East-central Tunisian patients with colorectal adenocarcinoma: a comparative study of the clinicopathological features between patients under 50 years of age and older patients

Patients du centre-est Tunisien ayant un adénocarcinome colorectal: étude comparative des caractéristiques cliniques et anatomopathologiques entre les patients âgés de moins de 50 ans et les patients plus âgés

Mohamed Salah Jarrar[1], Malek Barka[1], Mohamed Zied Ben Abdessalem[1], Radhouane Toumi[2], Soumaya Mrabet [3], Nihed Abdessayed[4], Mohamed Hedi Mraidha [1], Asma Sghaier[1], Fehmi Hamila[1], Sabri Youssef[1]

1. *Department of General and Digestive Surgery - Farhat Hached University Hospital - Sousse / Faculty of Medicine of Sousse*
2. *Intensive Care Unit - Farhat Hached University Hospital - Sousse / Faculty of Medicine of Sousse*
3. *Department of gastroenterology- Farhat Hached University Hospital - Sousse / Faculty of Medicine of Sousse*
4. *Department of pathology- Farhat Hached University Hospital- Sousse/ Faculty of Medicine of Sousse*

Abstract

Introduction: Colorectal cancer is a major public health problem. In younger patients, its incidence continues to rise and its prognosis appears to be worse. Its treatment is based on curative surgery associated with neo-adjuvant and adjuvant therapies.

Aim: To describe the clinical and pathological characteristics of colorectal cancers in young patients.

Methods: In this monocentric cohort study, we retrospectively analyzed the clinicopathological features in colorectal cancer patients who underwent treatment from 2002 to 2014. Data of younger (group A, ≤50 years) vs older (group B, >50 years) patients were compared.

Results: Two hundred and sixty-six patients met inclusion and non-inclusion criteria. The younger and older groups consisted respectively of 25.2% and 74.8% of patients. Both groups were comparable regarding the symptom presentation and duration. Synchronous tumors were more frequent amongst the group A (10.7% vs 1.0%, p = 0.024). Preoperative staging showed a higher frequency of tumors classified as advanced stage (stages III and IV) in the group A (p = 0.001). The patients of group A were diagnosed with a higher proportion of poorly differentiated or undifferentiated adenocarcinomas (13.4% vs 3.5%, p = 0.005), the mucinous character was also more frequent in the group A (28.4%). According to the pTNM (tumor, nodes and metastases) classification, tumors were more advanced in the group A than in group B (80.6% vs 48.7%, p < 0.001),

Conclusion: This study revealed that colorectal adenocarcinomas in the younger patients, compared to the older ones, were more aggressive with a higher proportion of poorly differentiated or undifferentiated adenocarcinomas, more often mucin production and more advanced tumors.

Keywords: Colorectal cancer; Young patients; Prognosis; Early onset

Résumé

Introduction : Le cancer colorectal constitue un problème majeur de santé publique. Chez les jeunes patients, son incidence ne cesse d'augmenter et son pronostic semble s'aggraver. Son traitement repose sur la chirurgie curative associée à des thérapies néo-adjuvantes et adjuvantes.

Objectif : Etudier les caractéristiques cliniques et anatomopathologiques des patients atteints de cancers colorectaux chez les jeunes patients.

Méthodes : Dans cette étude de cohorte monocentrique, nous avons analysé rétrospectivement les caractéristiques cliniques et anatomopathologiques chez les patients atteints de cancer colorectal ayant été pris en charge entre 2002 et 2014. Les données des patients jeunes (groupe A, ≤50 ans) et plus âgés (groupe B, >50 ans) ont été comparées.

Résultats : Deux cent soixante-six patients répondaient aux critères d'inclusion et de non-inclusion. Les groupes A et B représentaient respectivement 25,2% et 74,8% des patients. Les deux groupes étaient comparables en ce qui concerne la présentation et la durée des symptômes. Les tumeurs synchrones étaient plus fréquentes chez les patients du groupe A (10,7% contre 1,0%, p = 0,024). La stadification préopératoire a montré une fréquence plus élevée de tumeurs diagnostiquées à un stade avancé (stade III et IV) dans le groupe A (p = 0,001). Les patients du groupe A ont été diagnostiqués avec une proportion plus élevée d'adénocarcinomes peu différenciés ou indifférenciés (13,4% contre 3,5%, p = 0,005), le caractère mucineux était également plus fréquent dans ce groupe (28,4%). Selon la classification pTNM (tumor, nodes and metastases), les tumeurs étaient plus avancées dans le groupe A comparativement au groupe B (80,6% contre 48,7%, p < 0,001),

Conclusion : Cette étude a révélé que les cancers colorectaux chez les patients jeunes étaient plus agressifs avec une plus grande proportion d'adénocarcinomes peu différenciés ou indifférenciés, plus souvent une production de mucine et des tumeurs plus avancées.

Mots clés : Cancer colorectal ; Jeunes patients ; Pronostic ; Diagnostic précoce

Correspondance

Mohamed Salah Jarrar
Department of General and Digestive Surgery - Farhat Hached University Hospital - Sousse / Faculty of Medicine of Sousse
Email: hammadi.jarrar@gmail.com

INTRODUCTION

Colorectal cancer (CRC) is the fourth cause of death by cancer worldwide counting more than 600000 death per year [1]. As a general rule, CRC is considered to affect mainly old people, with more than 90% of patients being diagnosed after 50 years of age [2]. Meanwhile, the incidence of CRC in people younger than 50 years has appeared to be increasing [3-7]. Currently, CRC represents the fourth cause of death by cancer in younger patients [7]. CRC in younger patients is increasingly becoming a topic of interest in medical literature [1, 3, 7-9]. Sporadic CRC is included, in rare cases (ie; less than 15%) as part of a genetic hereditary syndrome [6].While some studies consider young age as a factor of bad outcome [8], others haven't found a difference in their rate of survival compared to the older [9].The aim of the study was to describe the clinical, radiological and pathological characteristics of CRC in the younger population compared to older people, in order to identify factors affecting its prognosis. we tried to verify whether young age is associated with poor prognostic factors in colorectal adenocarcinoma.

METHODS

Study design: This was a transversal retrospective monocentric study conducted over 13 years, grouping all patients who have been operated on for colorectal adenocarcinoma between January 1st 2002 and December 31st 2014, in the Department of General and Digestive Surgery in Farhat HACHED University Hospital of Sousse. The study was approved by the ethical committee of the hospital (Approval number: CER: 25-2022).

Population: We included all patients who were treated in the aforementioned department for colorectal adenocarcinomas diagnosed between January 2002 and December 2014. Patients presenting with other types of colorectal tumors were not included in this study (eg: lymphomas, sarcomas, neuroendocrine tumors, epidermoid carcinomas, melanomas …). All CRC occurring in the context of familial cancer were excluded (ie: familial adenomatous polyposis and hereditary non polyposis colorectal cancer). Incomplete medical charts (ie: lack of pathological report) were excluded from the study. A regular smoker is a person who reports smoking at least one cigarette (or equivalent) per day [10].

Applied protocol: We divided the patients into two groups according to the age: Group A: patients who were 50 years of age or younger; and Group B: patients who were older than 50 years of age. We conducted a comparison between the two groups. Clinical, radiological and pathological data were compared between the two groups, demonstrating the progression stage and aggressivity of the tumor.

Collected data: The collected data were: sex, age, medical and surgical history, clinical presentation, radiological findings, endoscopic data, operative techniques, histological data, and postoperative complications. Imaging was performed to assess extension (ultrasound, computerized tomography (CT-scan) and magnetic resonance imaging (MRI)).

Statistical analysis: We entered the data on the software package Epi Info (version 8). Descriptive data were expressed as counts and proportions for categorical variables. Continuous variables, not normally distributed, were presented as median with interquartile range (IQR). Statistical analysis was performed using the Chi-squared test or the exact Fisher test for comparison of categorical variables and the Mann-Whitney U test for continuous variables. The differences were considered significant at a two-sided p-value < 0.05.

RESULTS

During the study period, a total of 451 patients were operated on for a colorectal adenocarcinoma. Two hundred and sixty-six patients met inclusion and non-inclusion criteria, thus representing the study group. Among the 266 patients, 67 (25.5%) were 50 years of age or younger (group A) and 199 (74.8%) were older than 50 years of age (group B). The demographic, clinical, and tumor characteristics of patients according to the age categories are represented in **Table 1**.

The difference between both groups was not statistically significant relating to the symptom presentation and duration. No significant difference was discerned between both groups concerning positive family history of any cancer.

No statistical difference was observed between the two groups concerning family history of cancer.

Regarding endoscopy results, there was no statistically significant difference between groups A and B as to the site of the tumor.

There was no significant difference between both groups concerning the size of the tumor, the presence of metastasis and whether or not the mesorectum was affected in the case of rectal tumors.A statistically significant difference was noted between groups A and B as to the presence of lymphadenopathy. There was also a significant difference regarding the estimated tumor, nodes and metastases (TNM) stage between both groups. The tumor was judged as being at an advanced stage (III or IV). There were no statistical differences between the two groups regarding post operative complications (**Table 2**). Histological characteristics of tumors according to the age categories are represented in **Table 3**. Pathological findings revealed more undifferentiated or poorly differentiated tumors in group A than in group B. The existence of a mucinous contingent was significantly more present within group A. There was no significant difference between groups concerning the presence of vascular emboli or perineural invasion. The tumor was statistically more frequently diagnosed at an advanced stage (III or IV) within group A compared to group B.

Table 1. Patients demographic and clinicopathological characteristics based on age group.

Variable	Category	Total n = 266	Group A≤50 years n = 67	Group B n = 199 >50 years	p-value
Sex, n (%)	Female	119 (44.7)	36 (53.7)	83 (41.7)	0.087 (1)
	Male	147 (55.3)	31 (46.3)	116 (58.3)	
Symptom, n (%)	Abdominal pain	148 (55.6)	41 (61.2)	107 (53.8)	0.29 (1)
	Melena/ rectal bleeding	118 (44.4)	33 (49.3)	85 (42.7)	0.351 (1)
	Diarrhea	37 (13.9)	9 (13.4)	28 (14.1)	0.979 (1)
	Consipation	87 (32.7)	22 (32.8)	65 (32.7)	0.896 (1)
	Alternating bowel patter	57 (21.4)	18 (26.9)	39 (19.6)	0.21 (1)
	Occlusion	49 (18.4)	14 (20.9)	35 (17.6)	0.546 (1)
Family history of cancer, n (%)		9 (3.4)	3 (4.5)	6 (3.0)	0.567 (2)
Smoker, n (%)		91 (34.2)	18 (26.9)	73 (36.7)	0.143 (1)
Diabetes mellitus, n (%)		48 (18.0)	4 (6.0)	44 (22.1)	**0.003** (2)
Arterial hypertension, n (%)		65 (24.4)	4 (6.0)	61 (30.7)	**<0.005** (2)
Coronary heart disease, n (%)		16 (6.6)	0 (0.0)	16 (8.0)	**0.0017** (3)
Interval between symptom onset and diagnosis, median (months) and extreme values		6 (1-18)	5 (1-18)	6 (1-18)	0.24 (3)
Tumor location, n (%)					0.44 (1)
	Right Colon	61 (22.9)	15 (22.4)	46 (23.1)	
	Left Colon	109 (41.0)	32 (47.7)	77 (38.7)	
	Rectum	96 (36.1)	20 (29.9)	76 (38.2)	
Tumor size, median (cm) and extreme values		7 (2-15)	7 (2-15)	7 (2-15)	0.912 (3)
TNM stage, n (%)	I	-	-	-	-
	II	93 (35.0)	14 (20.9)	79 (39.7)	**0.001** (1)
	III	98 (36.8)	31 (46.3)	67 (33.7)	0.131 (1)
	IV	47 (17.7)	18 (26.9)	29 (14.6)	**0.04** (1)
	III+ IV (advanced)	145 (54.5)	49 (73.2)	96 (48.3)	**0.001** (1)
	Unknown	28 (10.5)	4 (5.9)	24 (12.0)	

TNM: Tumor, Nodes, Metastases
Quantitative data were median (interquartile)
(1) Chi-squared test
(2) Exact Fisher test
(3) Mann-Whitney U test

Table 2. Post-operative complications based on age group

Complications	Total n = 266	Group A≤50 years n = 67	Group B>50 years n = 199	p-value
Medical complications, n (%)				0.46 (1)
Pulmonary infection	5 (1.9)	1 (1.5)	4 (2.0)	
Urinary infection	16 (6.0)	6 (8.9)	10 (5.0)	
Venous thromboembolism	2 (0.7)	0 (0.0)	2 (1.0)	
Specific complications, n (%)				0.136 (1)
Wound infection	19 (7.1)	4 (6.0)	15 (7.5)	
Postoperative peritonitis	23 (8.6)	2 (3.0)	21 (10.5)	

(1) Exact Fisher test

Table3. Histological characteristics of tumors based on age group

Variable	Category	Total n = 266	Group A≤50 years n = 67	Group B>50 years n = 199	p-value
Tumor differentiation, n(%)	Well	61 (23.0)	14 (20.9)	47 (27.3)	0.466 (1)
	Moderately	157 (59.0)	39 (58.2)	118 (59.3)	0.413 (1)
	Poor/ Undifferentiated	16 (6.0)	9 (13.4)	7 (3.5)	**0.005** (2)
	Unknown	32 (12.0)			
Mucin production, n(%)		37 (13.9)	19 (28.4)	18 (9.0)	**<0.001** (1)
Vascular invasion, n(%)		41 (15.4)	12 (17.9)	29 (14.6)	0.642 (1)
Perineural invasion, n(%)		39 (14.6)	13 (19.4)	26 (13.1)	0.280 (1)
TNM stage, n(%)	I	5 (1.9)	2 (3.0)	5 (2.5)	0.893 (2)
	II	81 (30.5)	7 (10.4)	74 (37.2)	**<0.001** (2)
	III	108 (40.6)	38 (56.7)	70 (35.2)	**0.005** (1)
	IV	43 (16.2)	16 (23.9)	27 (13.5)	0.075 (1)
	III+ IV (advanced)	151 (56.8)	54 (80.6)	97 (48.7)	**<0.001** (1)
	Unknown	27 (10.8)			

TNM: Tumor, Nodes, Metastases
(1) Chi-squared test
(2) Exact Fisher test

DISCUSSION

The results suggest that in young patients, CRCs have a worse prognosis. Synchronous tumors discovered endoscopically were more prevalent in younger patients. These patients more frequently had lymphadenopathies discovered on the CT. The group of younger patients had high rates of advanced TNM stages (III and IV) on imaging. Likewise, they received more postoperative chemotherapy. Regarding pathological characteristics, the group of younger patients was distinguished histologically by a predominant undifferentiated or associated to a mucinous component typing, they also had a more severe lymphatic node extension and more advanced pTNM staging. Our study focuses on CRC which is a trending topic and a serious issue of public health [1]. Although its incidence amongst younger patients is rising, CRC is still generally considered a disease of the old patient [9]. Thus, CRC in younger patients is increasingly becoming a subject of major interest in medical literature [1-3, 6-9].

Demographic and clinicopathological data

Studies dealing with this topic are controversial as to its prognosis and pathological peculiarities [6-9]. A few studies in Tunisia have been conducted in order to analyze particularities of CRC in younger patients [11]. In our study, we attempted to establish a status report regarding this issue by pointing out epidemiological, clinical, therapeutic and prognostic characteristics of CRCs in young adults on a cross section of the population in the east-center of Tunisia. The main limitation of the study was a methodological one. As a matter of fact, it is a retrospective study, carried out by data collected from patients' medical charts onto a data collection sheet. Some of the charts were missing information and thus not completely exploitable. The lack of data from medical charts resulted in a reduction of size of the population (from 451 to 266; 59%). Furthermore, some of the operative reports were not clear. In fact, there was no standardization regarding the reported descriptive data during surgery. Lastly, the data analysis concerning morbidity and mortality were limited due to a number of patients lost to follow-up after surgery.

Although most studies define young adults as being 40 years old or less [2, 12-16], most recent studies set the age limit at 50 years of age [1, 3, 5-7, 11, 17-24], and others set it as 45 years of age [25]. We set 50 years of age as the limit seen as it is the recommended age for initial screening of CRCs in most screening programs [26]. Over the 2002-2022 period, CRC are declining in most occidental countries [4]. However, the incidence of CRC amongst young adults has been increasing [2-4]. In the United States of America, authors have predicted an increase in the frequency of rectal cancer, by 2030, of 124.2% in patients aged between 20 and 34 years old and of 46% in patients aged between 35 and 49 years old.

In Tunisia, Missaoui et al. [11] analyzed pathological characteristics of CRCs in the center of Tunisia over a period of 15 years (1993-2007). In his study, the frequency of CRCs in patients aged younger than 50 years of age was 29.3%. In our study, the frequency of CRCs in patients aged younger than 50 years of age was 25.2%, which complies with the data cited in the literature.

Most studies concentrating on younger patients, ours included, haven't established a significant difference between these patients according to sex [12].

Inaugural symptoms of CRC in young adults do not differ with those in old patients [8, 9, 11, 12]. Neither does data collected from physical examination [14]. Most studies suggested a belated diagnosis of CRC in young patients. Such delay is mainly attributed to the lack of knowledge of the disease's symptoms, which would explain a considerable delay of a first consultation.

In about 20% of these patients, the delay is due to a problem of medical care in front-line medical services [1, 12, 19].

Most published studies noted that the rectum and left colon are the most common locations of CRC in young adults [12, 19, 27], which are in occurrence with our results. A study carried out by Nath et al. [15] states that, compared to the older patients, the younger ones had a higher rate of tumors located at the bottom third of the rectum, which has a poor prognosis. At the moment of diagnosis, lymphatic nodes involvement seems to be more frequent in younger patients compared to the older.

In a study conducted by Mitra et al. [24] including 246 patients operated on for rectal cancer of which 136 were younger than 50 years of age, all patients seen for follow up had a pelvis MRI scan as part of assessment of extension. It was demonstrated that lymphadenopathies were visible in 73.8% of the younger patients compared to 53.1% of the older patients, with a significant difference (p=0.001). Likewise, Lino Silva et al. [16] showed that 54.2 % of young patients compared to 39.1% of the older patients had evidence of lymphatic nodes involvement in imaging (p=0.048). Our study showed that at the time of diagnosis, lymphadenopathies were more frequently visible in younger patients compared to the older, with a significant difference.

The initial staging is very important in the management of CRC since the therapeutic choices depend on the stage of the disease at the time of diagnosis [4]. CT-scan is recommended for the assessment of loco-regional extension of colon cancer [28]. As for rectal cancer, MRI is recommended for loco-regional staging [28]. The most commonly used classification in Northern America is the TNM staging system of the American Join Committee on Cancer [29]. Most studies concluded that young patients had a more advanced TNM stage preoperatively [5, 16, 19, 24]. Chen et al.'s study [19] showed more frequent advanced preoperative tumors stages (stages III and IV) in the group of younger patients compared to older ones (72.0% vs 63.0% ; p=0.03). Likewise, Lino Silva et al.'s work [16] revealed that young adults were more likely to be diagnosed with advanced stages of CRC, without a significant difference between younger and older patients (54.2% vs 44.2%; p=0.54). Wang et al.'s study [5] demonstrated that younger patients presented fewer early stages of tumors (stages I and II) and more advanced stages (stages III and IV) when compared to older patients, the difference was significant (p<0.001). Our work's findings were consistent to prior data.

Post operative complications

Studies investigating postoperative morbidity in young patients are rare [6, 8, 13, 18]. The majority of published papers showed very low, sometimes nil, rates of preoperative morbidity and premature preoperative mortality in younger patients who were mostly in good condition overall [6, 13, 18]. Such results were found in studies by Schellerer et al. [18], Pocard et al. [13].

Histological data

Admittedly, many authors described the absence of significant difference in the size of the tumor between younger and older patients [27]. However, most studies, including the present study, showed a higher rate of undifferentiated or poorly differentiated tumors, described as high grade, in younger patients compared to older patients [2, 5, 6, 8, 15]. A higher rate of mucinous cancers in young patients than in older ones has also been noted in many studies [5, 12, 18, 20, 30, 31]. Our work's findings are consistent with the data of the literature: the mucinous aspect was more frequent in the group of younger patients compared to older one (28.4% vs 18.0%, respectively) with a statistically significant difference (p<0.005).

Vascular embolisms and perineural tumoral invasion are also more frequent in younger patients in comparison to older ones [30]. In the present study, these two factors were noted at similar rates between the younger and older patients. As for the wall extension, many authors objectified a high rate of locally advanced tumors (grades pT3 and pT4) in younger patients [4, 15, 25]. Matuchansky et al. [4] showed that younger patients had a higher rate of tumors grades pT4. The difference between the two age groups was significant (p=0.0267). In Kim et al.'s study [25], younger patients were found to have a higher rate of wall invasion graded pT4 compared to older patients (19.6% vs 13.7%; respectively, p<0.001).The majority of studies revealed a higher rate of lymphatic node involvement at the time of positive diagnosis of CRC, amongst younger patients [3, 17]. Amri et al. [21] demonstrated that lymphatic node involvement was found more in younger patients compared to older patients (54.6% vs 39.4%; p=0.02). In Yang et al.'s research [31], 50.6% of patients less than 45 years old presented lymphatic node involvement versus 43.0% of older patients (p=0.002). Yeo et al. [32] showed a difference of the extent of lymphatic node involvement between the two age groups with a higher rate in younger patients (p=0.001).

In consequent, most authors describing younger patients operated on for CRC, demonstrate a higher rate of advanced pTNM stages [3, 20-22]. Amongst these authors, Taggarshe et al. [22] showed that more advanced stages of the disease (stage III and IV) were more noted in young patients. In addition, You et al. [20] used their national Center Database to analyze clinical and pathological characteristics of patients younger than 50 years of age who had CRC. In his study, younger patients had a higher rate of advanced stages of cancer than older patients (colon cancer: 63.4% vs 49.0% ; p<0.01 ; rectal cancer: 57.3% vs 46.2% ; p<0.01). Our study showed findings that are consistent with the literature. In fact, stage III of pTNM classification was noted in 60.3% of younger patients and 39.8% of older ones (p=0.005). Also, more advanced stages (stages III and IV) were noted at a higher rate in younger patients compared to older patients (85.7% vs 55.1%; respectively, p<0.001).

CONCLUSION

CRC of the younger patient has particular pathogenic, clinical and pathological characteristics giving it a poor prognosis. Thereby, it is critical that its medical management is conceived in a multidisciplinary environment. Unfortunately, CRC in younger patients is burdened with a considerable delay in diagnosis. Mucinous colloid carcinomas as well as poorly differentiated and undifferentiated adenocarcinomas are common, and the histological grades at the moment of diagnosis are oftenly advanced. Colorectal cancers remain particularly severe with a poor prognosis in young adults, despite diagnostic and therapeutic progress, hence the need to insist on public health education and on screening especially for predisposed individuals in hope of early diagnosis, which is the only hope for curative therapy and better chance of survival.

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