 22-90 years).
Tumour staging of CRC was evaluated according to the American Joint Committee on Cancer (AJCC), TNM classification [13]. Pan-colonoscopy and radiological staging by Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) was performed in all patients to assess tumour extension. The extent of the tumour (local and distant) at the time of diagnosis was confirmed by imaging [CT, MRI, or Positron Emission Tomography (PET)].
Primary tumours located at the cecum, ascending colon, and transverse colon were considered as right colon cancer (RCC), whereas primary tumours located at the splenic flexure, descending colon, and sigmoid colon were considered as left colon cancer (LCC). Primary tumour considered as rectal cancer if it was located within 12 cm from anal verge [14].
Blood samples from the patients were analysis for CEA levels before treatment by electrochemiluminescence immunoassay (double antibody sandwich ELISA). A CEA level equal or higher than 5 ng/ml was considered abnormal [15].

Treatment and follow-up.

Radical surgery was done in329 patients (70.6%), palliative surgery was done in 80 patients, and no surgical intervention for 57 patients how had metastasis at the time of diagnosis. Colonoscopy and/or sigmoidoscopy with biopsy were performed in these patients for histopathological diagnosis.
According to the guidelines were established in our institute. Adjuvant combined chemotherapy based on FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and/or XELOX (oxaliplatin and capecitabine) was given to 318 patients and 113 patients received palliative chemotherapy with FOLFIRI (folinic acid, fluorouracil, and irinotecan) and/or capecitabine. In addition, 35patients did not receive chemotherapy who had early stage and/or were not eligible for chemotherapy. Neoadjuvant concurrent chemoradiotherapy was given to rectal cancer patients (n=186).
Follow-up of patients was carried out every 3 months for 2 years, 6 months for 5 years, and thereafter every 1 year. Disease recurrence (local and distant metastases) was confirmed by colonoscopy and imaging (CT, MRI, or PET) performed when clinical symptoms suggestive of disease recurrence were present. Patients outcomes were considered as follows: overall survival (OS), duration between the date of pathological diagnosis to the date of death and/or to date of the end follow up period; disease-free survival (DFS), duration between the date

of pathological diagnosis to the date of diagnosis of recurrence (local and/or distant metastases) or death [16].
Patients were followed up until death or to the end of the observation period (until December 2021). The median follow-up duration was 46 months (range, 4-116months). At the end of follow up period, 205 patients (44%) had died of CRC.

Statistical analysis.
The variables of the material were grouped into logical classes and descriptive statistics calculated for the continuous variables using SPSS 26.0 for Windows (SPSS, Inc., Chicago, USA). Frequency tables were analysed using the Chi-square test, with likelihood ratio (LR) to assess the significance of the correlation between the categorical variables. For survival analysis, Kaplan- Meier curves were plotted, and differences between the curves analyzed using the log-rank test. Multivariate survival analysis for the outcome measure (overall survival, and disease-free survival) was carried out using Cox's proportional hazards model in a backward stepwise manner with the log-likelihood ratio (L-R) significance test, using the default values for enter and exclusion criteria. In all tests, values of $p< 0.05$ were regarded as statistically significant.

Ethical approval.
The cohort study was done under research ethics approval by ethical committee at the National Cancer Institute, Misurata. Written informed consent was obtained from all patients for surgical treatment, pathologic examinations and investigations performed according to the institutional guidelines of the National Cancer Institute, Misurata, Libya.

Results
Patient sociodemographic and genetic characteristics.
Patient sociodemographic and genetic characteristics of study population (n = 466) are shown in Table 1. The mean age of patient was 53.2 years (range: 22-90 years) and the highest proportion were observed in age group >50 years (60.9%) Figure 1. The highest incidence was recorded in year 2017 (37.8.1%) followed by 2016 (20.4%) while the least incidence was recorded in 2009 (2.4%).

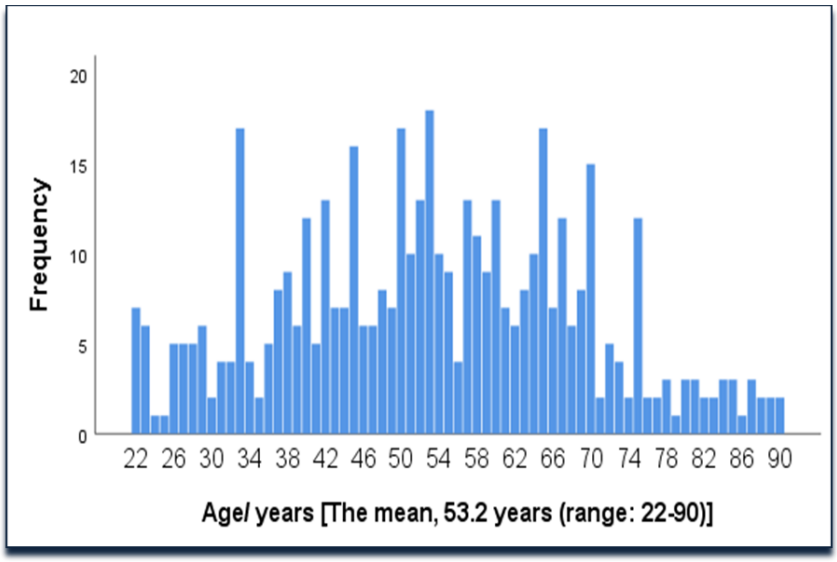

Figure 1: Age distribution of 466 patients with colorectal cancer in Libya (2008-2017).

Gender distributions was nearly the same frequent in males and females (50.2% and 48.9%, respectively). The majority of patients were married and live in an urban area (89.3% and 81.1%, respectively). The most frequent blood group was blood group A (44.0%), followed by O and B (41.0% and 12.0%, respectively) and blood group AB in decreasing frequency (3.0%). While, Rh antigen was positive in the majority of patients (82.8%).
In this study,112 patients (24%) had past medical history of chronic disease and only fifteen patients had a family history of CRC.

Table1: Sociodemographic and genetic characteristics of 466 patients with colorectal cancer.

Variables		Number of patients (n=466)	Percent (%)
Age(years)	< 50	182	39.1
	≥ 50	284	60.9
Gender	Male	234	50.2
	Female	232	49.8
Marital status	Single	50	10.7
	Married	416	89.3
Address	Urban	378	81.1
	Rural	88	18.9
Occupation	Employed and free work	184	39.5
	Retired and house wife	282	60.5
ABO blood group	A	205	44.0
	B	56	12.0
	AB	14	3.0
	O	191	41.0
Rh antigen	Rh +	80	17.2
	Rh -	386	82.8
Body Mass Index	Underweight	25	5.4
	Normal	238	51.1
	Overweight	130	27.8
	Obese	73	15.7
Co-morbidity	Yes	112	24.0
	No	354	76.0
Family history	Positive	15	3.2
	Negative	451	96.8

Clinicopathological and biological characteristics of patients

Clinicopathological and biological characteristics of patients are summarized in Table 2. Regarding the symptoms at presentation, intestinal obstruction was the most common presenting symptom between the patients (41.6%), followed by bleeding per rectum (34.1%) and bowel habits change (11.2%). Of the 466 patients, 115 had tumours in right colon (24.7%), whereas 165 patients had left sided tumours (35.4%) and rectal cancer was detected in 186 patients, Adenocarcinma was the most histopathological type (82.0%) and most patients had moderate differentiated tumours (60.5%).

The most frequent T stage was T3 (55.4%), followed by T4 (16.1%), and T2 and T1 in decreasing frequency (6.7 and 1.9, respectively), while tumour size status could not be assessed in 93 patients (20%). A total of 223 patients (47.9%) had positive lymph nodes and negative lymph nodes were detected in 145 patients (31.1%), while lymph node status could not be assessed in 98 patients (21. 0%). In term to the AJCC staging system, 137 patients were at stage IV (29.4%), 188 patients (40.3%) were at stage III, 118 patients were at stage II and 23 patients were at stage I. The liver was the commonest metastatic site (70.5%) followed by lung (13.8%), bone (7.6%) peritoneum (6.3%) and brain (1.9%). For biological variables, CEA levels were lower than 5ng/ml in 162 samples (34.7%), and ≥ 5ng/ml in 237 samples (50.9%), whereas, pre-treatment CEA data was not available in 67 patients (14.4%).

Table2: Clinicopathological and biological variables of 466 patients with colorectal cancer.

Variables		Number of patients (n=123)	Percent (%)
Site of tumour	Right colon	115	24.7
	Left colon	165	35.4
	Rectum	186	39.9
Histological types	Adenocarcinoma	411	88.0
	Other types	55	12.0
Histological grade	Grade I	60	11.8
	Grade II	282	60.5
	Grade III	124	26.6
Lymph node status	Positive	223	47.9
	Negative	145	31.1
	Nx	98	21.0
Number of examined lymph nodes	< 12	134	28.8
	≥ 12	234	50.2
	Nx	98	21.0
Surgical margins	Positive	43	9.2
	Negative	291	62.4
	Unknown	132	28.4
Lympho-vascular invasion	Present	103	22.1
	Absent	196	42.1
	Unknown	167	35.8
T	T1	9	1.9
	T2	31	6.7
	T3	258	55.4
	T4	75	16.1
	Tx	93	20.0
N	N0	143	30.7
	N1	110	23.6
	N2	118	25.3
	Nx	95	20.4
M	M0	329	70.6
	M1	137	29.4
Stage	I	23	4.9
	II	118	25.4
	III	188	40.3
	IV	137	29.4
***CEA level (u/ml)**	< 5	162	34.7

	≥ 5	237	50.9
	Unknown	67	14.4
Surgical treatment	Radical	329	70.6
	Palliative	80	17.2
	No surgery	57	12.2
Systemic treatment	Adjuvant chemotherapy	318	68.2
	Palliative chemotherapy	113	24.3
	No chemotherapy	35	7.5
Concurrent chemoradiotherapy	Yes	88	18.9
	No	378	81.1

CEA= Carcinoembryonic antigen at cut point of 5ng/ml

Correlation of sociodemographic, genetic, clinicopathological and biological variables with survival outcomes.

The median follow-up was 46 months (maximum 116 months). At the cutoff date of this analysis, 205 patients (44%) had died of CRC. Univariate survival analysis (survival rates) with sociodemographic, genetic, clinicopathological and biological variables are shown in Table 3 and 4.

Table 3: Univariate survival analysis with sociodemographic and genetic variables in Libyan colorectal cancer patients (n=466)

Variables	**Threshold**	**No of patients**	**Survival analysis**			**P-value**
			Median survival (months)	**Mean survival (months)**	**Survival rate (percent)**	
All patients		466	46.0	47.4	56.0	
Age	< 50	182	38.17	41.10	44.0	**<0.0001**
	≥ 50	284	47.79	49.05	63.7	
Gender	Male	234	45.0	46.01	58.1	0.357
	Female	232	45.81	46.4	53.9	
Marital status	Single	50	44.00	46.62	36.0	0.324
	Married	416	46.94	47.10	58.4	
Address	Urban	378	46.56	47.06	57.1	0.307
	Rural	88	41.17	42.00	51.1	
Blood group	O +	244	44.44	45.59	51.2	0.081
	A+	125	44.2	44.71	58.4	
	B+	47	49.0	51.11	70.2	
	Other groups	50	45.9	46.00	60.0	
Body Mass Index	Underweight	25	46.6	48.2	64.0	0.150
	Normal	238	47.0	47.16	58.8	
	Overweight	130	43.05	43.4	47.7	
	Obese	73	44.33	47.42	58.9	
Co-morbidity	Yes	112	42.33	43.4	52.7	0.415

	No	354	46.75	47.07	57.1	
Family history	Positive	15	53.0	53.6	80.0	0.057
	Negative	451	45.33	45.69	55.2	

The survival rate was higher in older patients ≥50 years than younger<50 years (63,7% and 44.0%, respectively). The best survival rate was associated with early stage (94.9%), no metastasis (75.4%), low grade tumour (73.3%), negative lymph nodes (91.7%), negative surgical margins (77.7%)and absent lymphovasular invasion (83. 2%).While, short survival was associated with advanced stage (p <0.0001), distant metastasis (p<0.0001), high grade tumour (p <0.0001), positive lymph nodes (p <0.0001), positive surgical margins (p <0.0001) and present lymphovascular invasion (p <0.0001).

Biologically, univariate survival analysis (survival rates) with CEA expression at a cut-off point of 5 ng/ml are shown in Table 4. The survival rate was 80.9% in patients with low CEA expression and 38.8% in patients with high expression profile (P<0.0001). In addition, the correlation of surgical and/or systemic treatment with patient outcomes was observed in the present study, as shown in Table 4. Patients who underwent radical surgical treatment were associated with longer survival than who underwent palliative surgical treatment or no surgical intervention (p <0.0001). The best survival was observed in patients receiving adjuvant chemotherapy compared with patients receiving palliative chemotherapy or supportive care only (p <0.0001).

The analysis using Kaplan-Meier survival curves showed that patients with older age, low grade tumour, no metastasis and early stage had longer survival time Figure 2. While, patients with younger age (p <0.0001), high grade tumour (p <0.0001), distant metastasis (p <0.0001) and advanced stage (p <0.0001) had short disease-free survival Figure 3. However, gender, address, marital status, blood group, body mass index, comorbidity, family history of CRC, tumour site and histological type did not show a significant correlation with CRC patients' outcome (p> 0.05).

Table 4: Univariate survival analysis with Clinicopathological and biological variables in Libyan colorectal cancer patients (n=466)

Variables	**Threshold**	**No of patients**	**Survival analysis**			P-value
			Median survival (months)	**Mean survival (months)**	**Survival rate (percent)**	
All patients		466	46.00	47.4	56.0	
Site of tumour	Bowel	280	44.54	46.00	55.0	**0.590**
	Rectum	186	45.00	47.94	57.5	
Histological types	Adenocarcinoma	411	46.00	46.82	56.2	0.436
	Other types	55	38.00	41.18	54.5	
Histological grade	Grade I	60	54.5	57.00	73.3	**<0.0001**
	Grade II	282	45.61	46.6	59.6	
	Grade III	124	37.88	41.35	39.5	
Lymph node status	Positive	223	42.9	43.00	54.7	**<0.0001**
	Negative	145	60.00	63.81	91.7	
	Nx	98	24.56	26.33	6.1	
Surgical margins	Positive	43	39.5	40.33	4.7	**<0.0001**
	Negative	291	52.2	53.41	77.7	
	Unknown	132	28.00	31.33	25.0	

Lympho-vascular invasion	Present	103	43.2	44.5	50.5	**<0.0001**
	Absent	196	56.13	57.61	83.2	
	Unknown	167	33.95	35.46	27.5	
Stage	Early Stage (I and II)	138	60.63	65.16	94.9	**<0.0001**
	Late stage (III and IV)	328	36.81	37.68	38.6	
Metastasis	M0	329	52.00	54.08	75.4	**<0.0001**
	M1	137	24.63	26.42	9.5	
***CEA level (u/ml)**	< 5	162	54.45	55.15	80.9	**<0.0001**
	≥ 5	237	36.85	39.41	38.8	
	Unknown	67	43.0	46.81	56.7	
Surgical treatment	Radical surgery	329	52.00	54.08	75.4	**<0.0001**
	Palliative surgery	80	25.00	27.61	8.8	
	No surgery	57	23.00	24.74	10.5	
Systemic treatment	Adjuvant chemotherapy	318	50.22	52.92	73.9	**<0.0001**
	Palliative chemotherapy	113	24.79	26.43	9.7	
	No chemotherapy	35	42.00	45.57	42.9	

CEA= Carcinoembryonic antigen at cut point of 5ng/ml

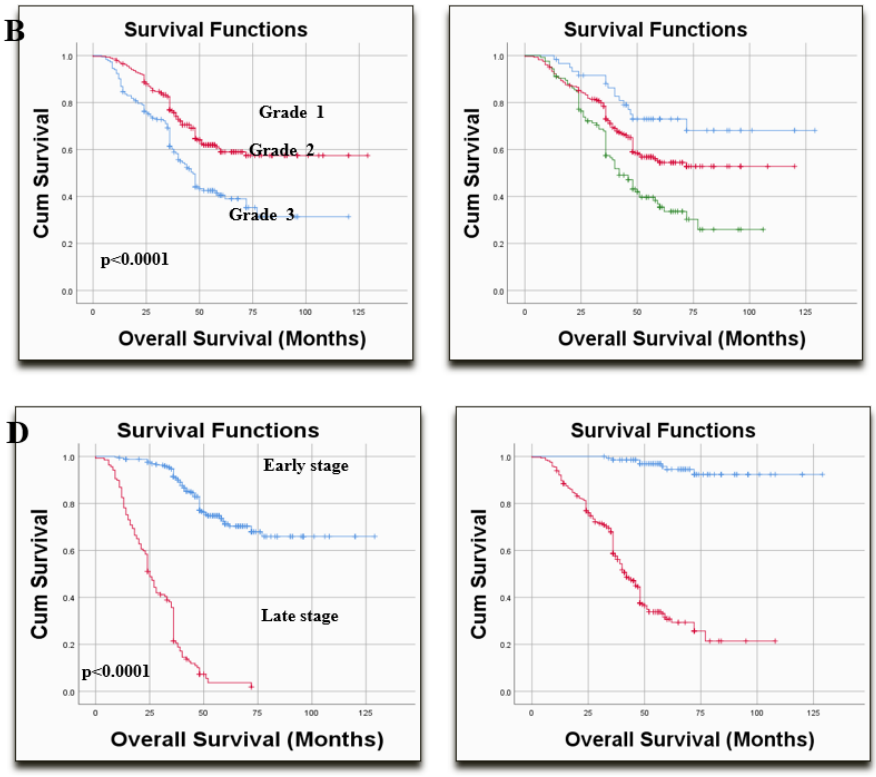

Figure 2. Overall survival according to the demographic and clinicopathological variables (n= 466). (A) Patients age. (B) Histological grade. (C) Clinical stage. (D) Metastasis

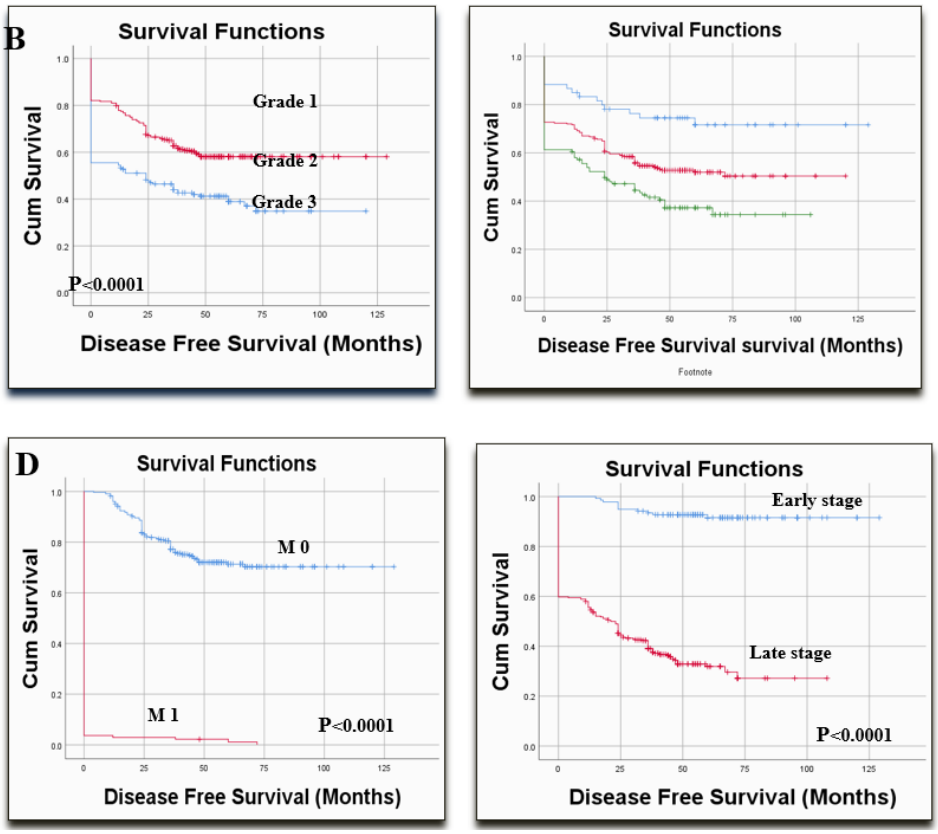

Figure 3. Disease free survival according to the demographic and clinicopathological variables (n= 466). (A) Patients age. (B) Histological grade. (C) Clinical stage. (D) Metastasis.

Multivariate analysis

Multivariate analysis was done according to the Cox model to determine if the survival correlation is independent of other factors. Multivariate Cox's regression analysis observed that clinical stage and age at diagnosis are an independent of overall survival as assessed in a multivariate survival (Cox) analysis containing gender, tumour site, histology type and histological grade variables. In this multivariate model, the clinical stage is an independent predictor of overall survival with hazard ratio = 20.532 (95% CI 9.547 – 44.155, p<0.0001), and the age at diagnosis was also an independent predicator with hazard ratio = 1.407(95% CI 1.063– 1.861, p = 0.017).

For DFS, the same model was used to assess the role of these variables (age at diagnosis, gender, tumour site, histology type, histological grade and clinical stage) as an independent predictor of DFS. The clinical stage also proved to be an independent predictor with HR = 11.673 (95% CI 6.393–21.650, p <0.0001), again with age (HR = 1.378, 95% CI 1.055–1.799, p = 0.019).

Discussion

CRC is a common malignant tumour and leading cause of morbidity and mortality worldwide with wide geographical variation [3 and 17]. In 2018, over one million new cases and more than 500.000 deaths from the disease [18]. As CRC is a group of heterogeneous diseases with different genetic and biological behaviour that explain diverse tumour characteristics and outcomes [11]. The patient's outcome with CRC different greatly between the patients, and survival rates ranging from 10% to 90% based on disease stage and other variables [12]. The prognosis of CRC depends mainly on disease stage as considered by the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) TNM staging classification. Anyhow, the differences in clinical outcomes and prognosis within patients of the same pathological stage are considerable [19,20]. The identification of prognostic and predictive markers may be important to identify patients at a high risk of recurrence or metastases for improved management of the disease. The present cohort performed a detailed retrospective analysis of 466 patients with CRC diagnosed and treated

at the National Cancer Institute, Misurata, Libya. The sociodemographic, genetic, biological variables and tumour characteristics along with their prognosis were analysed.

In this study, the mean age of patient was 53.2 years and the majority of patients was in the age group above 50 years (60.9%), our result is in an agreement to those reported in Libya and others developing countries and are much higher than in western countries [17,21,22]. While approximately 40% of Libyan CRC patients were found below age of 50 years compared to 38% and 4% in African and European countries respectively [23-25]. This could be due to difference between population structures and life expectancy in developing and developed countries. Health service aspect is important, but biological factors as explanation of difference should not be excluded. Various studies reported that young patients with CRC were associated with a high grade of malignancy and an advanced stage in compare with old ones [26,27].

One of the most important finding at this study regarding gender distribution of CRC patients, the frequency between two gender was nearly the same with slightly more in the male. No explanation for the similarity. Some studies in Africa showed that the majority CRC patients are females [24]. This is in contrast to results from developed countries where men are more common [28,29].

About 80% of CRC occur in people with no genetic risk and those with positive family history have 2-3-fold greater risk of disease [30]. A number of genetic syndromes such as hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are also associated with CRC occurrence [1,31]. Radical surgical intervention (total proctocolectomy) may be recommended for people with FAP as a preventive procedures due to the high risk of malignancy. In this study, 15 patients (3.2%) had a family history of CRC.

The blood group and Rh antigen subgroups were investigated in this cohort, our results show the prevalence of blood group A and O, as well as Rh antigen positivity were more frequent among CRC patients (44.0%, 41.0 and 82.8%; respectively). Our findings are consistent with previous reported data [32 and 33]. Kahramanca et al, reported that the incidence of CRC was found to be significant in patients with A positive blood group [32].

We observed that intestinal obstruction, and rectal bleeding was the commonest presentation for CRC in this study which in the same line with other studies reported in Libya and other developing countries [17,24].

Regarding tumour site, our study noted that colon cancer was more common than rectum cancer, this finding in agreements with other studies [21, 24, 34 and 35]. Anyhow, a tendency over time towards a progressive increase in colonic cancer and decrease in rectal cancer as noted by Ponz de leon et al [36]. In our study, we also observed that colon cancer was more in left side confirm to reports done in Libya and other developing countries [17,37]. This in contrast from certain developed countries which reported that right side was more common [38 and 39].

The commonest histological type of CRC is Adenocarcinoma and most of patients had moderate differentiated tumours as reported in this study and others [40,41]. In this context, a large proportion (65.7%; n =306) of patients were diagnosed with intermediate stages (stages II and III) disease at diagnosis and stage III is the most frequent (40.3%). These figures are consistent with other published data from Arabic and other developing countries [34. 42 and 43]. The most of Egyptian patients (57%) with CRC were diagnosed with mid stage (stage II and III) disease and stage II was the most frequent (30.6%) as noted by Suliman et al [24]. On other hand, these results are higher than those reported in developed countries [35].

These current and previous data point to an enduring and concerning trend regarding early detection and strongly indication the need for establishment screening program in high-risk patients. Libya, like other some developing countries does not have a population-based screening program. Stage at diagnosis provides strong prognostication for patients with CRC and it's the most important prognostic factor for determining survival [11,44]. Thus, greater efforts should be made to establishment and promote population-based CRC screening programs in Libya. In addition, we found that liver was the most common metastatic site followed by lung and bone, which agreed with numerous previous results [24, 45-47].

The most important finding of the present study was undoubtedly the significant correlation of sociodemographic and clinicopathological variables with disease progression, especially overall survival and disease-free survival. The median follow-up time of the cohort study was 46 months 44 % of patients had died of CRC at the end of the follow-up period.

This study showed that CRC patients under 50 years of age had a higher rate of recurrence and shorter survival time than ≥50 years. These finding confirms results of other studies [15,48]. The incidence of CRC is uprising among young individuals in the world [49]. Though, CRC is mainly a disease of the elderly [28]. The effects of age on the survival of CRC patients are studied in numerous studies and the results was controversial. Some studies reported the younger patients did not have poor outcome compared to the older ones despite having an advanced stage, while other studies have observed a poor survival in younger group [15,48,50]. Moreover, in agreement of our findings, Zhao et al., reported that young age tumour was an independent risk factor for mortality (15).

In addition, this study observed that the patients who had tumours with early stage, with no metastasis and with low grade *tumour* were associated with longer survival time. While patients who had tumours with advanced stages, with distant metastasis and with high grade tumour were associated with shorter survival time. The analysis using Kaplan Meier curves showed that patients with advanced stages and high grade had short diseases free survival. Multivariate survival analysis in this study showed that clinical stage appears to have powerful an independent effect on the overall survival ($p<0,0001$) and was associated with age at diagnosis ($p =0.017$). Clinical stage was also an independent predictor of disease free survival ($p<0,0001$) and was associated with age at diagnosis ($p = 0.019$). These results are consistent with other published data [19,20, 51,52].

However, gender, address, marital status, blood group, body mass index, comorbidity, family history of CRC, tumour site and histological type did not show significant correlation with CRC patients' outcome.

In fact, numerous factors were investigated to predict the prognosis of CRC such as stage, pathological features and biological markers. The extent of the tumour (local and distant) according to the TNM system classification provides strong prognostication for patients with CRC. A higher T stage is associated with poor survival and increased risk of relapse as well as increased incidence of distant metastasis [51- 53]. Positive lymph nodes are considered the second powerful predicator of outcome in patients with CRC, after distant metastasis [54]. Patients who had lymph nodes involvement were associated with poor survival and high recurrence rates and adjuvant therapy is highly recommended for those patients to reduce the risk of distant metastasis [55,56].

Distant metastasis in CRC patients remains the strongest predicator of outcome and the 5-year survival rate is ~10% in patients with metastasis [57,58]. Despite marked advances in treatment strategies, metastatic CRC remains incurable and the goals of therapy range from relief of symptoms to prolonging survival [58]. The degree of tumour differentiation is an adverse prognostic factor independent of stage in CRC and its associated with increased risk of recurrence [59,60].

In this study, the survival rates are lower than in developed countries [35]. Anyhow, variations in CRC survival exist globally and even within regions [61]. This variety can reflect differences in development stages of health care system, particularly the limited facilities of the Libyan CRC patients for early diagnosis and treatment as well as unavailability of a population-based screening program in Libya. The question arises whether the difference is caused by stages of development in medical care between western and African counties (Libya as an example), or whether there are other causes (including genetic and/or biological differences). Schneider et al; suggested that CRC is a group of heterogeneous diseases with different genetic and biological behaviour that explain diverse tumour characteristics and outcomes [11]. However, final conclusions on the issue can only be drawn after more intensive studies in various parts or Africa, Europe and America.

Authors' contributions

MA conceived the present study, drafted the manuscript, and wrote the text. MF, MG, AJ, ML, FB, AS, AR, conducted the patient survey. AA, FO, SE, AL, MF, AE and MK analyzed the data and reviewed the manuscript. AE and MA performed the data interpretation and analysis, writing and proofreading, and discussions. EE performed the statistical analysis. Prepared the figures and tables and reviewed the study, interpreted the data, and helped write and proofread the manuscript. All authors critically reviewed and approved the final version of the manuscript.

References

1. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N (March 2010). "Colorectal cancer". Lancet. 375 (9719): 1030–1047.

2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. (December 2012). "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". Lancet. 380 (9859): 2095–2128.
3. Forman D, Ferlay J (2014). "Chapter 1.1: The global and regional burden of cancer". In Stewart BW, Wild CP (eds.). World Cancer Report. the International Agency for Research on Cancer, World Health Organization. pp. 16–53.
4. Merika E, Saif MW, Katz A, Syrigos K, Syrigos C, Morse M (2010). "Review. Colon cancer vaccines: an update". In Vivo. 24 (5): 607–628.
5. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010). "Colorectal Cancer Incidence, Mortality and Prevalence Worldwide in 2008 – Summary". Archived from the original on October 17, 2012.; "GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10". Lyon, France: International Agency for Research on Cancer. Archived from the original on May 8, 2011.
6. Done JZ, Fang SH. Young-Onset Colorectal Cancer: A Review. World J Gastrointest Oncol. 2021;13(8):856–66.
7. Saad El Din K, Loree JM, Sayre EC, Gill S, Brown CJ, Dau H, et al. Trends in the epidemiology of young-onset colorectal cancer: A worldwide systematic review. Vol. 20, BMC Cancer. BioMed Central Ltd.; 2020.
8. Bosman FT (2014). "Chapter 5.5: Colorectal Cancer". In Stewart BW, Wild CP (eds.). World Cancer Report. the International Agency for Research on Cancer, World Health Organization. pp. 392–402.
9. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FA, et al. (June 2016). "Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement". JAMA. 315 (23): 2564–2575.
10. "Colon Cancer Treatment (PDQ®)". NCI. May 12, 2014. Archived from the original on July 5, 2014. Retrieved June 29, 2014.
11. Schneider, N.I.; Langner, C. Prognostic stratification of colorectal cancer patients: Current perspectives. Cancer Manag. Res. 2014, 6, 291.
12. O'Connell, J.B.; Maggard, M.A.; Ko, C.Y. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J. Natl. Cancer Inst. 2004, 96, 1420–1425.
13. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.
14. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D; ESMO Guidelines Committee (2017) Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 28(suppl_4): iv22- iv40.
15. Zhao L, Bao F, Yan J, Liu H, Li T, Chen H, et al. Poor prognosis of young patients with colorectal cancer: a retrospective study. Int J Color Dis. 2017; 32(8):1147–56.
16. Punt CJA, Buyse M, Köhne CH, Hohenberger P, Labianca R, Schmoll HJ, et al. Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials. J Natl Cancer Inst. 2007;99(13):998–1003.
17. Elamyal R, Kamoka H, Hashmi H. Clinico-Demographic Profile of Colorectal Cancer Patients in National Cancer Institute of Sabratha – Libya. JMSCR. 2017; 5: 31123-31126.
18. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (November 2018). "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries". CA: A Cancer Journal for Clinicians. 68 (6): 394–424. doi:10.3322/caac.21492.
19. Fang, S.H.; Efron, J.E.; Berho, M.E.; Wexner, S.D. Dilemma of stage II colon cancer and decision making for adjuvant chemotherapy. J. Am. Coll. Surg. 2014, 219, 1056–1069.
20. Zhang, C.; Yin, S.; Tan, Y.; Huang, J.; Wang, P.; Hou, W.; Zhang, Z.; Xu, H. Patient Selection for Adjuvant Chemotherapy in High-Risk Stage II Colon Cancer: A Systematic Review and Meta-Analysis. Am. J. Clin. Oncol. 2020, 43, 279–287. [CrossRef] 6. Brierley, J.D.; Gospodarowicz, M.K.; Wittekind, C. TNM Classification of Malignant Tumours; John Wiley & Sons: Hoboken, NJ, USA, 2017.
21. Cado A, Ebeid B, Abdelmohsen A, Axon A. Colorectal cancer in Egypt is commoner in young people: Is this cause for alarm? Alexandria J Med. 2014; 50: 197-201.
22. Qaseem A, Crandall CJ, Mustafa RA, Hicks LA, Wilt TJ, Forciea MA, et al. (November 2019). "Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement From the American College of Physicians". Annals of Internal Medicine. 171 (9): 643–654.
23. Seleye-Fubara D, Gbobo I: Pathological study of colorectal carcinoma in adult Nigerians: a study of 45 cases. Niger J Med 2005, 14:167–172.
24. Suliman MA, Zamzam ML, Omar AT, Fahmy NN (2020) Clinicopathological Profile of Colorectal Cancer Patients in Suez Canal University Hospitals-Egypt. J Cancer Biol Res 8(1): 1127.

25. Mitry E, Benhamiche AM, Jouve JL, Clinard F, Finn-Faivre C, Faivre J: Colorectal adenocarcinomain patients under 45 years of age: comparison with older patients in a well-defined French population. Dis Colon Rectum 2001, 44(3):380–387. 5.
26. Makela JT and Kiviniemi H (2010) Clinicopathological features of colorectal cancer in patients under 40 years of age Int J Colorectal Dis 25 823–828.
27. 20217423.
28. Connell LC, Mota JM, and Braghiroli MI, et al (2017) The rising incidence of younger patients with colorectal cancer: questions about screening, biology, and treatment Curr Treat Options Oncol 18(4) 23 https://doi.org/10.1007/s11864-017-0463-3 PMID: 28391421.
29. Bosman FT (2014). "Chapter 5.5: Colorectal Cancer". In Stewart BW, Wild CP (eds.). World Cancer Report. the International Agency for Research on Cancer, World Health Organization. pp. 392–402. ISBN 978-92-832-0443-5
30. Siegel RL, Fedewa SA, Miller KD, Goding-Sauer A, Pinheiro PS, Martinez-Tyson D, et al. Cancer statistics for Hispanics/Latinos, 2015. CA Cancer J Clin. 2015; 65: 457-480.
31. Watson AJ, Collins PD (2011). "Colon cancer: a civilization disorder". Digestive Diseases. 29 (2): 222–228.
32. Juhn E, Khachemoune A (2010). "Gardner syndrome: skin manifestations, differential diagnosis and management". American Journal of Clinical Dermatology. 11 (2): 117–122.
33. Kahramanca, Turgut Anuk, Ali Cihat Yıldırım, Oskay Kaya. Blood Group Characteristics in Colorectal Cancers. Turk J Colorectal Dis 2018; 28:76-79.
34. Cao X, Wen ZS, Sun YJ, Li Y, Zhang L, Han YJ. Prognostic value of ABO blood group in patients with surgically resected colon cancer. Br J Cancer 2014; 111:174-180.
35. El-Moselhy EA, Hassan AM, El-Tiby DM, Abdel-Wahed A, Mohammed A, El-Aziz AA. Colorectal cancer in Egypt: clinical, lifestyle and sociodemographic risk factors. PRAS1. 2017; 4: 1-15.
36. Ciccolallo L, Capocaccia R, Coleman MP, Berrino F, Coebergh JW, Damhuis RA, et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. Gut. 2005; 54: 268-273.
37. Ponz de Leon M, Rossi G, di Gregorio C, De Gaetani C, Rossi F, Ponti G, et al. Epidemiology of colorectal cancer: the 21-year experience of a specialised registry. Intern Emerg Med. 2007; 2: 269-279.
38. Seleye-Fubara D, Gbobo I: Pathological study of colorectal carcinoma in adult Nigerians: a study of 45 cases. Niger J Med 2005, 14:167–172.
39. Takada H, Ohsawa T, Iwamoto S, Yoshida R, Nakano M, Imada S, Yoshioka K, Okuno M, Masuya Y, Hasegawa K, Kamano H, Hioki K, Muto T, Koyama Y: Changing site distribution of colorectal cancer in Japan. Dis Colon Rectum 2002, 45:1249–1254.
40. Ponz de Leon M, Marino M, Benatti P, Rossi G, Menigatti M, Pedroni M, Di Gregorio C, Losi L, Borghi F, Scarselli A, Ponti G, Roncari B, Zangardi G, Abbati G, Ascari E: Trend of incidence, sub-site distribution and staging of colorectal neoplasms in the 15-year experience of a specialized cance registry. Ann Oncol 2004, 15:940–946.
41. Greene FL. Distribution of colorectal neoplasms. A left to right shift of polyps and cancer. Am Surg. 1983; 49: 62-65.
42. harua-Guindic L, Lagunes-Gasca AA, Villanueva-Herrero JA, JimenezBobadilla B, Avendano-Espinosa O, Charua-Levy E. [Epidemiological characteristics of colorectal cancer in the General Hospital of Mexico. A 20 years' analysis: 1988-2007]. Rev Gastroenterol Mex. 2009; 74: 99-104.
43. Eisa HH. Colorectal Cancer in Upper Egypt, Does Age Make A Difference in Survival? Med J Cairo Univ. 2010; 78: 145-150.
44. Chandrasinghe PC, Ediriweera DS, Hewavisenthi J, et al.: Colorectal cancer burden and trends in a South Asian cohort: Experience from a regional tertiary care center in Sri Lanka. BMC Res Notes 10:535, 2017.
45. Gosavi, R.; Heriot, A.G.; Warrier, S.K. Current Management and Controversies in Management of T4 Cancers of the Colon—A Narrative Review of the Literature. Dig. Med. Res. 2020, 3, 67.
46. Holch, J.W.; Demmer, M.; Lamersdorf, C.; Michl, M.; Schulz, C.; von Einem, J.C.; Modest, D.P.; Heinemann, V. Pattern and dynamics of distant metastases in metastatic colorectal cancer. Visc. Med. 2017, 33, 70–75.
47. Riihimäki, M.; Hemminki, A.; Sundquist, J.; Hemminki, K. Patterns of metastasis in colon and rectal cancer. Sci. Rep. 2016, 6, 29765.
48. Aykan NF, Yalçın S, Turhal NS, Özdoğan M, Demir G, Özkan M, et al. Epidemiology of colorectal cancer in Turkey: A cross-sectional disease registry study (A Turkish Oncology Group trial). Turk J Gastroenterol 2015; 26: 145-153.
49. McKay A, Donaleshen J, Helewa RM, Park J, Wirtzfeld D, Hochman D, et al. Does young age influence the prognosis of colorectal cancer: a population-based analysis. World J Surg Oncol. 2014;12(1):370.
50. Kasi PM, Shahjehan F, Cochuyt J, Li Z, Colibaseanu D, Merchea A. Rising proportion of young individuals with rectal and colon cancer. Clin Colorectal Cancer. 2018;18(1):e87–95.

51. Jones HG, Radwan R, Davies M, Evans M, Khot U, Chandrasekaran T, et al. Clinicopathological characteristics of colorectal cancer presenting under the age of 50. Int J Color Dis. 2015;30(4):483–9.
52. Diaconescu, M.; Burada, F.; Mirea, C.S.; Moraru, E.; Ciorbagiu, M.C.; Obleaga, C.V.; Vilcea, I.D. T4 Colon Cancer-Current Management. Curr. Health Sci. J. 2018, 44, 5–13.
53. Smith, N.; Bees, N.; Barbachano, Y.; Norman, A.; Swift, R.; Brown, G. Preoperative computed tomography staging of nonmetastatic colon cancer predicts outcome: Implications for clinical trials. Br. J. Cancer 2007, 96, 1030–1036.
54. Grossmann, I.; Klaase, J.M.; Avenarius, J.K.; de Hingh, I.H.; Mastboom, W.J.; Wiggers, T. The strengths and limitations of routine staging before treatment with abdominal CT in colorectal cancer. BMC Cancer 2011, 11, 433.
55. Gunderson, L.L.; Jessup, J.M.; Sargent, D.J.; Greene, F.L.; Stewart, A.K. Revised TN categorization for colon cancer based on national survival outcomes data. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2010, 28, 264–271.
56. Osterman, E.; Glimelius, B. Recurrence Risk After Up-to-Date Colon Cancer Staging, Surgery, and Pathology: Analysis of the Entire Swedish Population. Dis. Colon Rectum 2018, 61, 1016–1025.
57. Backes, Y.; Elias, S.G.; Bhoelan, B.S.; Groen, J.N.; van Bergeijk, J.; Seerden, T.C.J.; Pullens, H.J.M.; Spanier, B.W.M.; Geesing, J.M.J.; Kessels, K.; et al. The prognostic value of lymph node yield in the earliest stage of colorectal cancer: A multicenter cohort study. BMC Med. 2017, 15, 129.
58. Brierley, J.D.; Gospodarowicz, M.K.; Wittekind, C. TNM Classification of Malignant Tumours; John Wiley & Sons: Hoboken, NJ, USA, 2017.
59. Goldberg, R.M.; Rothenberg, M.L.; Van Cutsem, E.; Benson III, A.B.; Blanke, C.D.; Diasio, R.B.; Grothey, A.; Lenz, H.J.; Meropol, N.J.; Ramanathan, R.K. The continuum of care: A paradigm for the management of metastatic colorectal cancer. Oncologist 2007, 12, 38–50.
60. Derwinger, K.; Kodeda, K.; Bexe-Lindskog, E.; Taflin, H. Tumour differentiation grade is associated with TNM staging and the risk of node metastasis in colorectal cancer. Acta Oncol. 2010, 49, 57–62.
61. Barresi, V.; Reggiani Bonetti, L.; Ieni, A.; Caruso, R.A.; Tuccari, G. Histological grading in colorectal cancer: New insights and perspectives. Histol. Histopathol. 2015, 30, 1059–1067.
62. Jackson-Thompson J, Ahmed F, German RR, Lai SM, Friedman C. Descriptive epidemiology of colorectal cancer in the United States, 1998-2001. Cancer. 2006; 107: 1103-1111.