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Research Article

COLORECTAL CANCER IN PATIENTS YOUNGER THAN 40 YEARS: EXPERIENCE OF THE MOHAMED IV CENTER FOR THE TREATMENT OF CANCER

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ABSTRACT

Colorectal cancer (CRC) is the third most common type of cancer in the world. It's rare in younger adults, known as aggressive cancer. The aim of our study is to describe the epidemiological, clinical and therapeutic profile to young people compared of elderly adults.
Its comparative study of CRC in younger adults less than 40 years (G1) and elderly more than 40 years(G2) between 2014 and 2015, included all cases of CRC treated on Mohamed IV center for treatment of cancer.
330 patients were enrolled. (49 cases of G1 (14.1%) and 281 cases of G2 (85.1%).The sex ratio of 1.04 is noted. The first-degree history of CRC was reported in 11 cases in G1 (22.45 %) versus 25 in G2 (8.89 %) (p= 0.03).The primary location of CRC was rectum in G1 in 40.8 % of cases vs 51.6 % in G2. However, the sigmoid was the most common site of CRC in 2 groups.
Mucinous adenocarcinomas were found more in the group G1 (24.49% in G1vs 13.16 % inG2) (p=0.01).
Younger colorectal cancer (YCRC) is not a rare cancer in our country. Despite similar treatment patterns and survival outcomes, YCRC is more aggressive with poor prognosis.

INTRODUCTION

Colorectal cancer is the most frequent form of digestive cancers in the world; it comes in 3rd position in both sexes in the world it's considereda public health problem. In Morocco, the standardized incidence of colorectal cancer is 8.8 per 100 000 inhabitants per year for men and 10.6 per 100 000 inhabitants per year for women (RCRC, 2017); It occurs most often in elderly people (92% of colorectal cancers are diagnosed in people aged fifty years or older). People aged eighty or more still have a risk of colorectal cancer where 12.5% of cases are diagnosed after 85 years (Benson, 2007). In young subjects under 40 years, this entity is rare affecting 5% (Institute national du cancer, 2009), and known for it's poor prognosis with survival not exceeding 50% at 5 years (Tougeron, 2013). Its anatomoclinical and evolutionary features are not well known. The objective of this study is to identify the main epidemiological, clinical, histological, therapeutic characteristics, and prognosis of the colorectal cancer to young people compared to elderly people under our climate, in order to understand the reasons for poor prognosis.

Patients and methods

Population of study

This is a cross-sectional study conducted at the Mohamed VI Center for cancers treatment, spread over a two-year period from January 2014 to December 2015, collecting any patient with histologically confirmed colorectal cancer and divided according to age into two groups: G1 for less than or equal to 40 years and G2 for more 40 years. For the young subject, the age of 40 is considered by most authors as the border defining

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the young population in which this cancer is rare (Waterhouse, 2007).

The parameters studied were: sex, the age of onset of cancer, smokingbehaviour, alcoholism, a family history of colorectal cancer, the delay of consultation (a possible delay in diagnosis was evaluated by the duration of the symptoms preceding the diagnosis of this cancer), the clinical elements, the proportion of CEA (carcinoembryonic antigen), metastatic status, anatomopathological characteristics (the seat of tumor, the degree of parietal infiltration, the tumor stage, the degree of differentiation of the adenocarcinoma, the number of invaded ganglions) and finally treatments associated to the surgery (neo-adjuvant and adjuvant).The collection of variables was based on the patients' medical records and analysed using R software.

RESULTS

During the study period, 330 patients were treated at the Mohamed VI center of the treatment of cancers, which 49 were less than 40 years of age (15%). There is a slight male predominance, with a sex ratio of 1.04 in group 1 and 1.02 in group 2. The difference was not significant. The analysis of middle of residence, smoking and alcoholism did not find any significant difference between the two groups (Table 1).There was no personal history of colorectal cancer in both groups. The presence of a history of CRC in first-degree relatives was noted among 11 patients of the G1 group (22.45%) versus 25 in the G2 group (8.89%), this is statistically significant with a p-value of 0.03 (OR = 0, 50, 95% CI [0.211-1.185])(Table 1).

Concerning the G1 group, one patient (2%) had Hemorrhagic Rectocolitis (HRC).Eight patients had associated polyps (16.32%) of which two patients (4%) had polyps associated with familial adenomatous polyposis (FAP). For the G2 group, one patient had Lynch syndrome (0.35%) confirmed by molecular biology. One patient had HRC with Lynch's syndrome (0.7%).16 patients had associated polyps (5.69%), including two patients had FAP (0.7%),

Table 1 Lifestyle and history of cancer in the study population by age.

	Group G1 < 40 years N=49		Group G2 > 40 years N=281		
	Number	**Percentage**	**Number**	**Percentage**	**P value**
Sex					0.8
Man	25	51.02	142	50.53	
Woman	24	48.98	139	49.47	
Residence middle					0.6
Urban	41	83.67	218	77.58	
Rural	8	16.33	63	22.42	
Smoking status					0.08
Non-smoker	42	85.71	211	75.09	
Smoker	7	14.29	70	24.91	
Drinkingstatus					0.7
Yes	4	8.16	19	6.76	
No	45	91.84	262	93.24	
Family history of colorectal cancer					0.03
Yes	11	22.45	25	8.89	
No	38	77.55	256	91.10	
Family history of other types of cancers					0.8
Yes	6	12.45	38	13.52	
No	43	87.75	243	86.47	

In our study, the average delay of consultation in our study is of 6.5 months in the group1 vs9 months to the group 2 with extremes ranging from 7 days to 3 years.

Our results show that young people consult earlier: 78% of the patients in group 1, only 39% of the patients of group 2consultbefore 6 months.

On the clinical side, younger subjects report more with a transit disorders (G1: 65.31%, G2 55.51%, p = 0.1) weight loss (G1: 18.36%, G2 1.06%, p = 0.001), vomiting (G1: 14.28%, G2 1.42%, p = 0.001) and acute surgical abdomen (G1: 10.20%, G2 6.4%, p = 0.2).

Abdominal pain, rectal bleeding and rectal syndrome were more common in elderly subjects (Table 2).

Table 2 Clinical Modes of presentation of the colorectal cancer according to age

	Group G1 < 40 Years N=49		Group G2 > 40 years N=281		
	Number	**Percentage**	**Number**	**Percentage**	**P value**
Clinicalsigns abdominals pain					0.03
Yes	23	46.94	175	62.27	
No	26	53.06	106	37.72	
Rectal bleeding					0.001
Yes	21	42.85	235	83.62	
No	28	57.14	46	16.37	
Disturbances of transit					0.1
Yes	32	65.31	156	55.	
No	17	34.69	125	44.48	
Syndrome rectal					0.001
Yes	11	22.45	143	50.88	
No	38	77.55	138	49.11	
Weightloss					0.001
Yes	9	18.36	3	1.06	
No	40	81.36	278	98.93	
Vomiting					0.001
Yes	7	14.28	4	1.42	
No	42	85.71	277	98.57	
Surgicalsharp abdomen					0.2
Yes	5	10.20	18	6.40	
No	44	89.79	263	93.59	
Stage TNM					0.006
Stage I	14	28.57	51	18.15	
Stage II	20	40.81	77	27.40	
Stage III	10	20.40	86	32.03	
StageIV	5	10.20	36	22.42	

For the topographic distribution of colorectal cancers, the rectum is the most site frequent of tumors for both groups (40.8% for G1 vs 51.6% for G2). Moreover, the right colon was twice as affected in group 1 compared to group 2 (20.41% for G1 vs 10.67% for G2). This difference is not significant (p = 0.3) (Table 3).

Histopathological characteristics tumors in the both groups are dressed in the table II. According histology reports the Lieberkuhnian adenocarcinoma is the most frequent type in the both groups, (69.39 % of all tumorsin G1 vs 83% in G2, p=0,01).

On the other hand, the proportion of Mucinous adenocarcinomas was more frequent in young patients with a significant difference (24.49 % at G1 and 13.16 % at G2; p=0.01). The tumors were in most cases moderately differentiated are the majority with a proportion of 63.41% in

G1 vs 59.40% in G2 (p = 0.88). Undifferentiated adenocarcinomas represented a minority and similar in both groups (Table 3).

All patients benefited of an extension assessment including chest x-ray and abdominopelvic ultrasound. Abdominopelvic tomography was performed in 159 of G2 patients and 31 of G1 patients. Tumors have presented at a more advanced stage TNM (Stage II and III) for young people with a significant difference (p = 0,006).

The CRC was diagnosed at a metastatic stage 1/4 times in the elderly. The site of Metastasis was mainly hepatic (46.15% in G1 vs 64.04% in G2) and pulmonary in 20% of patients.

In terms of tumor markers, in G2 group, 53% of CRCs had high CAE at the time of diagnosis vs 35% in G1 and 42.5% in G2 had a high CA19-9 vs 28% in G1. The concentrations of CAE and CA 19-9 were significantly elevated in patients with stage IV CRCs compared to patients in stages II and III.

Table 3 Histopathological characteristics of colorectalstumours according to age

	Group G1 < 40 years N=49		Group G2> 40 years N=281		
	Number	Percentage	Number	Percentage	P value
Histological type					0.01
Lieberkhunian adenocarcinomas	34	69.39	234	83.27	
Mucinous adenocarcinomas	12	24.49	37	13.16	
Degree of differentiation					0.8
Differentiated well	10	27.77	72	30.76	
Moderately differentiated	21	61.11	139	59.40	
Not much differentiated or indistinct	5	11.89	28	11.96	
Vascular Emboles					0.07
Presents	17	34.69	71	25.26	
absents	32	65.31	210	74.74	
Perineuralneoplastic invasion					0.6
Presents	5	10.20	35	12.45	
absents	44	89.80	246	87.55	
Seat of tumour					0.3
Rectum	20	40.8	145	51.6	
sigmoïde Colon	14	28.57	71	25.26	
Left colon	4	8.16	24	8.54	
Right colon	10	20.41	30	10.67	
Transverse colon	1	2.04	11	3.91	
Aspect					0.7
Ulcérobourgeonning	30	61.22	191	67.97	
Infiltrating	12	24.48	67	23.84	
Burgeoning	16	32.65	13	4.62	
Metastasis					0.4
Presents	13	26.53	89	31.67	
absents	36	73.47	192	68.33	
Tumor markers					0.06
CAEhigh	17	34.6	149	53	
Ca 19-9 high	14	28.57	120	42.70	

In our study, the treatment protocols of colic cancer were in 51.72% in G1 and 83% in G2 by the combination of surgery and chemotherapy. Exclusive surgery was performed in 17.21% in G1 and 1.5% in G2 (p = 0.001), palliative chemotherapy in 31% of young people versus 15.44% in G2.

For rectal cancers, therapeutic protocols were preoperative radiotherapy associated with surgical treatment in 66% in G1 and 75% in G2. Postoperative radiotherapy was performed in 31.6% of G1 and 10% of G2, adjuvant chemotherapy in 73.3% of G2 and 39% of G1 (p = 0.007) and palliative care was performed in 3.3% in G1 and 11% in G2. Only two elderly cases were lost to follow-up (Table 4).

Table 4 Therapeutic modalities of colorectalstumours according to age

	Group G1 < 40 years N=49		Group G2 > 40 years N=281		
	Number	Percentage	Number	Percentage	P value
Therapeuticsmodalities					
Colicscancers	29		136		
Exclusive surgey	5	17.24	2	1.4	0.001
Surgery + chemotherapy	15	51.72	113	83.08	0.2
Palliative chemotherapy	9	31.03	21	15.44	0.04
Rectals cancers	20		145		
Preoperative radiotherapy+ Surgery	13	65	108	74.48	0.1
Previous resection	3	15	31	21.37	0.2
Abdominoperineal amputation	10	50	77	53.10	0.4
Surgery + postoperative radiotherapy	6	30	15	10.34	0.2
Adjuvante chemotherapy	14	70	57	39.31	0.007
Palliative chemotherapy	3	15	20	13.79	0.8
Palliative treatment	1	5	17	11.72	0.4

DISCUSSION

The incidence of colorectal cancer has increased dramatically in recent years. In Europe, the over 50 are not the only ones to run the risk of contracting a CRC. Incidence and mortality rates among young adults under 40 are increasing (Science Daily, 2009; Globocan, 2010).

Incidence rates of CRC increased by 22% between 2000 and 2013 and mortality rates increased by 13% in this population (Siegel, 2017).

The frequency of younger CRC is less than 5% in Europe.It varies between 19 and 36% in Africa: Egypt (31%) (Ramzya *et al*., 2015), Middle East countries: 25%, Saudi Arabia, Sudan and Iran: 17-36% and the other countries of Africa: 19% (South Africa) (Gado *et al*., 2014) and 31.5% (Nigeria) (Ibrahim *et al*., 2011).

In our study, the frequency of younger CRC was 15%. This figure is comparable to that found in the registry of cancers in the Greater Casablanca region for the period 2008-2012, which resulted in a young subject frequency of 12.83% (RCRC, 2017). This frequency is intermediate between the data of Europe and the countries of Africa. It reflects the demographic transition that Morocco knows. Indeed, Morocco has experienced a decline in the birth rate over the last ten years and an increase in the number of elderly people (aged 60 and over would be 11.5% in 2020 and 15.4% in 2030. The proportion of under-15s would increase from 31% in 2004 to 24.1% in 2020 and fall to nearly 20.9% by 2030 (RCRC, 2017).

The CRC occurs in our population in younger patients with an average age in the under 40 age group of 32.69. These numbers are also lower than that found in Canada, which is 38 years. There was a slight male predominance among young people of 51.02% according to a study carried out by Andrew in 2014, which noted a male predominance of 52.9%.

The etiopathogenesis of colorectal cancer is not apparently established, however, some risk factors appear to be able of

being incriminated. Around the world, smoking is the most confirmed and most frequent risk factor in digestive cancer, the same result is also found in Morocco (Aqodad *et al*., 2016). Botteri *et al*. (2008) showed that smokers had a 18% higher risk of developing CCR compared with individuals who had never smoked during their life.

In our study, smoking was found in 24.91% of elderly patients, compared to 14.29% of young people (p = 0.08). Tobacco use was exclusively for men in both groups. In addition, comparative studies of different populations tend to prove the effect of consumption of alcoholic beverages on the risk of developing colorectal cancers. According to WCRF / AICR 2011 (Bagny *et al*., 2015), the risk of CRC increases with the consumption of alcoholic beverages. However, alcohol consumption was rarely reported by our patients (8%), because we are in a Muslim country where the consumption of alcohol is prohibited by law for citizens of Muslim confession.

Several studies have shown the involvement of personal or family history of colorectal cancer, the proportion of patients with a family history of colorectal cancer is estimated to be 15% -20% (Viguier *et al.,* 2003). The proportion of young patients with a history of CRC is higher than that of the literature, it was noted in 22.45% of young patients vs 8.89% of the elderly. This rate can be explained either by the young age of our population or by a greater genetic predisposition to colorectal cancers in our undocumented population.

The diagnosis of colorectal cancer is often late. In our series, it was worn in all cases (100%) in front of symptoms. The advanced stage at the time of diagnosis makes this cancer a condition of poor prognosis. The mean diagnostic delay in the young was often between less than one month and six months in the Western series (Pocard *et al*., 1997; Kam *et al*., 2004; Zorluoqlu *et al*., 2004), which is less than the delay found in our study which was 6.5 months with extremes ranging from 7 days to 3 years. The elderly had a significantly longer time to the young subject.

The delay of the consultation was considered a factor of prognosis, the shorter the delay the better the prognosis. Lin *et al*. reported a five-year survival rate of 25, 16 and 0% in stages II, III and IV, respectively (Lin *et al*., 2005).

In our population, the delay diagnosis concerned the two age groups despite the presence of rectal bleeding, this would be on the one hand the lack of information of the patients with respect to the risks of colorectal cancer, on the other hand, the trivialization of symptoms, but especially access to the health system, socioeconomic level, geographical distance...

The main clinical signs of colorectal cancer of our young patients were abdominal pain, rectal bleeding and transit disorders according to the clinical symptomatology found in the various studies (Kam *et al*., 2004, Ferrari *et al*., 2008), as well as data from the Agency for the fight against cancer of British Columbia in 2011 [bleeding 52% and pain 50%] (Al-Barrak, 2011).

In clinical practice, young patients represents the transit disorders, bleeding and abdominal pain should be evaluated for colorectal cancer to allow for earlier diagnosis. Early detection may be the best way to improve their prognosis (Taggarshe *et al*., 2013).

On the other hand, it was noted in our study that the young subject had much more mucinous carcinomas than in elderly (24.49% vs 13.16% p = 0.01). This figure is comparable to that found in the Western series where colloid tumors represent 12% (Karsten *et al*., 2008). This type of cancer seems to have a worse prognosis due to the more aggressive characteristics of the tumor, due in particular to a greater frequency of mucinous types (Bagny *et al*., 2015).

Compared to the totality of CRC, it is reported that mucinous carcinomas occurs most often at a young age, this cancer is not only a distinct clinical and pathological entity, but also a separate genetic entity characterized by an increased frequency of K-ras gene mutations and microsatellite instabilities, as well as a decrease in P53 expression and mutations in the P53 gene. On the other hand, the proportion of adenocarcinomas moderately differentiated, are the majority in our series with proportions similar to those found in the literature.

These histological varieties have undoubtedly a poor prognosis; they increase the risk and the rapidity of invasion, of lymph node metastases and promotelocoregional recurrences.

Moreover, in our young population, the frequency of rectal and sigmoid colonic sites was high. Several series have reported the predominance of rectal and sigmoid involvement in young subjects studies (Al-Jaberi *et al*., 2003, Kam *et al*., 2004, Zorluoglu *et al*., 2004), while others have shown a higher frequency of right colic sites (Karsten *et al*., 2008).

In our series, the frequency of the right locations was higher in the group1 compared to the group 2 (20.41% of the young vs. 10.64% of the elderly). This high percentage of right colon cancers in young people may be related to the particular prevalence of HNPCC syndrome cases. The search for MSI status should be systematic in this population.

Young subjects had a localized TNM stage (stage II and III) more frequent than elderly subjects with a significant difference p = 0.006. Stage IV was found in 10.20% of G1 and 22.42% of G2 with metastases mainly involving the liver and lungs.

While several studies have reported a high frequency of Dukes' C and D stages of colorectal cancer in young subjects (Sahraoui *et al*., 2000; Al-Jaberi *et al*., 2003; Tohmé *et al*., 2008).

Lin *et al*. (2005) reported a frequency of 24% of the Dukes' III stages and 66% of the IV stages.

The young subject often arrives at a stage already advanced at the time of diagnosis, this can be explained by a delay in consultation by the patient, as most patients consult a shorter period of time than the elderly, but rather by a more aggressive tumor profile.

The biological evaluation is carried out in order to evaluate the impact of colorectal cancer and/or indicate to surgical therapies for the patient.

On the level of tumor markers, the concentration of CAE and CA 19-9 increases with the stage of tumor extension, they are

more sensitive to detect hepatic, peritoneal and pulmonary metastases.

In our series in the elderly, 53% of CRC have high CAE at diagnosis vs 35% of young people and 42.5% of older people have high CA 19-9 vs 28% of young people. Despite its lack of specificity. The determination of CAE is a valuable addition to clinical decision-making in patients with colorectal cancer. According to Al-Shuneigat *et al*. CAE and CA19-9 are interesting at various stages of CRC or can be used as prognostic factors (Al-Shuneigat *et al*., 2011). The preoperative value of CAE may be useful in distinguishing those patients who are at high risk for recurrence from non-invasive lymph node involvement.

For colon cancer, treatment in 83% in the elderly and 50% in the young was a combination between surgery and chemotherapy. Palliative chemotherapy was performed in 33% in young people versus 15.44% in the elderly. This figure joins the American observational series, which showed that only 50% of elderly patients had adjuvant chemotherapy compared with 87% in younger patients (Kahn *et al*., 2010).

Often disputed, the principles of management of colorectal cancers in young patients are the same as those of elderly patients. In the elderly, therefore, the therapeutic decision will depend not only on the nature and the tumor extension, but also on the patient as a whole (cardiovascular pathologies, disorders of higher functions and / or physiological changes related to their age).

CONCLUSION

The proportion of youngpatients with colorectal cancers in Morocco seems to be high because of our younger population, genetic and environmental factors may explain this higher frequency compared to Western countries. It is a poor prognosis; this is mainly due to the advanced stage of the disease at the time of diagnosis and the frequent occurrence of biologically aggressive tumors. The family history of this cancer proved to be one of the most important predictors of colorectal cancer for the young patients.

The prognosis of colorectal cancer has improved dramatically in recent years through earlier diagnosis, but it is still bleak in our context given the delayed diagnosis, hence the value of screening for all people at risk, a genetic study by molecular biology in the presence of predisposing antecedents is essential. The appearance of a typical digestive symptomatology of rectal bleeding, abdominal pain or transit disorder should raise the possibility of colorectal cancer, even for young people.

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