Clinicopathological features of colorectal cancers in Morocco based on the registry of the National Institute of Oncology in Rabat

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Abstract

Background and objectives: Colorectal cancer (CRC) is rising steadily, particularly in developing nations. In Morocco, colorectal cancer is ranking third most incident. Via this study, we present the epidemiological profile, clinical features of colorectal cancers, and chemotherapy outcome in a Moroccan population.

Materials and methods: This study is a retrospective investigation, run between January and December 2013 of 290 patients with colorectal cancer. A descriptive and analytical study was carried out via statistical analysis to correlate clinicopathological data with overall chemotherapy-related toxicity occurrence, by the Chi2 test. The non-parametric Mann-Whitney test was used for comparison between the occurrence of diarrhea and bilirubin levels.

Results: Most of the cases were between 40–59 years, and 50.5% (n = 147) were men. KRAS (12, 13 codon) was mutant in 10 patients (3.4%). Chemotherapy was administered to 146 patients (50.4%), and 85.6% had suffered from at least one toxic event during CMT treatment. The mean total bilirubin and mean conjugated bilirubin were found to be significantly high in patients who do not develop diarrhea, compared to those with diarrheal toxicity with a p-value of 0.02 and 0.03 respectively.

Conclusion: Our study reveals a significant percentage of toxicity occurrence among patients who underwent chemotherapy.

Keywords: Colorectal cancer, epidemiology, Moroccan population

(Received April 8, 2021; Accepted April 20, 2021)

INTRODUCTION

Colorectal Cancer (CRC) is the third cause of cancer deaths in the world and the third most commonly diagnosed form of cancer globally. It is rising steadily, particularly in developing nations. CRC incidence shows up to eight-fold variations between countries, while incidence rates increase proportionally to the human development index, highlighting a possible causal relationship. According to GLOBOCAN 2018 statistics, cancer of the colon and rectum are the fourth and eighth most incidents, respectively. In both sexes, the rates of age-standardized (world) mortality per 100,000 of CRC is 8.9². In Morocco, according to the cancer registry of Greater Casablanca, colorectal cancer is ranking third after breast and lung cancers³. Even in the face of increased incidence, CRC mortality has decreased with the improvements in treatments and early diagnosis. Treatment for colorectal cancer is based on surgery, radiotherapy, and chemotherapy, depending on the discovery stage of cancer. Thus, it is best treated with surgery when it is discovered at an early stage. However, additional radiation therapy might be required for rectal cancer to minimize the risk of recurrence. A combination of surgery, radiation, and chemotherapy, or surgery and chemotherapy, is used for advanced stages (stage III and stage IV) of colon cancer and rectal cancer respectively. The choice to use one regimen over the other relies on several conditions, including the clinicians’ decisions, the availability of chemotherapeutic agents, the tumor resistance, the toxicity occurrence, and the patients’ physical condition. Before each chemotherapeutic cycle or chemoradiation,
each patient is physically examined and any adverse toxic events are evaluated and graded for severity according to National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE) scales. Being a non-modifiable risk factor, hereditary mutations cause CRC in 7 to 10% of cases. However, awareness of the importance of testing for these conditions could increase survival rates.

Overall, a comprehensive understanding of the etiology pattern of colorectal cancer development, relating genetic risk and environmental factors, sedentary lifestyle, obesity, toxic habits (alcohol & smoking), red and processed meat, can empower researchers and physicians in treating and preventing this deadly neoplasm.

In order to present the epidemiological profile and clinical features of colorectal cancers, we carried out an epidemiological study at the National Institute of Oncology in Rabat, considered to be the main government hospital in the region. We also aimed to give an overview of toxicity occurrence after chemotherapeutic treatment.

**PATIENTS AND METHODS**

**Study population and data collection**

This study is a retrospective investigation run between January 2013 and December: 290 patients with colorectal cancer histologically confirmed were included. From patients’ medical records available in the registry of the National Institute of Oncology in Rabat. A complete and comprehensive database was performed, including age, sex, geographic origin, personal or family history of colorectal cancer or other cancers; medical history; surgical history; comorbidities; localization; histopathological type of the tumor; Tumor-Node-Metastasis (TNM) staging; and distant metastases sites at diagnosis. Treatment by chemotherapy; and occurrence of chemotherapyy-related toxicity and others.

**Statistical analysis**

Based on the collected data, descriptive and analytical study was carried out via statistical analysis using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). Descriptive clinical data were expressed in percentage or median or mean ± SD. Statistical analysis was performed to correlate clinicopathological data with overall chemotherapy-related toxicity occurrence, by the chi-squared test. Statistical significance was set at the p-value <0.05. The non-parametric Mann-Whitney test was used for comparison between the occurrence of diarrhea and bilirubin (total and conjugated) levels.

**Ethics approval and patients’ consent**

The Ethical Committee of Biological Research, Faculty of Medicine and Pharmacy – Rabat, approved the study under reference number 409/14. Due to the retrospective nature of the study, no patient’s consent was needed. The present publication does not compromise anonymity or confidentiality or breach local data protection laws.

**RESULTS**

Two hundred ninety patients were involved in the study. Table 1 summarizes the demographic characteristics of patients.

Most of the cases were between 40–79 years at diagnosis, with a percentage of 41.0% of 40–59 and 40.3% of 60–79 years. The patients were also divided into two age groups: patients of less than 50 years old (36.6%) and patients who were 50 years old or more (63.4%). In our series, 50.5% (n = 147) were male. 77.3% of the patients lived in urban areas, and the large majority of patients had medical insurance (90%) (Table 1).

The location of tumors was as follows: in the rectum cancer, the tumor was more frequently localized in the low rectum (18.3%) followed by recto-sigmoid junction (11.7%), the middle rectum (7.6%), and the top rectum (6.6%), while in the colon cancer 42.8 % of tumors were localized in the left-sided colon, 10.3% in the right-sided colon followed by 2.4% in the transverse colon (Table 2).

Personal history of colorectal cancer and other cancer types are found respectively in 3.4% of patients and 0.7% of patients. Family history of colorectal cancer is found in 3.4%. The majority of our study population was neither tobacco user nor alcoholic; 5.8% of our patients are chronic tobacco users, compared to only 1.4% who are alcoholics. Personal history of colorectal cancer and personal history of other types of cancer are found respectively in 3.4% of patients and 0.7% of patients. A family history of colorectal cancer is found in 3.4% of cases. The majority of our study population is neither tobacco nor alcohol consumers; 5.8% of our patients were chronic tobacco users, compared to only 1.4% who are alcoholics.

Concerning the delay between symptoms to diagnosis, 152 (59.4%) patients had CRC symptoms for less than 6 months before histopathological diagnosis while 104 (40.6%) had symptoms for longer than 6 months before histopathological cancer diagnosis. The clinical symptomatology has been dominated by rectal bleeding (59.8%), followed by abdominal pain 39.0%, weight loss (26.9%), poor general conditions (physical tiredness) (25.4%), intestinal obstruction (21.2%), solitary rectal ulcer syndrome, and constipation (16.3%).

Pre-therapeutic evaluation at diagnosis showed that 61.2% of the patients had localized tumor, and 38.9% had at least one distant metastatic localization with 25.8% in the liver, 14.2% in lung, 4.5% in peritoneum, and 1.5% in the bone. On the other hand, 48.6% of the cases pre-
Table 1  Demographic characteristics of Moroccan patients with colorectal cancer

| Characteristics                  | N (%)         |
|----------------------------------|---------------|
| Age (mean ± SD) (years)          | 56.16 ± 14.61 |
| Age ranges (years)              |               |
| <40                              | 44 (15.2)     |
| 40-59                            | 119 (41.0)    |
| 60-79                            | 117 (40.3)    |
| ≥80                              | 10 (3.4)      |
| Age groups                       |               |
| <50 years                        | 106 (36.6)    |
| ≥50 years                        | 184 (63.4)    |
| Sex                              |               |
| Male                             | 147 (50.5)    |
| Female                           | 144 (49.5)    |
| Living environment               |               |
| Urban                            | 225 (77.3)    |
| Rural                            | 66 (22.7)     |
| Medical insurance                |               |
| RAMED \(^{*}\)                   | 202 (77.4)    |
| AMO \(^{**}\)                    | 52 (19.9)     |
| Private insurance                | 7 (2.7)       |

*: Reference (7)
\(^{*}\): Régime d'Assistance Médicale
\(^{**}\): Assurance Maladie Obligatoire

Table 2  Clinical and paraclinical characteristics of Moroccan patients with colorectal cancer

| Characteristics                  | N (%)         |
|----------------------------------|---------------|
| Tumor localization colon         |               |
| Ascending/ right sided           | 30 (10.3)     |
| Descending / left sided          | 50 (17.2)     |
| Transverse                       | 7 (2.4)       |
| Undefined                        | 37 (12.8)     |
| Tumor localization rectum        |               |
| Top                              | 19 (6.6)      |
| Middle                           | 22 (7.6)      |
| Low                              | 53 (18.3)     |
| Rectosigmoid junction            | 34 (11.7)     |
| Comorbidity conditions           |               |
| Yes                              | 72 (25.9)     |
| No                               | 206 (74.1)    |
| Comorbidity conditions types     |               |
| HTA                              | 26 (9.4)      |
| Diabetes                         | 20 (7.2)      |
| Heart disease                    | 4 (1.4)       |
| Others                           | 34 (11.8)     |
| Personal history of CRC          | 9 (3.4)       |
| Personal history of other cancers| 2 (0.7)       |
| Familial history of CRC          | 9 (3.4)       |
| Familial history of other cancers| 23 (8.6)      |
| Lynch syndrome                   | 1 (0.4)       |

Smoking
- Tobacco
  - Chronic: 16 (5.8)
  - Former Chronic: 32 (11.7)
  - Occasionally: 5 (1.9)
  - None: 221 (80.7)
- Cannabis
  - Chronic: 6 (2.2)
  - None: 268 (92.4)

Drinking alcohol
- Chronic: 4 (1.4)
- Occasionally: 3 (1.0)
- None: 267 (92.1)
- Diagnosis delay
  - <6 months: 152 (59.4)
  - ≥6 months: 104 (40.6)

Symptoms of CRC
- Poor general condition (physical tiredness): 67 (25.4)
- Rectal bleeding: 158 (59.8)
- Constipation: 43 (16.3)
- Diarrhea: 29 (11.0)
- Alternating constipation/ diarrhea: 22 (8.3)
- Solitary rectal ulcer syndrome: 51 (19.3)
- Abdominal pain: 103 (39.0)
- Abdominal Masses: 7 (2.7)
- Weight loss: 71 (26.9)
- Intestinal obstruction: 56 (21.2)

Prior serum bilirubin, median, mg/l (interquartile)
- Total: 5.00 [4–7]
- Conjugated: 2.00 [2–3]

Genotyping tests status
- KRAS status
  - Wild-type: 9 (3.1)
  - Mutant: 10 (3.4)
  - Test not performed: 271 (93.4)
- MSI status
  - MSS (stable): 9 (3.1)
  - MSI (instable): 6 (2.1)
  - Test not performed: 275 (94.8)

Presence of Helicobacter pylori
- Yes: 3 (1.0)
- No: 1 (0.3)
- Not performed: 286 (98.6)

Treatment by Chemotherapy: 146 (50.4)

*: Delay between symptoms to diagnosis

Table 3  Histopathological features and tumor stages and extension at diagnosis

| Characteristics                  | N (%)         |
|----------------------------------|---------------|
| Histological types               |               |
| Lieberkühnien adenocarcinoma      | 241 (85.8)    |
| Adenocarcinoma well-differentiated| 126 (44.8)    |
| Moderately or poorly differentiated| 115 (40.9)    |
| Colloid or mucinous adenocarcinoma| 27 (9.6)      |
| Epidermoid carcinoma             | 3 (1.1)       |
| TNM staging                      |               |
| T                                |               |
| T1                               | 1 (0.7)       |
| T2                               | 11 (7.4)      |
| T3                               | 102 (68.5)    |
| T4                               | 35 (23.5)     |
| N                                |               |
| N0                               | 54 (38.8)     |
| N1                               | 51 (36.7)     |
| N2                               | 34 (24.5)     |
| M                                |               |
| M0                               | 40 (28.4)     |
| M1                               | 101 (71.6)    |
| Stage                            |               |
| I                                | 77 (37)       |
| II                               | 30 (14.4)     |
| IV                               | 101 (48.6)    |
| Metastases (at diagnosis)        |               |
| 0 site                           | 159 (61.2)    |
| 1 site                           | 67 (25.8)     |
| ≥2 sites                         | 34 (13.1)     |
| Metastases sites                 |               |
| Liver                            | 67 (25.8)     |
| Lung                             | 37 (14.2)     |
| Peritoneum                       | 13 (4.5)      |
| Bone                             | 4 (1.5)       |
| Other metastatic sites           | 13 (5.0)      |

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sented advanced stage (stage IV) at diagnosis.

Histological examination found a lieberkühnien adenocarcinoma in 241 patients (85.8%) which were well-differentiated in 126 cases, and moderately or poorly differentiated in 115 cases. The proportion of colloid or mucinous adenocarcinomas and epidermoid carcinoma represented 9.6% and 1.1% of cancers, respectively (Table 3).

As it is an expensive genetic test and not supported by public health, the KRAS status genotyping was performed in 19 patients only. KRAS (12, 13 codon) was mutant in 10 patients (3.4%). MSI (Microsatellite instability) phenotype was performed by immunochemistry in 15 cases, and the number of cases with probable MSI was 6 (1.0%). Three patients had Helicobacter pylori infection.

Among 146 patients (50.4%) who underwent chemotherapy (CMT), 85.6% had at least suffered from one toxic event during CMT treatment.

To study the differences between patients who encountered toxicities and the patients with no toxic event regarding demographic and clinicopathologic parameters, univariate and multivariable logistic regression analyses were used. No significant differences were revealed in baseline demographic and clinical characteristics between the two groups (Table 4).

The pre-therapeutic level of bilirubin (total and conjugate) was compared with the development of diarrheal toxicity among patients who had irinotecan-based regimens, and it was found that in patients who do not develop toxicities (diarrhea); the mean total bilirubin and the mean conjugated bilirubin are significantly higher than that of the group who had diarrhea with a p-value of 0.029 and 0.038, respectively (Table 5).

**DISCUSSION**

The mean age of our colorectal cancer patients is 56.16 ± 14.61 years. This result is comparable to the one (54 years old) recorded by Mrabti et al., 2016 and A. Bennousssa et al. 2013, and also to the age reported in the cancer registry of Rabat (53.5 years).7, 10 Similar frequencies were reported by the countries of North Africa, Tunisia 29.3%, Egypt 31% but different from those reported in North America and Europe10–13.

According to the registry of greater Casablanca, 67.7% of our patients are living in urban areas which is similar to the rate reported by Mrabti et al., 2016.10

Anatomo-pathological data from patients showed that Lieberkühnien adenocarcinoma was the most common histological type (85.8%), a similar finding to Moroccan cohorts and European ones.14–17. The registry of Rabat (2009–2012) reported that the most common type of colon cancer was intestinal-type adenocarcinoma. The

| Variables | Total bilirubin (mg/L) | p | bilirubin conjugated (mg/L) | p |
|-----------|------------------------|---|---------------------------|---|
| Diarrhea  | Yes                    | 4 [3–6]  | 0.029                    | 2 [1–3]  | 0.038 |
|           | None                   | 6 [4–7]  |                           | 2 [2–3]  |       |

| Variable | Number on metastasis sites | Total bilirubin (mg/L) | p | bilirubin conjugated (mg/L) | p |
|----------|---------------------------|------------------------|---|---------------------------|---|
|          | 0                         | 11 (52.4)              | 0.001 | 67 (55.4) | 0.013 |
|          | 1                         | 4 (19.0)               | 0.002 | 39 (32.2) | 0.001 |
|          | 2+                        | 6 (28.6)               | 0.003 | 12 (12.4) | 0.003 |

commitment to insure their employees14, 14. 77.3% of our patients are living in urban areas which is similar to the rate reported by Mrabti et al., 2016.10

Anatomo-pathological data from patients showed that Lieberkühnien adenocarcinoma was the most common histological type (85.8%), a similar finding to Moroccan cohorts and European ones.14–17. The registry of Rabat (2009–2012) reported that the most common type of colon cancer was intestinal-type adenocarcinoma. The
other histopathological types mainly belonged to colloid or mucinous adenocarcinoma with 9.6%, a similar frequency found in a previous Moroccan cohort16. This type of cancer seems to be with a worse prognosis.

The delay between the onset of symptoms and diagnosis was less than six months for 59.4% of the patients, and rectal bleeding represents the predominant symptom since it is present in 59.8% of cases which is the most frequently complained symptom from CRC patients15, 16, 18, 19.

European studies show that more than 70% of patients consult before 6 months while Moroccan studies show that more than 60% of patients consult late for more than 6 months20, 21. This delay of diagnosis in our context is explained by the negligence of the first symptoms by most patients.

In our series, particularly among patients who had irinotecan-based regimens, serum bilirubin levels (total and conjugated) were significantly higher in patients without toxicities (diarrhea) compared to those with diarrhea. However, the results need to be validated in other independent prospective studies.

The predictive value of pre-therapeutic levels of bilirubin has been studied previously in various populations. Starting from the fact that bilirubin is an endogenous protein glucuronidated by the same enzyme (UGT1A1) as SN-38, the active and toxic metabolite of the anticancer drug irinotecan, Serum bilirubin level was found to be associated with irinotecan-induced toxicities20. It was also reported to be a predictive biomarker of glucuronidation activity and thus, of severe neutropenia in patients receiving irinotecan23-25.

Data concerning irinotecan-based therapy and bilirubin are lacking in the Moroccan context. This warrants verification in prospective cohorts with sufficient power to detect the predictive accuracy of bilirubin baseline levels.

CONCLUSION

In this Moroccan population, colorectal cancer has similar features to those in North African countries. Chemotherapy is known to be the cornerstone of CRC treatment; however, related side effects and toxicities sound the alarm for more rational use. Our study revealed a significant percentage of toxicity occurrence among patients who underwent a chemotherapy regimen which is about 85.6%.

Because of the lack of data on this topic, further studies on larger size populations are warranted to prospectively notify and monitor chemotherapy-related toxicities with precise types and grades according to international terminology criteria. We thought that also pharmacogenetic studies will have great merit, contributing to better prevention of toxicity risk and prior adapted treatment of patients, candidates for chemotherapy.

Acknowledgements:
We thank the team from the epidemiology unit at the National Institute of Oncology for providing us with the necessary medical records needed for the study.

Abbreviation list:
Colorectal cancer: CRC
National Cancer Institute's Common Terminology Criteria for Adverse Events: NCI-CTCAE
Tumor-Node-Metastasis: TNM
Chemotherapy: CMT
MSI: Microsatellite instability

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