ORIGINAL ARTICLE

Colorectal carcinoma in gharbiah district, Egypt: Comparison between the elderly and non-elderly

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Abstract

Objective: This work was conducted to study colorectal carcinoma (CRC) in Gharbiah district, Egypt and to verify the effect of age on the treatments and their outcomes.

Methods: Between 2000 and 2002, 293 cases with CRC were identified in the Gharbiah population based cancer registry (GPBCR); 159 of whom were treated at Tanta Cancer Center (TCC). Patients were grouped into elderly and non-elderly (≥ and < 65 years, respectively).

Results: CRC was the 6th cancer in Egypt, representing 4% of the total cancers and 53% of GIT cancers. The median age was 53 years with male predominance. Colon cancers were more common than rectal cancers. Most patients had tumors that were localized, low grade and adenocarcinoma (AC). Constipation, abdominal pains and bleeding per rectum were the commonest complaints. Surgery, radiotherapy and chemotherapy were adopted in 84%, 28% and 72% of patients, respectively. The median OS and PFS were 23 and 25 months (95%CI: 17-29 and 11.8-18.2), respectively. Compared to non-elderly, elderly patients were more likely to have rectal tumors, non-AC histology, non-metastatic disease; more comorbidities were less likely to receive chemotherapy particularly in the adjuvant setting (P< 0.05 for all). The OS and PFS of elderly patients were not statistically different from the non-elderly.

Conclusions: Within the limits of this retrospective trial, elderly patients with CRC tend to have more rectal and non-metastatic cancers. They were more likely to have comorbidities and less likely to receive chemotherapy. However, the OS and DFS were comparable to non-elderly.

Key words

Egypt, Elderly, Gharbiah population-based cancer registry, Colon rectum neoplasms, Treatment, Survival

Introduction

Colorectal carcinoma (CRC) is predominately a disease of older persons. Despite this, elderly populations are either excluded or underrepresented in clinical trials particularly those administering adjuvant chemotherapies [1]. Trials comparing treatments outcomes in the elderly patients with colorectal cancer to their younger counterparts showed that elderly derive similar benefits [2]. However, elderly tend to have major comorbities that may significantly limit life expectancy and potentially reduce treatment benefits [1]. Colorectal cancer in the elderly has some clinicopathological features. It is commonly diagnosed at an advanced stage with right sided shift [3]. Population-based data from USA have

shown that use of adjuvant chemotherapy in stage III colon cancer declines with age from 78% at 65-69 years to 34% at 80-85 years [4]. Additionally, treatment discontinuation is more common in the elderly [5].

In Egypt, colorectal cancer is the 6th cancer both in males and females representing 4.5% and 3.6% of the total cancers with age-standardized rates (ASRs) per 100,000 population of 6.5% and 4.2% in males and females, respectively. ASRs rise to 110 and 85 above the age of 60 and 65 years, respectively [6]. In 2010, people aged 65 years or above constituted 3.7% of the population in Egypt compared to 12.8% of US population. In 2011, the life expectancy was 70 and 74 years among Egyptian males and females compared to 76 and 81 years among US males and females, respectively. The median age is 24 years in Egypt compared to 37 years in US [7, 8]. However, the growth of elderly people in developing countries, including Egypt, is projected to be faster than any other segment of the population and at a rate that higher than that of developed countries [9]. Thus studying CRC in Egypt as a function of age will have current as well as future implications.

The aim of this study is to compare CRC in Egypt among elderly (≥65 years) and non-elderly (<65 years) patients regarding clinicopathological characteristics, treatment choices and outcomes. The age of 65 years was chosen as a traditional cut-off that allows comparisons with similar data from more developed parts of the world [10, 11].

Methods

This is a retrospective study. Patients with CRC were identified through the Gharbiah population based cancer registry (GPBCR). GPBCR was the first population based cancer registry in Egypt. It covers the Gharbiah Governorate with an area of about 2000 square kilometers and more than 4 million people (~5% of Egyptian population) [6]. Data on age, sex, sub-site, histology, grade and stage were obtained from GPBCR. Further data on complaints, comorbidities, treatment modalities, relapse, dates of diagnosis, surgery and relapse, and survival were obtained for those subset of patients treated at Tanta Cancer Center (TCC). The study was approved by the IRB of the Egyptian National Cancer Institute.

Inclusion criteria were adult patients with colorectal cancers and a histology of carcinoma between 2000 and 2002. Exclusion criteria were non-carcinoma histology (e.g. lymphoma) and non-confirmed histologic subtype as those diagnosed based on death certificate, radiology or malignant neoplasm unspecified.

Between 2000 and 2002, 357 cases with colorectal cancers contained GPBCR were identified. Sixty-four cases of were excluded; 35 had no histological confirmation being diagnosed from death certificate or radiology, 12 cases with unspecified malignant tumor, 10 cases with Non-Hodgkin's lymphoma (NHL), 3 cases of gastrointestinal stromal tumor (GIST), 2 cases of leiomyosarcoma and 2 cases with neuroendocrine tumors.

Statistical analysis

All analyses were done using SPSS® software program version 15 (Chicago, USA). Nominal and categorical data were compared in the elderly and non-elderly using the Chi squared test. Survival was calculated using the Kaplan Meyer methods and groups were compared using the log-rank test. Logistic regression was used to study the effect of different factors on overall survival (OS) and progression free survival (PFS). A probability (*P*) of less than 0.05 (two sided) was considered statistically significant.

Results

Between 2000 and 2002, 293 cases of CRC contained in GPBCR were identified. All were histologically confirmed and subtyped. CRC was the 6th cancer in Egyptian males and females representing 4.5% and 3.6% of total male and female cancers in the study period, respectively. CRC represented 53% of 675 GIT cancers.

The median age was 53 years (Range 21-81 years) with male predominance (1.3:1). The colon was the commonest site and the right and left sides were equally affected. Stage II disease was the commonest stage. Adenocarcinoma (AC) was the

commonest histologic subtype. Other subtypes included anaplastic, undifferentiated, squamous and unspecified carcinoma. Low grade tumors were the commonest. Table 1 shows the characteristics of patients involved in the current study. Fifteen percent of the patients were elderly (≥65 years). Compared with non-elderly, elderly patients were more likely to harbor rectal and right colonic tumors, stage II & III and non-AC histology. (P = 0.04, 0.13, 0.06, 0.01, respectively, Table 1)

Table 1. Characteristics of 293 patients with colorectal carcinoma at GPBCR

	All ages number (%)	<65 years number (%)	≥65 years number (%)	*P*
Total	293 (100)	250 (85)	43 (15)	
Sex				
Male	164 (56)	138 (55)	26 (60)	
Female	129 (44)	112 (45)	17 (40)	0.32
Site				
Rectum	83 (28)	64 (26)	19 (44)	
Rectosigmoid junction	36 (12)	32 (13)	4 (9)	
Colon	174 (60)	154 (61)	20 (47)	0.04
Colon subsite				
Right side	72 (41)	62 (38)	10 (50)	
Left side	73 (42)	65 (42)	8 (40)	
Overlapping/unspecified site	29 (17)	27 (18)	2 (10)	0.13
TNM stage (263 cases)				
Stage I	37 (11)	34 (16)	3 (8)	
Stage II	96 (37)	75 (33)	21(55)	
Stage III	68 (29)	59 (26)	9 (24)	
Stage IV	62 (23)	57 (25)	5 (13)	0.06
Histology subtype				
Adenocarcinoma (AC)	286 (98)	247 (99)	39 (91)	
Other	7 (2)	3 (1)	4 (9)	0.01
Known grade (240 cases)				
G1-2	179 (75)	154 (75)	25 (71)	
G3-4	61 (25)	51 (25)	10 (29)	0.39

Abbreviations: GPBCR=Gharbiah population based cancer registry; SEER=Surveillance Epidemiology and End Results

Unfortunately, clinical data particularly pertaining to treatment and follow up, other than those mentioned above, were not contained in GPBCR. Thus we tried to further track as much cases as possible through reviewing cases that presented to Tanta Cancer Center (TCC), the main oncology center in Gharbiah governorate, Egypt. We could identify 159 cases whose information is discussed below in more details.

TCC cases were similar to the larger GPBCR group (Table 2). More rectal tumors and localized stages were also noticed among elderly patients. Distant metastases were encountered in 48 (30%) patients; liver (17), bone (7), lungs (6) and other unknown sites (18). Most patents had symptoms related to their disease (Table 3) with constipation, abdominal pains and bleeding per rectum being the commonest. Comorbidities (n=31) were mostly diabetes mellitus particularly type II (12), hypertension (8), hepatic (7) renal (6) or cardiac diseases (3). Eighty-four percent of patients underwent surgery mostly with curative intent. Radiotherapy was given to 28% of patients almost only in rectal tumors. Chemotherapy was adopted in 72% of patients for a median of 6 cycles (Table 3). Chemotherapy was 5FU/leucovorin in 104 patients, FOLFIRI in 3 patients, capecitabine and 5FU/leucovorin/cisplatin in 2 patients each and FOLFOX in one patient. Compared with the non-elderly, elderly patients were more likely to have comorbidities (P = 0.04), to be denied chemotherapy (P = 0.008) particularly in the adjuvant setting (P = 0.014).

Table 2. Characteristics of 159 patients with colorectal carcinoma treated at TCC

	All ages number (%)	<65 years number (%)	≥65 years number (%)	*P*
Total	159 (100)	142 (89)	17 (11)	
Sex				
Male	79 (50)	69 (49)	10 (59)	
Female	80 (50)	73 (51)	7 (41)	0.29
Site				
Rectum	46 (29)	40 (28)	6 (35)	
Rectosigmoid junction	22 (14)	20 (14)	2 (12)	
Colon	91 (57)	82 (58)	9 (53)	0.82
Tnm stage				
Stage I	18 (11)	18 (13)	0	
Stage II	51 (32)	41 (49)	10 (59)	
Stage III	42 (27)	38 (27)	4 (23)	
Stage IV	48 (30)	45 (31)	3 (18)	
TNM stage grouping				
Stage I/II	69 (43)	59 (42)	10 (59)	
Stage III/IV	80 (57)	83 (58)	7 (41)	0.2
Metastases				
No	111 (70)	96 (68)	15 (88)	
Yes	48 (30)	46 (32)	2 (12)	0.09
Histology subtype				
Adenocarcinoma (AC)	157 (99)	140 (99)	17 (100)	1.0
Other	2 (1)	2 (1)	0	
Grade (131 cases)				
G1-2	96 (72)	86 (73)	10 (77)	
G3-4	35 (28)	32 (27)	3 (23)	0.53

Abbreviations: TCC=Tanta Cancer Center

After a median follow up of 93 months (95% CI: 85-102 months), only 42 patients were alive; 37 free of disease and five with evidence of disease while 117 patients were dead. Deaths were disease related in all but 16 cases. The median overall survival (OS) and progression free survival (PFS) were 23 and 15 (95% CI: 17-29 and 12-18) months, respectively (Figure 1, 2). The 3- and 5-year OS rates were 35% and 25%, respectively. The 2- and 5-year PFS survival rates were 28% and 22%, respectively.

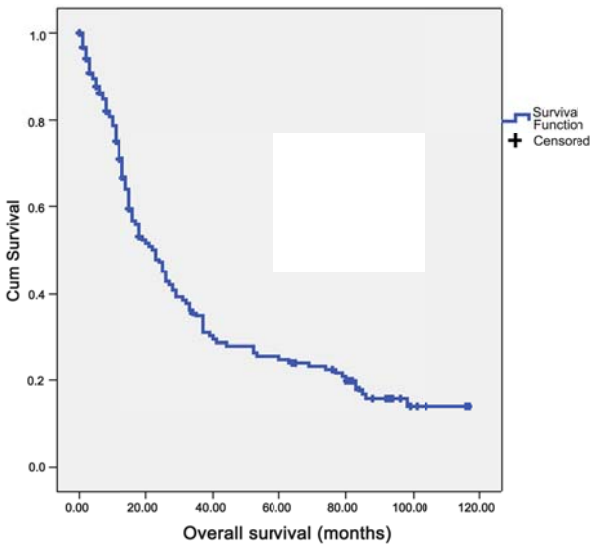

Figure 1. Overall survival in 159 patients with colorectal carcinoma

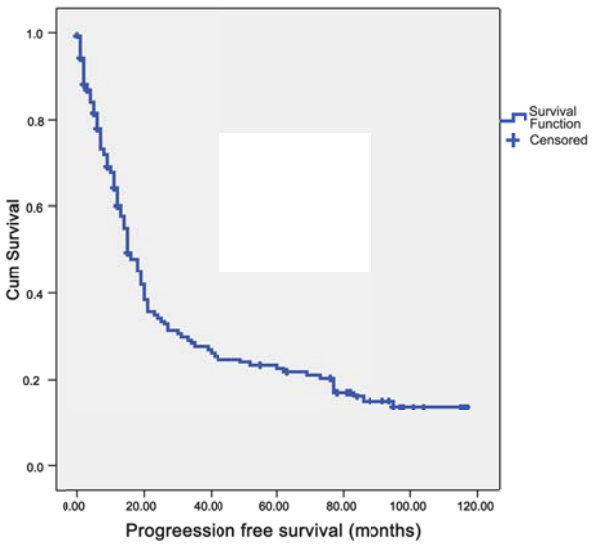

Figure 2. Progression free survival of 159 patients with colorectal carcinoma

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For stage I, II, III & IV patients, the median OSs were 85, 21, 28 & 13 months (95%CI: 16-155, 14-28, 19-37 & 11-15) and their 5-year OS rates were 58%, 31%, 30% & 4%, respectively (Figure 3, P<0.001). Also, the median PFS for stage I, II, III & IV patients were 41, 18, 16 & 11 months (95% CI: 9-73, 13-23, 6-26 & 5-17) and their 5-year OS rates were 41%, 30%, 25% & 4%, respectively (Figure 4, P<0.001). The median OS was 23 months both in the elderly and non-elderly patients (95% CI: 15-31 & 16-28, respectively, P = 0.97, Figure 5). Similarly, the median PFS was 15 months both in the elderly and non-elderly patients (95% CI: 7-23 & 11-19, respectively, P = 0.57, Figure 6). Patients with colon cancer had a median OS of 18 months compared to 26 months with rectal cancer (95% CI: 10-26 & 17-34, respectively, P = 0.29). The 2- and 5-year OS rates were 44% and 33% for patients with colon cancer compared to 53% and 16% for those with rectal cancer. The median PFS was 15 months for colon cancer patients compared to 18 months for rectal cancer patients (95% CI: 9-21 & 15-22, respectively, P = 0.21).

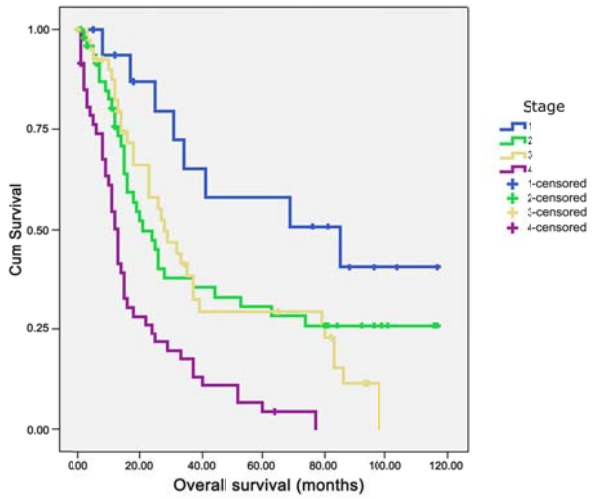

Figure 3. Overall survival of different stages of colorectal carcinoma ($P \leq 0.001$)

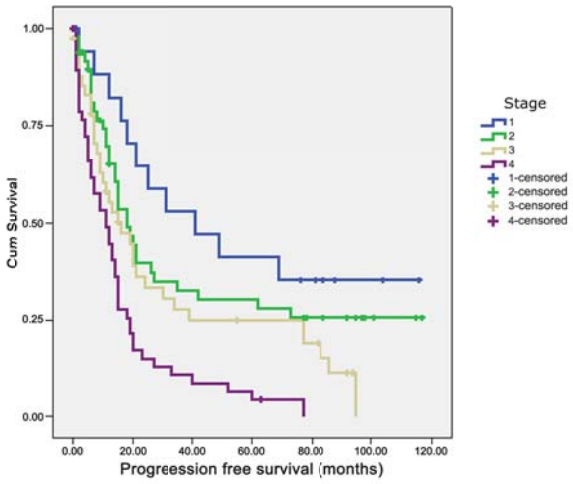

Figure 4. Progression free survival of different stages of colorectal carcinoma ($P \leq 0.001$)

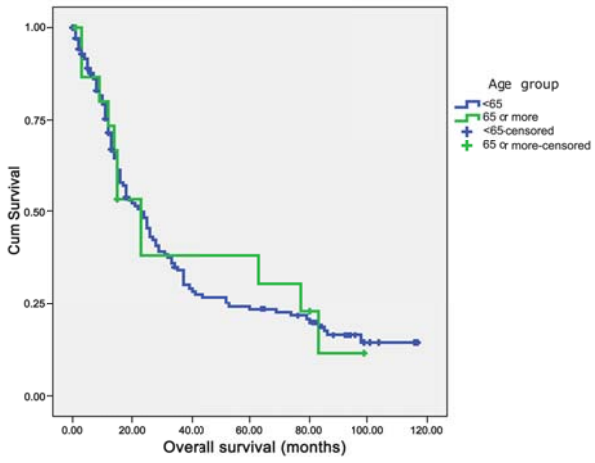

Figure 5. Overall survival in colorectal carcinoma according to age (Elderly ≥65 and non-elderly <65 years, P = 0.97)

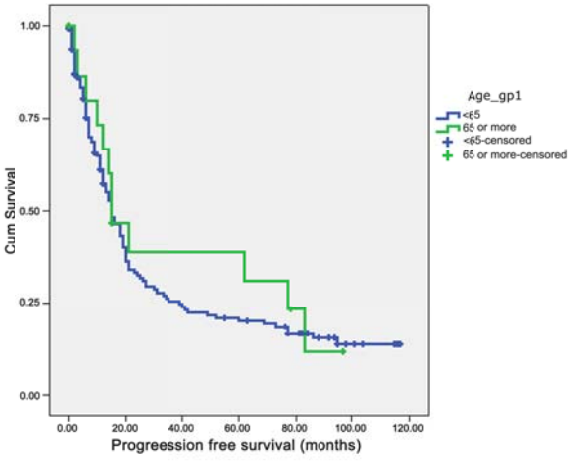

Figure 6. Progression free survival in colorectal carcinoma according to age (Elderly ≥65 and non-elderly <65 years, P = 0.57)

Table 3. More details on 159 patients with colorectal carcinoma who presented to TCC

	All ages number (%)	<65 years number (%)	≥65 years number (%)	*P*
Complaints				
No	25 (15)	18 (13)	2 (12)	
Yes (Detailed below)	134 (85)	119 (87)	15 (88)	0.64
Constipation	39 (25)	35 (25)	4 (24)	
Pains	31 (20)	26 (20)	2 (12)	
Bleeding per rectum	32 (20)	26 (18)	6 (35)	
Intestinal obstruction	14 (9)	12 (9)	2 (12)	
Diarrhea	9 (6)	9 (6)	0	
Others*	9 (6)	11 (2)	1 (6)	
Known comorbidities (134 cases)				
No	103 (77)	95 (80)	8 (54)	
Yes	31 (23)	24 (20)	7 (46)	0.04
Surgery				
No	26 (16)	24 (17)	2 (12)	
Yes (Detailed below)	133 (84)	118 (83)	15 (88)	0.58
Curative intent	115 (87)	103 (87)	12 (80)	
Palliative/unknown	18 (13)	15 (13)	3 (20)	0.44
Radiotherapy				
No	115 (72)	101 (71)	14 (82)	
Yes	44 (28)	41 (29)	3 (18)	0.33
Chemotherapy (All types)				
No	45 (28)	35 (25)	10 (59)	
Yes	114 (72)	107 (75)	7 (41)	0.008
Adjuvant chemotherapy (93 cases)				
No	21 (23)	14 (18)	7 (50)	
Yes	72 (77)	65 (82)	7 (50)	0.014
Relapse (111 cases)				
No	71 (64)	60 (62)	11 (79)	
Yes (Detailed below)	40 (36)	37 (38)	3 (21)	0.22
Local	21 (53)	24	2	
Distant	19 (47)	19	1	

*Includes vomiting, anemia and metastatic symptoms

Abbreviations: TCC=Tanta Cancer Canter, Egypt.

Table 4 shows the OS and PFS in different patients' sub-groups. Advanced stage, presence of comorbidities and non-use of surgery or chemotherapy were significantly associated with poor OS and PFS ($P< 0.05$ for all). With multivariate analysis, only advanced stage and presence of comorbidities were independent predictors of poor OS (P 0.007 & 0.047, respectively). Advanced stage was the sole independent predictor of poor PFS (P 0.008).

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Table 4. Univariate (UVA) and multivaraiate analysis (MVA) of factors affecting overall and progression-free survival in 159 patients with colorectal carcinoma

	Overall survival					**Progression-free survival**				
	UVA				MVA	UVA				MVA
	MOS	CILB	CIUB	*P*	*P*	MPFS	CILB	CIUB	*P*	*P*
Age										
< 65	23	17	29			15	11	19		
≥ 65	23	15	31	0.9	0.4	15	7	23	0.6	0.4
Sex										
Male	19	12	26			14	10	18		
Female	26	17	35	0.22	---	18	14	22	0.1	---
Primary										
Colon	18	9	27			12	8	16		
RS	22	13	31			19	13	25		
Rectum	26	17	35	0.6	---	18	15	21	0.7	---
Grade										
Low	25	20	30			19	15	23		
High	16	11	21	0.9	---	14	11	17	0.9	---
Stage										
1	85	16	154			41	9	73		
2	21	14	28			18	13	23		
3	28	19	37			16	6	26		
4	13	11	15	<0.001	0.007	12	7	17	<0.001	0.008
Co-morbidities										
No	29	21	37			20	15	25		
Yes	16	4	28	0.001	0.047	12	7	17	0.002	0.1
Surgery										
No	13	7	19			9	2	16		
Yes	25	21	29	<0.001	0.73	18	15	21	<.001	0.99
Radiotherapy										
No	18	13	23			13	10	16		
Yes	34	29	39	0.07	0.61	20	16	24	0.09	0.33
Chemotherapy										
No	15	13	17			8	3	13		
Yes	27	21	33	0.001	0.44	19	15	23	<0.001	0.057

Abbreviations: MOS=median overall survival; MPFS=median progression free survival; CILB=lower boundary of 95% confidence interval; CIUB=upper boundary of 95% confidence interval; RS=recto sigmoid.

Discussion

Colorectal cancer is a major cause of morbidity and mortality thorough the world with large geographical differences [12]. Colorectal cancer in Egypt, like most of the developing countries, is lower than that of developed countries with western lifestyle. In Egypt, it is the 6th ranked cancer representing about 4% of total cancers in both sexes compared to the 3rd rank and about 11% for USA [13, 14]. Variation in environmental risk factors particularly the higher content of dietary fibers, more physical activity and lower obesity rates can explain for the different incidence rates [12].

The equal male to female rates of CRC in the current study is similar to many developed and developing countries [3, 15]. In Egypt, the median age for CRC is more than a decade earlier than that in the developing countries like USA. As shown in the current study, only 15% of CRC patients are 65 years of above in Egypt, whereas the corresponding figure for Western countries is much higher reaching up to 62% in USA [16]. This can be due differences in population structures and in life expectancies. The life expectancy of Egyptians is 71 years compared to 78 years for the Americans and almost 95% of the

Egyptians are below 60 years compared to 13% for the Americans [7, 17]. Variation in environmental risk factors can be an important factor [12].

The predominance of colonic over rectal cancers in our study mimics the situation registries from Middle East countries as well as many developing and developed countries including Brazil, China, India, Canada, UK and USA [15, 18]. Similar to other researchers [3, 19-22], we reported higher, albeit insignificant, proportions of proximal colonic and rectal tumors in the elderly as well as lower rates of metastases compared to the younger counterparts. On the contrary, most of tumors in the elderly population in the current study were low-grade. The underlying mechanisms promoting the development of proximal colon cancers are unknown but may be related to the interplay between environmental and constitutional factors that change with advancing age including sex hormones, effect of bile acid, bowel transit time, bacterial flora, fibre intake, calorie intake or fat intake [3].

Similar to previous reports [3, 19, 23], elderly CRC patients in the current study tend to have well differentiated tumors and lower rates of lymph node and distant metastases compared to the non-elderly. This may be explained by a biologically less aggressive disease in the elderly [3]. However, there are other reports that showed an opposite trend with more advanced cancers in the elderly [24, 25]. This was reasoned by the possible delay in seeking care for symptoms like constipation. However, our study showed that symptoms of the elderly were not different from those of the non-elderly. It is to be noted that these reports reflect different time points with differences in medical service developments. Moreover, the whole issue is debatable and data from the Surveillance Epidemiology and End Results (SEER) registry suggest that age may not have a strong influence on stage at diagnosis [26].

Many studies have shown that elderly are less likely to undergo curative resection compared with their younger counterpart [20, 27]. This was not demonstrated in the current study. However, the patients above 70 were few and comorbidities, mostly diabetes and hypertension, were not significant and the absolute numbers were relatively small. Also, only 3% and 1% of patients for whom data on surgical intervention is available in the current study were older than 70 and 75 years respectively.

Elderly do benefit from and tolerate chemotherapy as their younger counterparts [28-30]. However, even after adjustment for potential confounders including severity of medical illness, age remained an independent predictor of getting chemotherapy [4, 31]. Even if elderly embark on chemotherapy, almost one third stops before the full 6 cycles with survival decline [5].

Similarly to prior reports [4, 20, 27, 31], elderly patients in the current study were less likely to be offered chemotherapy (P = 0.006) and radiotherapy (P = 0.3). This could be partially explained by the higher comorbidites in this population. However, it may reflect a general physicians' attitude of withholding chemotherapy for elderly patients based on age alone. However, there are signs that this trend is changing in USA [23].

The unfavourable impact on OS and PFS of lower adoption of chemotherapy and the higher comorbidites in the elderly shown in other trials [31, 33] was not shown is the current study as these survivals were similar to those of the non-elderly. This has some explanations. First, surgery which is the most critical and curative element in CRC treatment was not different in the two groups. Second, elderly had more localized tumors that were of low-grade and thus had a more favourable prognosis that can offset the bad consequences of missing adjuvant chemotherapy. Third, the relatively low life expectancy in the Egyptian population (68 years for males and 71 years for females) may abolish the effect of adjuvant therapy as patients may succumb to other diseases and not to CRC. Fourth, the numbers of the elderly patients in our study were relatively small and few were 75 years or more.

The overall survival rates in the current study are below that of developed countries with mild differences (~10%) with some UK registries [18] and marked differences (~40%) like USA SEER data [13]. Most improvements in CRC survival is in countries with high life expectancy and good access to modern specialized health care [12]. However, enormous disparities

in colorectal cancer survival exist globally and even within regions [13, 15, 34]. There is a 10% difference in 3-year survival between Europe and USA [18] and within the USA; there are differences in survival among different ethnic groups manifested by a 10% lower 5-year survival in blacks compared to whites [16]. This disparity can reflect differences in disease stages at diagnosis [18] health care systems [12] particularly the limited access of the Egyptian CRC patients to many of the state-of-art diagnostics and therapeutics as well differences in surgical practices [18]. For example there are no internationally adopted screening programs, limited medical insurance coverage, and very limited availabilities of the expensive medications. Wrigley 2008 showed that socioeconomic deprivation is adversely associated with survival in CRC patients. CRC survival is highly dependent on stage [12]. Higher fraction of the Egyptian patients present with distant disease (24%) compared to the USA (19%). Lower health awareness as well as cancer phobia can be contributing factor leading to delay in seeking medical care. The higher OS for rectal carcinoma than colonic carcinoma in the current study is similar to USA SEER data [16] and UK statistics [35]. This could be related to increased use of total mesorectal excision (TME) technique, preoperative radiation therapy and adjuvant chemotherapy [36].

Our study has strengths and limitations. To the best our knowledge, it is the first study from Egypt and our region that addresses the issue of CRC in the elderly patients guided by a cancer registry, the GPBCR. Despite this study is a retrospective one, we believe that it is not inferior to a possible prospective one that can describe CRC with stratification according to age. It accurately reflects the practice of the oncology community within the jurisdictions of the study. However, the issue of limited and incomplete information for some patients cannot be denied as is the setting in all retrospective studies particularly in a country like Egypt where the medical services are spanned among many providers like ministry of health, military, educational as well as private hospitals. The smaller number of elderly compared to the non-elderly, reflects the smaller percentage of this sector in the Egyptian population (3.7%) as the relatively low life expectancy (73 years). Even in the setting of prospective trials within the most developed countries where elderly represents 10% or more of its population, elderly representation in research remains low [8, 10, 11].

Generalizability of our results to CRC in Egypt is ensured by the similarity of population structure and human maturity index of the Gharbiah governorate to that of the Egyptian population at large and the comparability of GPBCR data to those from other sources particularly the well-developed hospital-based registry of the Egyptian National cancer Institute [6]. GPBCR data is included by the international Agency for Research on Cancer (IARC) in cancer incidence of five continents publications [15].

In conclusion, within the limits of this retrospective trial, elderly patients with CRC tend to have more rectal and non-metastatic cancers. They were more likely to have comorbidities and are less likely to receive chemotherapy particularly in the adjuvant setting. However, the OS and DFS were comparable to non-elderly. To improve treatment outcomes including survival in CRC in Egypt, a combination of a screening program and provision of the state of the art diagnostics and therapeutics is recommended. Physicians should not deny elderly patients effective therapies merely because of their chronological.

Acknowledgment

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Conflict of interest

The authors declare that there is no conflict of interest statement.

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