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Original Article

Survival Analysis and Prognostic Factors for Colorectal Cancer Patients in the Wilaya of Batna (Algeria) during the period between 2015-2020

Analyse de survie et facteurs pronostiques des patients atteints de cancer colorectal dans la wilaya de Batna (Algérie) au cours de la période 2015-2020

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ABSTRACT

Colorectal cancer (CRC) is a major public health problem due to its increasing incidence worldwide. According to Globocan 2022, colorectal cancer ranks in third place in terms of incidence but second in terms of mortality. In Algeria; it is the second cancer after breast cancer and the third leading cause of cancer mortality after breast cancer and lung cancer.

Our objectives were to estimate the probabilities of survival after diagnosis at 1, 3 and 5 years in new Colorectal Cancer patients recorded in the wilaya of Batna (Algeria) in 2015. Then, study the impact of prognostic factors on their survival.

Material and method: This is a descriptive study aimed at determining survival of new cases colorectal cancer recorded by the cancer registry of the wilaya of Batna during the period 2015-2020. The recruitment period is from January 1 to December 31, 2015. The final judgment criteria is the occurrence of death before the various point dates. The analysis of the survival curve was conducted according to the Kaplan Meier method supported by a multivariate study by regression according to the Cox model.

Results: The overall 5-year survival was 38.5%. In multivariate analysis, the risk of death increased with stage IV (HR = 11.12), initial leukocytosis (HR = 9.4), disease progression in radiological examinations at 3 and 6 cycles of 1st line chemotherapy (HR = 15.19, HR = 18.57) respectively, concomitant radio-chemotherapy as the first treatment implemented (HR = 3.3), concomitant radio-chemotherapy + surgery ± chemotherapy as therapeutic protocol (HR = 5.04), the initial pathological level of CA19-9 (HR = 4.97), the synchronous mode of metastases (HR = 3.74) and the development of metastases (HR = 4.1 for hepatic metastases, HR = 6.3 for extra-hepatic metastases and HR = 6.84 for hepatic and extra-hepatic metastases).

Conclusion: It is thanks to screening and early detection associated with appropriate treatment that survival has progressed in developed countries. It is time to launch the organized screening program in our country without any further delay.

KEYWORDS: Cancer survival; Prognostic factors; Colorectal cancer; The overall 5-year survival.



RESUME

Le cancer colorectal (CCR) constitue un problème majeur de santé publique en raison de son incidence croissante à l'échelle mondiale. Selon Globocan 2022, il occupe la troisième place en termes d'incidence mais la seconde en termes de mortalité. En Algérie, il représente le deuxième cancer après le cancer du sein et la troisième cause de mortalité par cancer après les cancers du sein et du poumon. Nos objectifs étaient d'estimer les probabilités de survie post-diagnostic à 1, 3 et 5 ans chez les nouveaux patients atteints de CCR enregistrés dans la wilaya de Batna (Algérie) en 2015, puis d'étudier l'impact des facteurs pronostiques sur leur survie.

Matériel et méthode : Il s'agit d'une étude descriptive visant à déterminer la survie des nouveaux cas de CCR enregistrés par le registre du cancer de la wilaya de Batna sur la période 2015-2020. La période de recrutement s'étend du 1^{er} janvier au 31 décembre 2015. Le critère de jugement final est la survenue d'un décès avant les différentes dates de point. L'analyse de la courbe de survie a été réalisée selon la méthode de Kaplan-Meier, complétée par une étude multivariée de régression selon le modèle de Cox.

Résultats : La survie globale à 5 ans était de 38,5%. En analyse multivariée, le risque de décès augmentait avec : le stade IV (HR = 11,12), la leucocytose initiale (HR = 9,4), la progression de la maladie aux examens radiologiques aux cycles 3 et 6 de la chimiothérapie de 1^{re} ligne (HR = 15,19 ; HR = 18,57 respectivement), la radio-chimiothérapie concomitante comme premier traitement mis en œuvre (HR = 3,3), le protocole radio-chimiothérapie concomitante + chirurgie ± chimiothérapie (HR = 5,04), le taux pathologique initial de CA19-9 (HR = 4,97), le mode synchrone des métastases (HR = 3,74) et le développement de métastases (HR = 4,1 pour les métastases hépatiques ; HR = 6,3 pour les métastases extra-hépatiques ; HR = 6,84 pour les métastases hépatiques et extra-hépatiques).

Conclusion : La progression de la survie dans les pays développés est attribuable au dépistage et au diagnostic précoce associés à un traitement adapté. Il est impératif de lancer sans délai supplémentaire un programme de dépistage organisé dans notre pays.

MOTS CLES : Survie au cancer ; Facteurs pronostiques ; Cancer colorectal ; Survie globale à 5 ans.

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Introduction

Colorectal cancer (CRC) is a major public health problem due to its increasing incidence worldwide. According to Globocan 2022, it is the third most common cancer in the world after lung cancer and breast cancer, and it is considered the second leading cause of cancer death worldwide after lung cancer [1].

In Algeria; colorectal cancer is second after breast cancer with an age-standardized incidence rate equal to 17.1 cases per 100,000 people. And it is considered the third leading cause of cancer mortality after breast cancer and lung cancer with an age-standardized mortality rate equal to 9.4 deaths per 100,000 P [2].

In Batna, the CRC, from 2016-2017, came second in cancer after lung cancer in men and breast cancer in women [3]. These figures speak for an urgent need to understand the burden of colorectal cancer in the country to come up with the right and appropriate guidance for screening and care actions.

Clinico-pathological and biological prognostic criteria have long been recognized as essential to the treatment of colorectal cancer. The number of positive lymph nodes has a prognostic value which is integrated into the TNM classification. An important prognostic factor is parietal invasion, represented in the TNM classification [4,5]. Complete excision of the tumor has long been identified as a major prognostic factor: R1 or unanalyzable resection margins predict recurrence [6]. The grade of tumor differentiation also has prognostic value: tumor grade is significantly associated with survival in stages II, III, and IV [7]. The carcinoembryonic antigen (CEA) test has its place in the initial assessment of the prognosis: several retrospective studies have shown that a preoperative serum CEA concentration greater than 5 ng/ml was a poor prognosis and was correlated with a reduction in overall survival after surgical resection [8]. The presence of venous emboli and lymphatic and perineural invasion (VELIPI) is considered the first step in a process of metastatic dissemination. The presence of more than one VELIPI factor was of worse prognosis than the presence of only one [9].

The initially obstructive or perforated character of the tumor is also considered as a prognostic factor. Patients with both occlusive and perforated lesion had significantly poorer recurrence-free survival whatever the stage of the tumor, the histological grade and the presence of vascular emboli [10]. There are many prognostic and predictive molecular biomarkers for colorectal cancer [5]. Some are already in clinical use, while others show promise for future use. The most commonly used biomarkers are:

KRAS (Prognostic value likely unfavorable in advanced disease, predicts resistance to anti-EGFR therapy, found in up to 40% of CRC, now used to predict response to cetuximab and panitumumab), *BRAF V600E mutation* (Prognostic value likely unfavorable, appear to predict resistance to anti-EGFR Therapy, may predict response to BRAF inhibitors, found in up to 10% of CRC), *PIK3CA mutations* (Prognostic value likely unfavorable, appear to predict resistance to anti-EGFR therapy), *PTEN loss* (Prognostic value likely unfavorable, appear to predict resistance to anti-EGFR therapy), *Microsatellite instability MSI* (Favorable prognosis and overall survival in patients with MSI-H tumors, patients with MSI-H cancers do not derive survival benefits from treatment by 5-FU based adjuvant chemotherapy, found in up to 15% of CRC, not yet in routine clinical use as a predictive biomarker), *18q deletions or loss of heterozygosity LOH* (Unfavorable prognosis, but may not be independent of CIN/MSS, may predict resistance to 5-FU, clinical value remains to be determined, as evidence not yet conclusive), *Thymidylate synthase TS expression* (High thymidylate synthase expression may be associated with tumor recurrence in stage II and III colon cancer, low thymidylate synthase TS levels are associated with better clinical response to fluorouracil-based chemotherapy and higher risk of toxicity, clinical value remains to be determined, as evidence not yet conclusive) [5].

The analysis of survival together with the results of cancer incidence and mortality is important for evaluating the progress made in the field and the efforts to be undertaken in the future, in order to improve survival and give hope to people with cancer. Survival rates established through cancer registries can be used to assess the overall efficiency of the health system, that is to say both the quality of care and the habits of using the healthcare system, which, in particular, condition the precocity of diagnosis. For this reason, the evaluation of the CRC survival rate in the Wilaya of Batna, which was based on the incident cases collected by the population register of this Wilaya, is very informative (indeed).

Our study was carried out in a context marked by the poverty of survival data, the establishing of multiple cancer centers, the improvement of therapeutic techniques, and the implementation of the cancer plan 2015-2019 (pending the launch of organized CRC screening).

Our principle objective is to estimate the probabilities of survival at 1, 3 and 5 years respectively in patients diagnosed with CRC in the wilaya of Batna (Algeria) in 2015. The secondary objective is to study the impact of prognostic factors on the survival of patients with CRC.

Material and Methods

This is a non-experimental observational study (retro-prospective) aimed at determining survival of new cases colorectal cancer recorded by the cancer registry of the wilaya of Batna during the period 2015-2020 where anonymity was respected.

Our *study population* is made up of all patients diagnosed histologically for CRC during the year 2015, and residing in the wilaya of Batna. *Inclusion criteria*: patients with CRC residents and originals from the wilaya of Batna; of all ages with newly diagnosed CRC during the study period. *Non-inclusion criteria*: non-resident patients in the wilaya of Batna, diagnostic bases other than histology (radiological diagnosis), in-situ cancers. During the year 2015, 127 cases of CRC meeting the inclusion criteria were identified. The collection of cases is active, continuous and exhaustive, on a descriptive survey sheet containing civil status and medical information (date and basis of diagnosis, morphology, location, etc...). This information is treated in a strictly confidential manner.

The main sources of information are the medical oncology and radiotherapy departments of the Anti-Cancer Center of Batna (ACC), the anatomopathology laboratories of the Batna university hospital center and the ACC of Batna in addition to death certificates and the register of civil status of Batna.

Regarding the information system, the Batna registry uses the latest version of CanReg 5 developed by the International Agency for Research on Cancer (IARC).

The date of histological confirmation of the cancer is considered as the date of incidence (coding rule for tumor registers). The stage of discovery, determined from the TNM classification recommended by the International Union Against Cancer (UICC) and the

American Joint Committee on Cancer (AJCC) (8th edition) simplified into 4 stages I, II, III, IV.

Data analysis: Creation of an input mask on a computer medium developed with SPSS version 22 software from the survey sheet, the data collected is entered as it is. Missing data has been flagged. The results are expressed in raw values (numbers and percentages) for the qualitative variables and in means $\pm$ (1.96 error standard) for quantitative variables, in addition to incidence rates and standardized rates on the world population (WHO 2000-2020).

Final Judgment Criteria: For the one-year survival study; it is the occurrence of death before the cut-off date set at 31/12/2016. For the 3-year survival study; it is the occurrence of death before the cut-off date set at 31/12/2018. For the 5-year survival study; it is the occurrence of death before the cut-off date set at 31/12/2020.

The analysis of the survival curve in terms of the main prognostic factors was conducted according to the Kaplan Meier method, supported by a multivariate study by regression according to the Cox model.

Results

The number of cases of CRC in the wilaya of Batna during the year 2015 is 127, which represents 11.25% of cancers diagnosed during this period. The Standardized incidence rate is equal to 15.8 cases per 100 000 people (16.3 cases per 100,000 people in men and 15 cases per 100,000 people in women). The 52% of CRC cases are males, with a sex-ratio of 1.08. The 75.5% of CRC patients are over 50 years old at the time of diagnosis, with extremes ranging from 5 years to 92 years, the Mean age = 59.28 ± 2.52 years. We note a predominance of colon cancer, the sigmoid localization of which is the most frequent. The histological study showed that Luberkhunian adenocarcinoma was the predominant histological type, followed by mucinous adenocarcinoma. The proportion of well-differentiated CRC is the highest. The presentation of sociodemographic, clinical, histoprognostic characteristics of patients is shown in table n°01.

The total number of deaths recorded during the period from 01/01/2015 to 31/12/2020 is 70, which corresponds to a fatality rate of 55.1%. The 82.8% of deaths during the five years of follow-up were over 50 years old.

The overall survival of CRC is 38.5% at 5 years (95% CI: 29.28-47.71) with a mean survival time = 38.56 months (95% CI: 33.05-44.07). Median 5-year survival (50% of study population) = 37 months (95% CI: 16.87-57.12) (figure n°01).

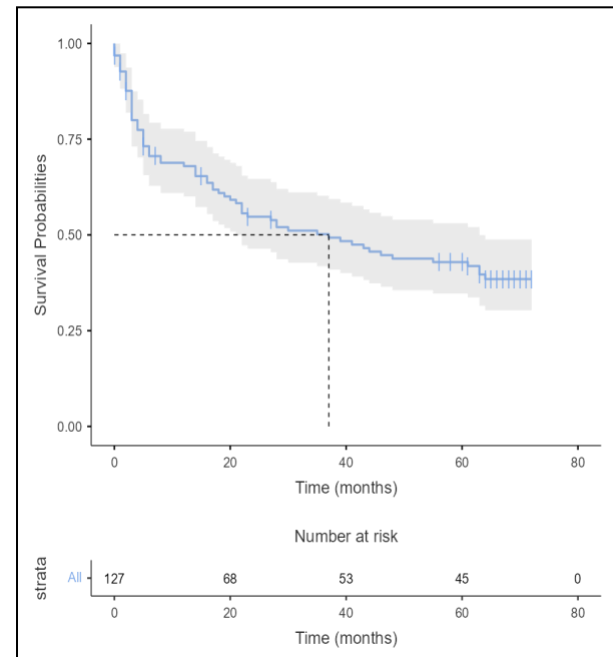


Figure 01: Survival curve at 05 years of patients with CRC. Batna 2015

The 5-year survival is no different between the two sexes ($p=0.07$ Log Rank (Mantel-Cox) (Table n°02), (figure n°02). The survival study of cases under 50 years and over 50 years shows an identical prognosis regardless of the age group (Log-Rank=2.73; $p=0.09$) (table n°02), (figure n°03). The poor prognosis is related to stages III and IV with a significant difference (Log-Rank=45.38, $p<0.0001$) (Table n°02), (figure n°04). The survival curve indicates a poor prognosis for subjects with CRC with an initial rate of pathological CEA and the difference is significant (Log-Rank=8.65, $p=0.003$) (table n°02). The survival curve shows a poor prognosis for subjects with CRC with an initial level of pathological CA19-9 and the difference is significant (Log-Rank=14.72, $p<0.0001$) (table n°02). The survival curve also shows a poor prognosis for patients with CRC with a pathological initial level of leukocytes (Leukocytosis) and the difference is significant (Log-Rank=14.22, $p<0.0001$) (table n°02).

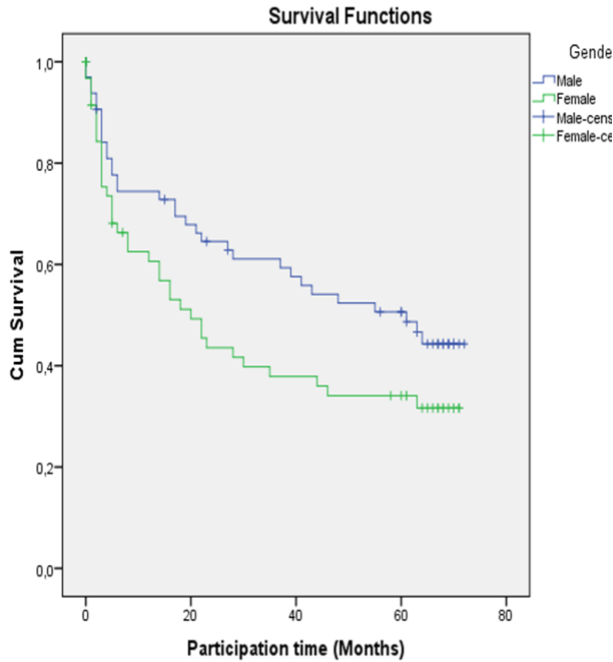


Figure 02: Survival curves of CRC patients by gender. Batna 2015

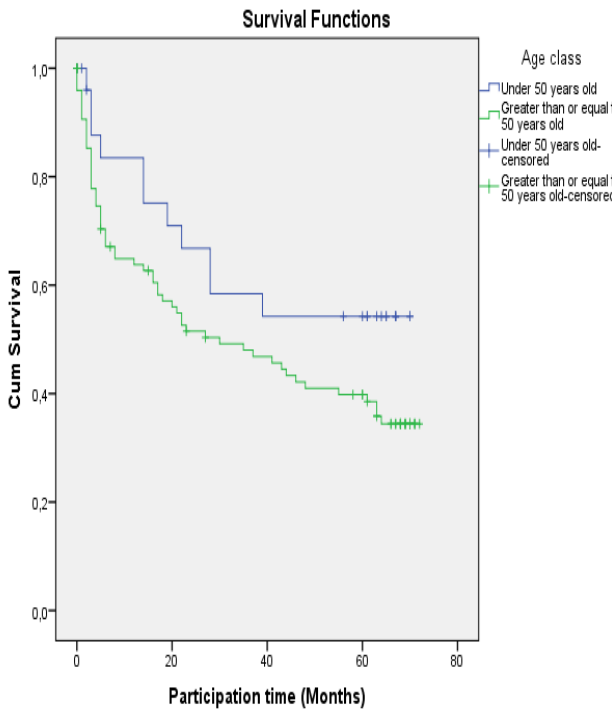


Figure 03: Survival curves of CRC patients by age groups. Batna 2015

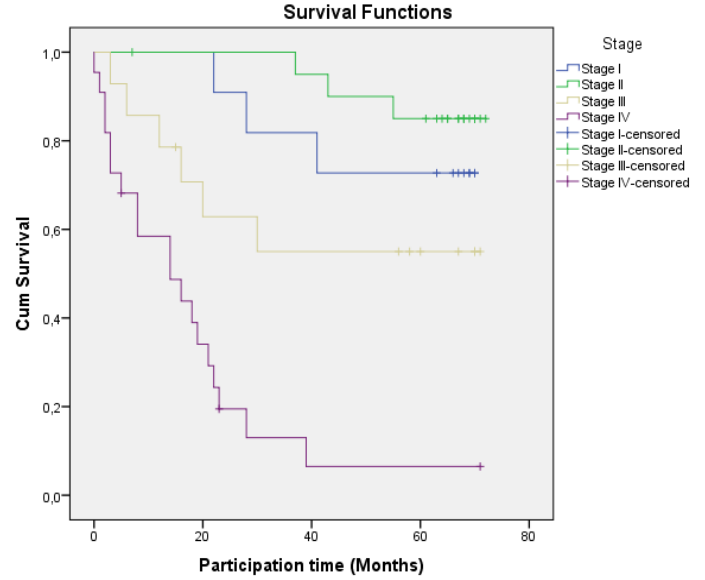


Figure 04: Survival curves of patients with CRC according to the initial stage of diagnosis of the tumour. Batna 2015

Survival is better in patients who have received initial treatment such as cancer surgery with a significant difference (Log-Rank=9.84, $p=0.002$) (table n°02). The survival curve indicates a poor prognosis for patients with CRC with radiological stabilization or progression of the disease at 6 cycles of chemotherapy and the difference is significant (Log-Rank=33.87, $p<0.0001$) (table n°02).

Univariate analysis showed several factors of poor prognosis for CRC among them we observed: Stage IV, initial leukocytosis, stabilization or progression of the disease in radiological examinations at 3 cycles of chemotherapy, progression of the disease in radiological examinations at 6 courses of chemotherapy, high initial levels of CA19-9 and CEA tumor markers, grade III of histological differentiation, concomitant radio-chemotherapy as the first treatment implemented, presence of metastases at the time of diagnosis and the synchronous mode of these metastases (table n°03). Multivariate analysis produced these independent factors of poor prognosis for CRC: Stage IV, initial leukocytosis, disease progression in radiological examinations at 3 cycles of chemotherapy, the initial pathological levels of CA19-9, disease progression in radiological examinations at 6 cycles of chemotherapy, the presence of metastases at the time of diagnosis, concomitant radio-chemotherapy as the first treatment implemented and the synchronous mode of these metastases (table n°04).

Table 01: Sociodemographic, clinical, histoprognostic characteristics of CCR patients. Batna 2015

Characteristics	Variables	Subgroups of factors studied	Patients (N)	Percentage %
Sociodemographic characteristics	Age (N=127)	< 50 years	29	22,83
		≥ 50 years	98	77,16
	Gender (N=127)	M	66	51,96
		F	61	48,03
Clinical characteristics	Obesity (BMI>30) or overweight (BMI 25-30) (N=53)	No	29	54,71
		Yes	24	42,28
	Smoking (N=47)	Active smoker	20	42,55
		Passive smoker	1	2,12
		Non-smoker	26	55,31
	Personal history of CRC, Polyps or Lynch Syndrome (N=76)	No	68	89,47
		Yes	8	10,52
	Family history of CRC, Adenoma, Familial adenomatous polyposis (N=77)	No	67	87,01
		Yes	10	12,98
	Localization (N=127)	Recto-sigmoïde Junction	12	9,44
		Colon	71	55,90
		Rectum	44	34,64
Histological characteristics	Histological type (N=127)	Adenocarcinoma, NOS	106	83,46
		Mucinous adenocarcinoma	8	6,29
		Adenocarcinoma in tubulovillous adenoma	4	3,14
		Adenocarcinoma in adenomatous polyp	2	1,57
		Carcinoma, NOS	1	0,78
		Squamous cell carcinoma, NOS	1	0,78
		Adenocarcinoma in villous adenoma	1	0,78
		Villous adenocarcinoma	1	0,78
		Mucin-producing adenocarcinoma	1	0,78
		Signet ring cell carcinoma	1	0,78
		Lymphome SAI	1	0,78
			1	

Characteristics	Variables	Subgroups of factors studied	Patients (N)	Percentage %
Histological characteristics	Histological grade (N=101)	<i>Grade I (Low grade): "well differentiated"</i>	67	66,33
		<i>Grade II (intermediate): "moderately differentiated"</i>	27	26,73
		<i>Grade III (High grade): "poor differentiated or undifferentiated"</i>	7	6,93
	Stage (TNM)(N=68)	<i>I</i>	11	16,17
		<i>II</i>	21	30,88
		<i>III</i>	14	20,58
		<i>IV</i>	22	32,35
Biological characteristics	Initial leucocytosis (N=60)	<i>No</i>	55	91,66
		<i>Yes</i>	5	8,33
	CEA Rate (N=53)	<i>Normal</i>	32	60,37
		<i>Pathological > 5 ng/ml</i>	21	39,62
	CA19-9 Rate (N=47)	<i>Normal</i>	35	74,46
		<i>Pathological > 37 UI/ml</i>	12	25,53
	Mutations of KRAS, NRAS genes (N=24)	<i>Yes</i>	13	54,16
		<i>No</i>	11	45,83
Treatment	First treatment implemented (N=73)	<i>Cancer Surgery</i>	41	56,16
		<i>Concomitant Radio-chemotherapy</i>	32	43,83
	Therapeutic Protocol (N=79)	<i>Cancer Surgery +/- metastases + adjuvant chemotherapy</i>	36	45,56
		<i>Concomitant Radio-chemotherapy + Surgery +/- chemotherapy</i>	31	39,24
		<i>Strictly palliative Treatment</i>	12	15,18
	Variables	Subgroups of factors	Patients (N)	Percentage %

Characteristics		studied		
Radiological response	Objective radiological response to 3 cycles of 1st line chemotherapy (N=49)	<i>Complete Response</i>	<i>29</i>	<i>59,18</i>
		<i>Stabilization</i>	<i>9</i>	<i>18,36</i>
		<i>Progress</i>	<i>11</i>	<i>22,44</i>
	Objective radiological response to 6 cycles of 1st line chemotherapy (N=48)	<i>Complete Response</i>	<i>30</i>	<i>62,50</i>
		<i>Stabilization</i>	<i>7</i>	<i>14,58</i>
		<i>Progress</i>	<i>11</i>	<i>22,91</i>
Metastases	Mode of occurrence of metastases (N=33)	<i>Metachrone</i>	<i>10</i>	<i>30,30</i>
		<i>Synchrone</i>	<i>23</i>	<i>69,69</i>
	Metastases (N=82)	<i>No</i>	<i>49</i>	<i>59,75</i>
		<i>Hepatic</i>	<i>12</i>	<i>14,63</i>
		<i>Extrahepatic</i>	<i>11</i>	<i>13,41</i>
		<i>Hepatic extrahepatic</i> <i>et</i>	<i>10</i>	<i>12,19</i>
Year of death		<i>2015</i>	<i>28</i>	<i>40,0</i>
		<i>2016</i>	<i>16</i>	<i>22,9</i>
		<i>2017</i>	<i>11</i>	<i>15,7</i>
		<i>2018</i>	<i>7</i>	<i>10,0</i>
		<i>2019</i>	<i>4</i>	<i>5,7</i>
		<i>2020</i>	<i>4</i>	<i>5,7</i>

Table 02: Observed survival and its 95% CI according to the various prognostic factors. Batna 2015

Variables	Subgroups of factors studied	Patients (N)	Event (n)	S at 5 years (%)	95% CI	p
Overall survival	.	127	70	38,5	[29,28_47,71]	.
Age (N=127)	< 50 years	29	11	54,3	[34,3_74,29]	0,09
	≥ 50 years	98	59	34,4	[24,4_44,39]	.
Gender (N=127)	M	66	33	44,3	[31,36_57,23]	0,07
	F	61	37	31,7	[18,96_44,44]	.
Stage (TNM)(N=68)	I	11	3	72,7	[46,43_98,96]	<0,0001
	II	21	3	85	[69,32_100,68]	.
	III	14	6	55	[28,14_81,85]	.
	IV	22	19	6,5	[-5,26_18,26]	.
Initial leucocytosis (N=60)	No	55	22	57,4	[43,87_70,92]	.
	Yes	5	5	0	.	<0,0001
Objective radiological response to 3 cycles of 1st line chemotherapy (N=49)	Complete Response	29	3	89,7	[78,52_100,87]	<0,0001
	Stabilization	9	7	14,8	[-11,26_40,86]	.
	Progress	11	9	0	.	.
Objective radiological response to 6 cycles of 1st line chemotherapy (N=48)	Complete Response	30	3	90	[79,22_100,78]	<0,0001
	Stabilization	7	5	21,7	[-13,48_56,28]	.
	Progress	11	10	0	.	.

Variables	Subgroups of factors studied	Patients (N)	Event (n)	S at 5 years (%)	95% CI	p
First treatment implemented (N=73)	<i>Cancer Surgery</i>	<i>41</i>	<i>12</i>	<i>68,6</i>	<i>[53,9_83,3]</i>	<i>0,002</i>
	<i>Concomitant Radio-chemotherapy</i>	<i>32</i>	<i>20</i>	<i>31,1</i>	<i>[14,04_48,15]</i>	<i>.</i>
Therapeutic Protocol (N=79)	<i>Cancer Surgery +/- metastases + adjuvant chemotherapy</i>	<i>36</i>	<i>10</i>	<i>70,3</i>	<i>[54,81_85,78]</i>	<i><0,0001</i>
	<i>Concomitant Radio-chemotherapy + Surgery +/- chemotherapy</i>	<i>31</i>	<i>19</i>	<i>32,3</i>	<i>[14,85_49,74]</i>	<i>.</i>
	<i>Strictly palliative Treatment</i>	<i>12</i>	<i>10</i>	<i>16,7</i>	<i>[-4,46_37,86]</i>	<i>.</i>
CEA Rate (N=53)	<i>Normal</i>	<i>32</i>	<i>8</i>	<i>73,3</i>	<i>[57,42_89,17]</i>	<i>0,003</i>
	<i>Pathological > 5 ng/ml</i>	<i>21</i>	<i>12</i>	<i>37,5</i>	<i>[15,74_59,25]</i>	<i>.</i>
CA19-9 Rate (N=47)	<i>Normal</i>	<i>35</i>	<i>10</i>	<i>70,2</i>	<i>[54,71_85,68]</i>	<i><0,0001</i>
	<i>Pathological > 37 UI/ml</i>	<i>12</i>	<i>9</i>	<i>19</i>	<i>[-4,52_42,52]</i>	<i>.</i>

Variables	Subgroups of factors studied	Patients (N)	Event (n)	S at 5 years (%)	95% CI	p
Histological grade (N=101)	Grade I (Low grade): "well differentiated"	67	33	45,6	[32,86_58,34]	0,035
	Grade II (intermediate): "moderately differentiated"	27	18	29,2	[11,36_47,03]	.
	Grade III (High grade): "poorly differentiated or undifferentiated"	7	4	20	[-15,08_55,08]	.
Localization (N=127)	Recto-sigmoïde Junction	12	6	47,6	[18,2_77]	0,74
	Colon	71	37	42,9	[30,74_55,05]	.
	Rectum	44	27	29,1	[14,2_43,99]	.
Luberkhunien adénocarcinoma (N=127)	No	21	10	46,4	[23,46_69,33]	0,49
	Yes	106	60	37,1	[27,1_47,09]	.
Obesity or overweight (N=53)	No	29	14	49,8	[30,98_68,61]	0,79
	Yes	24	9	56,1	[34,34_77,85]	.
Mode of occurrence of metastases (N=33)	Metachrone	10	7	26,7	[-2,7_56,1]	0,003
	Synchrone	23	20	6,2	[-5,16_17,56]	.
Metastases (N=82)	No	49	13	71,1	[57,77_84,42]	<0,0001
	Hepatic	12	8	27,8	[1,14_54,45]	.
	Extrabepatic	11	10	0	.	.
	Hepatic et extrabepatic	10	9	10	[-8,62_28,62]	.

Table 03 : Univariate analysis of observed survival as a function of prognostic factors. Batna 2015

Variables	Modalities	HR	95% CI	p
Stage (TNM)(N=68)	<i>I</i>	.	.	.
	<i>II</i>	0,5	[0,1_2,48]	0,39
	<i>III</i>	2,22	[0,55_8,89]	0,26
	<i>IV</i>	9,78	[2,78_34,35]	<0,000 ₁
Initial leucocytosis (N=60)	<i>No</i>	.	.	.
	<i>Yes</i>	5,54	[2,01_15,23]	0,001
Objective radiological response to 3 cycles of 1st line chemotherapy (N=49)	<i>Complete Response</i>	.	.	.
	<i>Stabilization</i>	13,9	[3,47_55,55]	<0,000 ₁
	<i>Progress</i>	22,3 ₇	[5,88_85,14]	<0,000 ₁
Objective radiological response to 6 cycles of 1st line chemotherapy (N=48)	<i>Complete Response</i>	.	.	.
	<i>Stabilization</i>	14,34	[3,3_62,27]	<0,000 ₁
	<i>Progress</i>	20,0 ₇	[5,36_75,15]	<0,000 ₁
First treatment implemented (N=73)	<i>Cancer Surgery</i>	.	.	.
	<i>Concomitant Radio-chemotherapy</i>	2,97	[1,45_6,09]	0,003

Variables	Modalities	HR	95% CI	p
Therapeutic Protocol (N=79)	<i>Cancer Surgery +/- metastases + adjuvant chemotherapy</i>	.	.	.
	<i>Concomitant Radio-chemotherapy + Surgery +/- chemotherapy</i>	3,01	[1,4_6,49]	0,005
	<i>Strictly palliative Treatment</i>	4,82	[1,99_11,67]	<0,0001
CEA Rate (N=53)	<i>Normal</i>	.	.	.
	<i>Pathological > 5 ng/ml</i>	3,54	[1,43_8,73]	0,006
CA19-9 Rate (N=47)	<i>Normal</i>	.	.	.
	<i>Pathological > 37 UI/ml</i>	5,19	[2,04_13,2]	0,001
Histological grade (N=101)	<i>Grade I (Low grade): "well differentiated"</i>	.	.	.
	<i>Grade II (intermediate): "moderately differentiated"</i>	1,66	[0,93_2,97]	0,08
	<i>Grade III (High grade): "poor differentiated or undifferentiated"</i>	3,03	[1,06_8,67]	0,03
Mode of occurrence of metastases (N=33)	<i>Metachrone</i>	.	.	.
	<i>Synchrone</i>	3,7	[1,47_9,31]	0,005
Metastases (N=82)	<i>No</i>	.	.	.
	<i>Hepatic</i>	4,19	[1,72_10,24]	0,002
	<i>Extrahepatic</i>	6,61	[2,84_15,38]	<0,0001
	<i>Hepatic et extrahepatic</i>	7,06	[2,96_16,82]	<0,0001

Variables	Modalities	HR	95% CI	p
Stage (TNM)(N=68)	<i>I</i>	.	.	.
	<i>II</i>	<i>0,53</i>	<i>[0,1_2,65]</i>	<i>0,44</i>
	<i>III</i>	<i>2,31</i>	<i>[0,56_9,45]</i>	<i>0,24</i>
	<i>IV</i>	<i>11,12</i>	<i>[3,02_40,92]</i>	<i><0,0001</i>
Initial leucocytosis (N=60)	<i>No</i>	.	.	.
	<i>Yes</i>	<i>9,4</i>	<i>[1,92_45,79]</i>	<i>0,006</i>
Objective radiological response to 3 cycles of 1st line chemotherapy (N=49)	<i>Complete Response</i>	.	.	.
	<i>Stabilization</i>	<i>6,44</i>	<i>[0,39_104,68]</i>	<i>0,19</i>
	<i>Progress</i>	<i>15,19</i>	<i>[1,03_223,52]</i>	<i>0,04</i>
Objective radiological response to 6 cycles of 1st line chemotherapy (N=48)	<i>Complete Response</i>	.	.	.
	<i>Stabilization</i>	<i>8,83</i>	<i>[0,54_142,97]</i>	<i>0,12</i>
	<i>Progress</i>	<i>18,57</i>	<i>[1,3_264,49]</i>	<i>0,03</i>
First treatment implemented (N=73)	<i>Cancer Surgery</i>	.	.	.
	<i>Concomitant Radio-chemotherapy</i>	<i>3,3</i>	<i>[1,25_8,69]</i>	<i>0,01</i>

Table 04: Multivariate analysis of observed survival according to prognostic factors

Variables	Modalities	HR	95% CI	p
Stage (TNM)(N=68)	<i>I</i>	.	.	.
	<i>II</i>	<i>0,53</i>	<i>[0,1_2,65]</i>	<i>0,44</i>
	<i>III</i>	<i>2,31</i>	<i>[0,56_9,45]</i>	<i>0,24</i>
	<i>IV</i>	<i>11,12</i>	<i>[3,02_40,92]</i>	<i><0,0001</i>
Initial leucocytosis (N=60)	<i>No</i>	.	.	.
	<i>Yes</i>	<i>9,4</i>	<i>[1,92_45,79]</i>	<i>0,006</i>

Variables	Modalities	HR	95% CI	P
Objective radiological response to 3 cycles of 1st line chemotherapy (N=49)	<i>Complete Response</i>	.	.	.
	<i>Stabilization</i>	<i>6,44</i>	<i>[0,39_104,68]</i>	<i>0,19</i>
	<i>Progress</i>	<i>15,19</i>	<i>[1,03_223,52]</i>	<i>0,04</i>
Objective radiological response to 6 cycles of 1st line chemotherapy (N=48)	<i>Complete Response</i>	.	.	.
	<i>Stabilization</i>	<i>8,83</i>	<i>[0,54_142,97]</i>	<i>0,12</i>
	<i>Progress</i>	<i>18,57</i>	<i>[1,3_264,49]</i>	<i>0,03</i>
First treatment implemented (N=73)	<i>Cancer Surgery</i>	.	.	.
	<i>Concomitant Radio-chemotherapy</i>	<i>3,3</i>	<i>[1,25_8,69]</i>	<i>0,01</i>
Therapeutic Protocol (N=79)	<i>Cancer Surgery +/- metastases + adjuvant chemotherapy</i>	.	.	.
	<i>Concomitant Radio-chemotherapy + Surgery +/- chemotherapy</i>	<i>5,04</i>	<i>[1,69_15,00]</i>	<i>0,004</i>
	<i>Strictly palliative Treatment</i>	<i>0,94</i>	<i>[0,29_2,98]</i>	<i>0,92</i>
CA19-9 Rate (N=47)	<i>Normal</i>	.	.	.
	<i>Pathological > 37 UI/ ml</i>	<i>4,97**</i>	<i>[1,94_12,73]</i>	<i>0,001</i>
Mode of occurrence of metastases (N=33)	<i>Metachrone</i>	.	.	.
	<i>Synchrone</i>	<i>3,74**</i>	<i>[1,4_9,96]</i>	<i>0,008</i>
Metastases (N=82)	<i>No</i>	.	.	.
	<i>Hepatic</i>	<i>4,1**</i>	<i>[1,67_10,05]</i>	<i>0,002</i>
	<i>Extrahépatique</i>	<i>6,3**</i>	<i>[2,63_15,04]</i>	<i><0,0001</i>
	<i>Hépatique et extrahépatique</i>	<i>6,84**</i>	<i>[2,75_17,01]</i>	<i><0,0001</i>

**** Adjustment for age and sex factors. The rest is adjusted for age, sex and clinical stage.**

Discussion

In 2015, in the wilaya of Batna, the overall survival rate for colorectal cancer at 5 years is 38.5% after diagnosis. This latter rate is significantly lower than that reported by the cancer registry of Tlemcen (a wilaya in western Algeria) for cases of CRC diagnosed between January 1, 2011 and December 31, 2012; the five-year survival was 65% [11]. A better 5-year survival is found in the study published in 2021, concerning the countries of sub-Saharan Africa; 43.5% (95% CI 40.6-46.3%) [12]. Same for Eastern Mediterranean region 57.26% (95% CI, 50.43-64.10) [13]. The highest 5-year survival rates were seen in Southeast Asia, including rates of 71.8% and 71.1% for colon and rectal cancers in South Korea [6].

It is difficult to compare our results with other studies given the different inclusion criteria and the different recruitment periods (therapeutic protocols evolve very quickly at all levels: surgery, radiotherapy and especially medical treatment with the emergence of targeted therapies and immunotherapy) but we can also say that this difference in survival rates compared to developed regions may be linked to the effectiveness of colorectal cancer screening programs implemented in these countries. In Algeria, for the moment, such a program has not yet been developed.

There is controversy over the survival of younger versus older patients [14,15]. A population-based cohort study analyzing 279,623 patients with CRC, shows that patients aged 20 to 40-year-olds have better survival outcomes than older patients (> 50 years) [16]. In our study, the 5-year survival of patients aged under 50 is 54.3% (95% CI: 34.3_74.29) versus 34.4% (95% CI: 24.4_44.39) which corresponds to that of older patients (> 50 years) but the difference is not significant. This is probably related to the size of our cohort which is relatively small. Findings regarding prognostic differences between the two genders have been less consistent.

Several studies have found superior survival in women [17-19] however, other studies have found no difference [20].

Consistent with multiple studies, analysis confirmed that cancer stage and pTNM staging at diagnosis are strong factors affecting survival of CRC patients [21,22]. In our study, more than half of the study population whose stage is known (52.9%) presented with advanced stages (stage III and IV). The absolute reason for the delay in finding a treatment is unclear, but several studies suggest that insufficient knowledge of colorectal cancer and a lack of public awareness could contribute to this problem [23-25]. In our study, we found a 5-year survival rate of 72.7% in stage I and

85% in stage II, an aberrant result that may be due to information bias. The multivariate analysis shows that patients diagnosed at stage IV had the highest risk of death with a (HR) of 11.12 (95% CI: 3.02_40.92). This result was comparable to results from several national cancer registries around the world [26,27].

The degree of differentiation of colorectal cancers has been known for a long time, but it is rarely used as an independent prognostic factor. In our study, the univariate analysis of this factor shows a risk of death multiplied by 3.03 (95% CI: 1.06_8.67) for patients with poorly differentiated or undifferentiated CRC (High grade). Multivariate analysis of prognostic factors in several studies shows that histologic grade is an independent predictor of survival, with high-grade tumors associated with increasing wall penetration, greater number of lymph nodes and distant metastases, and a worse prognosis [28].

Analysis of data for preoperative tumor markers CEA and CA19-9, in 1487 patients with this disease (CRC) diagnosed and treated at the University Hospital Ulm in Germany and overall survival or disease-free survival showed that increased tumor markers are correlated with lower life expectancy and reduced disease-free survival [29]. Although diagnostic benefits are not observed, it is recommended to measure tumor markers CEA and CA19-9 for prognostic purposes before proceeding with primary surgery. Several retrospective studies have shown that a preoperative serum concentration above 5 ng/ml for the CEA marker is correlated with a reduction in overall survival after surgical resection [8,30]. The univariate analysis of data from our series shows that the initial high AEC level increases the risk of death by 3.54 (95% CI: 1.43_8.73). For an initial CA19.9 level greater than 37 IU/ml, the analysis of our data found a risk of death multiplied by 5.19 (95% CI: 2.04_13.2) in univariate and by 4.97 (95% CI: 1.94_12.73) in multivariate (adjustment for age and stage). A meta-analysis of relevant studies showed an association between high serum CA 19-9 levels before treatment and poor survival in CRC patients [31]. Serum CA 19-9 level can be used as a marker to facilitate treatment planning and prognostic evaluation of CRC patients.

The univariate and multivariate analysis of our data found a risk of death multiplied by 5.54 (95% CI: 2.01_15.23) and by 9.4 (95% CI: 1.92_45.79) for patients with initial hyperleukocytosis. Currently, the association between blood inflammatory markers and survival has been suggested in various malignancies [32-35].

We found that patients whose treatment protocol was "cancer surgery +/- metastases + adjuvant chemotherapy" have a better 5-year survival (70.3%) compared to those who followed the protocol

“Concomitant radio-chemotherapy + surgery +/- chemotherapy” (32.3%); HR=3.01 (95% CI: 1.4_6.49) univariate and HR= 5.04 (95% CI: 1.69_15) multivariate. This confirms that surgical resection remains, in the absence of contraindications, the best therapeutic weapon in the management of CRC [36].

Unfortunately, it is impossible to compare the survival of groups of patients with different locations and different treatments. The study of survival in colon cancer is significantly linked to the tumor location (colon or rectum) and even if it is colon cancer the prognosis is different between the left and right colon. In addition; the therapeutic weapons in the two locations are different in terms of efficacy, side effects. The tumor stage is the most important prognostic factor and it is normal to find a lower survival rate in metastatic situations compared to early stages, consequently the comparison of our results with those in the literature becomes complicated given the inclusion criteria of our study. Because the large clinical, therapeutic and prognostic differences between these two groups, the ideal is to focus on a single location (colon or rectum) and a single stage (early or metastatic stages) in another future study.

Like any scientific work, the constraints encountered and the limits noted during the realization of this survival study should be noted: The quality of the data provided in the medical files, particularly the socio-demographic, clinical and biological information, is often meager. The survival analysis that we performed only concerned new cases of colorectal cancer in 2015. In order to obtain more precise results, a study with a larger number of patients should be conducted for better extrapolation of results and better comparability. Nevertheless, these results provided an overview of the current situation regarding the survival rate of colorectal cancer patients in the wilaya of Batna and can be used for possible future cancer education and screening programs and activities.

To improve monitoring of colorectal cancer and cancer in general, and to guarantee optimal care for patients affected by this serious pathology we offer: Expand the study to investigate the effect of other prognostic factors to guide the development of more effective therapeutic approaches for CRC in this region. Immediately launch organized national screening programs subjects at moderate risk of colorectal cancer, from the age of 50. Strengthening the role of primary prevention centered on Information Education Communication; healthy food, regular physical activity ... etc...

Conclusion

²²In our study, the overall survival rate for colorectal cancer at 5 years is 38.5% after diagnosis. Over half (52.9%) of the cohort with a known stage presented with advanced disease (stage III/IV). While the exact etiology for the delay in finding a treatment is unclear, it is potentially attributable to insufficient public awareness and knowledge of colorectal cancer. We found a 5-year survival rate of 72.7% in stage I and 85% in stage II, an aberrant result that may be due to information bias. Multivariate analysis confirmed that cancer stage and pTNM staging at diagnosis are strong factors affecting survival of CRC patients. To improve patient outcomes, we recommend: 1) expanding research into additional prognostic factors to guide therapeutic development; 2) the immediate implementation of organized national screening for moderate-risk individuals starting at age 50; 3) enhancing primary prevention strategies focused on Information, Education, and Communication (IEC) promoting healthy diets and physical activity ...and such...

Conflicts of interest

Authors do not declare any conflict of interest.

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