Clinical and Biological Profile of Metastatic Colorectal Cancers Treated at the Bejaia University Hospital Center. About a Series of 93 Patients

Chahira Mazouzi
Medical Oncology University, University Hospital of Béjaia, Algeria

Rachida Afis
Medical Oncology University, University Hospital of Béjaia, Algeria

Radia Benyahia
Diagnostic Radiology University, CPMC Algiers, Algeria

Kamel Hail
General Surgery University, Mustapha University Hospital of Algiers, Algeria

Nabil Blik
Nephrology, University of Béjaia, Algeria

Abstract
In Algeria, the incidence of colorectal cancer has risen alarmingly, ranking it as the second most common cancer. Our study focused on 93 individuals with metastatic colorectal cancer diagnosed at the CHU of Bejaia between January 2018 and April 2022. Our aim was to describe the clinical and molecular profiles of these patients, as well as associated risk factors. The results of the epidemiological study show a steady increase in the incidence of metastatic colorectal cancer, a male predominance (sex ratio of 2.7) and an average age of 63 years. Most patients had few known risk factors for colorectal cancer.

Clinical symptoms were dominated by rectal discharge, abdominal pain, iron-deficiency anemia, and transit disorders. Nine patients underwent emergency surgery for intestinal obstruction.

Anatomopathological study revealed a predominance of liberkühnian adenocarcinomas, mainly well-differentiated. The most frequent primary location was the left colon. Metastases were most frequently found in the liver (63% of cases).

Molecular analysis revealed mutations in at least one gene involved in colorectal cancer in 62.4% of patients. The most frequent mutation was in RAS, present in 37.6% of cases.

Introduction
Colorectal cancer is a public health problem due to its frequency and severity. It is the third most diagnosed cancer in the world, with around 1.8 million new cases each year, after lung cancer and breast cancer [1]. In Algeria, the wilaya of Béjaia is particularly affected by colorectal cancer, with the highest number of cases recorded in the cancer registries of the East and South-East regions in 2015. According to the WHO, between 30% and 50% of cancer deaths could be avoided by reducing or removing major risk factors and implementing prevention strategies based on existing evidence [2]. When it comes to colorectal cancer, approximately 15-30% of patients with this disease are diagnosed at the metastatic stage. This means that if effective prevention measures were put in place to reduce the risk factors associated with this disease, a significant percentage of cases could be avoided. Additionally, if early detection of colorectal cancer was improved, this could help identify metastatic cases at an earlier stage, thereby increasing the chances of treatment and survival. Hence the need for careful research and data collection to better understand colorectal cancer in the Béjaia region with a view to reducing the morbidity and mortality of this disease. However, despite its significant impact on our population, few studies have been carried out to define the clinical and molecular profile as well as the
therapies available at the university hospital center to manage colorectal cancer in the metastatic situation. This issue raises several key questions:

- What are the clinical profiles of patients with metastatic colorectal cancer in the wilaya of Béjaïa, particularly in terms of age, sex, risk factors and clinical symptoms?
- What is the prevalence of common molecular alterations in metastatic colorectal tumors in this region?

**Primary Objective**

- Describe the clinical and molecular profiles of patients with metastatic CRC treated in the oncology department of Béjaïa University Hospital from January 2018 to April 2022.

**Secondary Objectives**

- Describe the risk factors for colorectal cancer in patients with metastatic CRC treated in the oncology department of Béjaïa University Hospital from January 2018 to April 2022.

**Methodology**

**Patients and methods**

Our study focused on the files of patients suffering from colorectal cancers, collected in the oncology department during the period January 2018-April 2022. The study we undertook is a descriptive study focused on patients with metastatic colorectal cancer treated at the University Hospital of the wilaya of Bejaia between January 2018 and April 2022. The inclusion criteria are:

- Male or female patients aged over 15 years and 11 months, suffering from primary cancer of the colon and/or rectum at the metastatic stage, treated at the University Hospital of the wilaya of Bejaia.
- The positive diagnosis of colorectal cancer was made based on the pathological data.
- The anatomopathological types included in our study are adenocarcinomas.

Data collection was done passively from the archives of the oncology department, with a study of patients' medical files in order to collect the different parameters on the epidemiological sheet previously developed.

The analysis of the results was carried out using SPSS 20 software and EXCEL version 2013. It included a descriptive analysis with calculation of frequencies. The results were expressed as a percentage for qualitative variables and as an average for quantitative variables. They are reported in tables or represented in the form of a bar or histogram or sectors.

**Results**

From January 2018 to April 2022, 93 cases of metastatic colorectal cancer were evaluated during this period at the University Hospital of the wilaya of Bejaia. Representing more than a third of colorectal cancer at all stages. For both sexes combined, we note that the highest incidence rate of patients with metastatic colorectal cancer was recorded in 2021 with a percentage of 30.11%. According to the results, we see that the gender distribution indicates a male predominance with a sex ratio (M/F) of 2.72.
A peak frequency is observed in the population aged 60 to 70 years for males with 25 cases out of 68 or (36.8%) of the male population. While among women the most dominant age group is 50 to 60 years old with a percentage of 28% of the female population. The results show that 90% of our population had no family members up to the second degree affected by colorectal cancer. In the 10% of patients with a family history of colorectal cancer, 4% were first-degree relatives and 6% were second-degree relatives.

Figure 4: The Distribution of Patients with Metastatic Colorectal Cancer by Age and Sex at the University Hospital of the Wilaya of Bejaia Between 2018-2022

We note that 57% of our study population was non-smoking. The proportion of smokers represented 29.0% of the cases recorded, tobacco consumption exclusively concerned men. Smoking tobacco is the tobacco consumed by the majority of smoking patients, but the others consumed both smoking tobacco and chewing tobacco. 14% did not have sufficient data about their tobacco consumption. Among the 93 cases studied, only 80 had sufficient data about their alcohol consumption; among them, 16% were consumers. In our study population, 64% of patients had normal weight and 14% were overweight.

Figure 6: Cases of Metastatic Colorectal Cancer According to Exposure to Smoking at the University Hospital in the Wilaya of Bejaia Between 2018-2022

Diagnostic
Straight bleeding represents the major symptom, revealing the disease in nearly 40.9% of cases, followed by abdominal pain in 32.3% of cases and weight loss in 30.1% of cases. In 4.3% of cases, colorectal cancer was not responsible for any symptoms, we then speak of a chance discovery. For the tumor site, three sites were determined: right colon, left colon and rectum. We note in our series that the left colon is the most frequent tumor site with 49.5% of cases, followed by the rectum with 30.1% of cases and finally the right colon with 20.4% of cases. The proportion of cancers in the proximal colon, distal and rectum is respectively 19.1%, 47.1% and 33.8% in men and 24%, 56% and 20% in women. The left colon remains the most common location in both sexes combined.
Figure 7: Representation of Cases of Metastatic Colorectal Cancer According to the Revealing Signs at the University Hospital of the Wilaya of Bejaia Between 2018-2022

Figure 8: Distribution of the Primary Site of the Colorectal Tumor According to Sex in Patients with Metastatic CRC at the University Hospital of the Wilaya of Bejaia Between 2018-2022

Right colon: Cancers of the right colon were most often revealed by abdominal pain in 10.75%, followed in 8.6% of cases by weight loss and 6.5% by chronic iron deficiency anemia. Melenas were found in 5.3% of cases.

Left colon: Cancers of the left colon were mainly revealed by rectal bleeding in 21.5%, followed by abdominal pain in 16.1%, weight loss in 11.8% of cases. An intestinal obstruction was the cause of the diagnosis in 9.6% of cases.

Figure 9: Circumstances of Discovery in Patients with Metastatic Right Colon Cancer at the University Hospital of the Wilaya of Bejaia Between 2018-2022

Figure 10: Circumstances of Discovery in Patients with Metastatic Left Colon Cancer at the University Hospital of the Wilaya of Bejaia Between 2018-2022
Rectum: Rectal cancers were also revealed by rectal bleeding in 18.27%, a rectal syndrome was present in 8.6% of cases. Lieberkhunian adenocarcinoma is the only histological variety revealed by the biopsies in our series. Well-differentiated adenocarcinomas are the majority in our series, they represent 64.5% of cases of Lieberkhunian adenocarcinomas. A perineural sheath was found in 6.5% of the study population, and a vascular emboli in 7.5%. Among the 93 files studied, only 88 of them allowed us to find the pre-therapeutic values of the ACE marker and 98 files for the CA19.9 marker, due to a lack of usable data. Our results showed that 68 patients among the 88 patients who measured their CEA levels had positive preoperative values. Regarding CA19-9, 50 patients had normal values while 39 had values above the norm. In this study series, 67 patients or 62.4% were able to benefit from a search for molecular markers including KRAS, BRAF, NRAS, TP53 and PIK3CA. A RAS mutation was detected in 35 patients, or 37.6% of the study population, while 29% of patients had RAS wild-type status. We also found 8 cases (8.60%) presenting a TP53 mutation then 6 cases or 6.5% PIK3CA, 5 cases (5.4%) BRAF positive. The most represented therapeutic strategy was chemotherapy associated with targeted therapy with a percentage of 43%, and to which surgery was associated in 19.35%. 6.4% of cases underwent exclusive chemotherapy in the never operable setting.

Figure 11: Circumstances of Discovery in Patients with Metastatic Rectal Cancer at the University Hospital of the Wilaya of Bejaia Between 2018-2022

Discussion
From January 2018 to April 2022 we collected 93 colorectal cancer files. The distribution of our patients over the five years included in the study showed that the annual recruitment of CCRs in the service varies from one year to the next. There is a continued increase in the incidence of metastatic colorectal cancer and this is not only due to the significant demographic and epidemiological transition of the population, as described in the series by [3], but also to the recent establishment of the oncology hospital center in the region, thus leading to an increase in patient recruitment and the carrying out of various screening campaigns at the level of hospitals in the Wilaya from Bejaia. In our series, the average age for both sexes combined is 63.10 +/- 13.05 years with extremes ranging from 33 years to 90 years. These results converge with those found in Western literature where the average age of onset is between 65 and 75 years, as well as with the results of the [4] series. Contrary to our results, studies carried out in the United States and France reported a younger average age estimated respectively at 50 years[6] and 56 years [5], this can be explained by the aging nature of populations, lifestyles and different diets. According to these data, we can consider that age is a very important risk factor, the older we get, the more the risk of developing CRC increases. These results are in agreement with those obtained in a study carried out on an Asian population [6], where the risk of CRC increases by 90% after the age of 50. This relationship goes back to several particularities linked to aging, which results from the cessation of the work of telomerase, the enzyme responsible for the lengthening of telomeres, and this leads to a loss of some functions [7]. In addition, there are other particularities at the psychological level such as psychiatric disorders (anxiety, depression, etc.) and professional status which can present one of the risk factors for having cancer [8]. A peak in frequency is observed in the population aged 60-70 years for the male sex with 25 cases out of 68 or (36.8%) of the male population. While among women the most dominant age group is of [50-60] years with a percentage of 28% of the female population. Our figures are close to those found in the series [9] and [22] but go against those of [9] where the peak frequency of CRC is between 60 and 69 years in males while it is between 70 and 79 in females. The distribution of CRC according to sex and
age in our patients shows that CRC occurs at a later age in men than in women with an average age in men of 60.7 years and 55.3 years in women; these results are similar to those of [10] and this reinforces the hypothesis that age over 50 years and male sex constitute a major risk factor for developing CRC. When distributing the prevalence of colorectal cancer according to sex at the level of the wilaya of Bejaia we note that the male population is the most affected by colorectal cancer compared to the female population with a sex ratio of 2.72. This is consistent with Western literature, where we note a marked male predominance with a sex ratio of between 1.5 and 2 [11]. This male predominance has also been revealed in several other studies around the world, such as that of A. Moussa et al.

Since the discovery of the carcinogenic potential of secondary bile salts and the objectification of the effect of cholecystectomy on the bacterial degradation and metabolism of these bile salts, epidemiological studies tend to show an association between the history of this surgery and cancers. of the cecum and ascending colon [12]. According to the results of this study, it was found that patients with a family history of colorectal cancer in question represent 10% of our population, of which 4% are first-degree relatives, thus approaching the results of [5]. This rate is slightly lower but consistent with that reported in the literature which estimates the proportion of patients with a family history of colorectal cancer to be 15% to 20% [13]. Our study shows that the hereditary form of cancer colorectal is less common compared to the sporadic form with respective rates of 10% versus 90% [12]. In agreement with the French study which found that colorectal cancer most often occurs sporadically and it is only a hereditary condition in approximately 5% of cases [21]. Smoking is found in 29% of our patients. In this part of the study, the female sex is neglected because the smokers were only men.

Our results are similar to those of [13]. These data agree with the meta-analysis which found that current smokers have an increased risk of CRC than non-smokers [20]. The effect would be limited to the genesis phase of the adenoma, with a dose-effect relationship. The higher the number of cigarettes consumed per day, the greater the risk of CRC, in agreement with several studies which have shown that there are two main factors involved: the number of cigarettes consumed in a day and the duration in year [13]. In this study, 80 files (86%) had data on alcohol consumption, among them 16% have already been and/or were at the time of diagnosis consumers of alcohol which is a contributing factor to colorectal cancer. Our results converge with those of M. Belloul [22]. In our study series, the diagnosis of colorectal cancer is mainly made based on symptoms, however in 4.3% of cases, colorectal cancer was not responsible for any symptoms, and was discovered incidentally. This low proportion can be explained generally by the absence of a national mass screening policy for accessible cancers, including colorectal cancer. The mode of initial presentation in the different studies is characterized by the significant predominance of two symptoms: rectal bleeding and abdominal pain. Transit disorders come second with a significant frequency. Rectorrhagia has been found in 70% of cases in the literature. This figure roughly matches that found in the Belloul series [22] where rectal bleeding represents 45% of the revealing symptoms. In our series, rectal bleeding was found in 40.9% of patients. hence our reflection that the Algerian only consults by the presence of an alarming sign such as bleeding. Furthermore, the series by [15] described transit disorders as being the major revealing symptom with a rate of 66%. The discordance in the results of the main symptoms can be explained by the delay in diagnosis, the number of samples, and the frequency of colon cancer compared to rectal cancer. The [14] series reports 11 cases of acute intestinal obstruction revealing out of 101 colon cancers included in this series of colon cancers, this is close to the results of our study where 10 cases of intestinal obstructions revealed colorectal cancer. We essentially attribute these complicated forms of colon cancer in our context to the significant delay in diagnosis which means that many patients end up with this complication which has a pejorative prognostic value, these are patients with often locally advanced cancer with less survival. Good. Symptoms in colon cancer vary depending on the anatomical location of the tumor. It is for this reason that in our study we will distinguish: **Cancers of the Right Colon**

They represent almost a quarter of all colon cancer locations in our study, or 20.4% of cases. The clinical picture is dominated by abdominal pain (10.75%) followed by weight loss 8.60% and chronic iron deficiency anemia in 6.5% of cases. These results match those found in the study by Mazouzi et al [22] where right colon cancers were revealed by abdominal pain in 11.1%, weight loss in 9.1% and anemia in 8.8% [15].

**Cancers of the Left Colon**

They represent the elective site of all the topographies of colorectal cancer in our study with a rate of 49.5%, this rate is discordant with that of Mr. Belloul where the right colon wins over the left with a rate of 56% and that of B. Bakary where the rectum has the highest rate, i.e. 45.9%. They have a main clinical characteristic, which is the high frequency of colon cancers complicated by acute intestinal obstruction, i.e. 9.7% in our study. The elective site of this complication is the sigmoid colon. The diagnosis of colorectal cancer is made late in the majority of our patients. Thus, approximately 56.98% of patients who presented with colorectal...
adenocarcinoma belonged to stage IV and 37.63% to stage III at the time of diagnosis. Which is in agreement with the results obtained by [16]. This can be explained by patients' neglect of symptoms until the cancer reaches an advanced stage in the body. In our study population, a RAS mutation was detected in 28 patients or 30.1% of cases, while 23.6% of patients presented wild-type RAS status. We also found 8 cases (8.60%) presenting a TP53 mutation then 6 cases or 6.5% PIK3CA, 5 cases (5.4%) BRAF positive. These results are consistent with a retrospective study which found KRAS (42.1%), BRAF (5.4%) and PIK3CA (6.4%) mutations [17]. According to studies, the prognostic value of KRAS mutations in the progression of CRC is currently uncertain and contradictory [19]. However, it is well established that mutations in the KRAS gene have biological and functional consequences which could influence the choice of therapeutic protocol in CRC [18]. It turns out that the KRAS mutation is a predictive factor for poor response to anti-EGFR treatment. And have a significantly worse prognosis than those without mutations.

**Conclusion**

At the end of this work, we note that metastatic colorectal cancer is a frequent entity which preferentially affects elderly male subjects. Its prevalence is influenced by different factors, such as gender, age. Colorectal cancer may be asymptomatic in early stages. However, as the disease progresses, symptoms may appear, such as rectal bleeding, abdominal pain, bowel movements and iron deficiency anemia without an obvious cause. These signs should be taken seriously and require a thorough medical evaluation. Treatment for colorectal cancer depends on several factors, such as the stage of the disease, the location of the tumor, and the patient's general health. Treatment options typically include surgery, chemotherapy, radiation therapy, and in some cases immunotherapy. A multidisciplinary approach involving medical, surgical, and oncologic specialists is often necessary to design an individualized treatment plan. Prevention and awareness remain the best way to combat this pathology and its consequences.

**References**


