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Stage II colon cancer: epidemiological, clinical characteristics, and comparison of survival according to prognostic factors

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ABSTRACT

Colorectal Cancer (CRC) is a major public health problem in Morocco and ranks second among digestive cancer after gastric cancer. The indication for adjuvant chemotherapy for stage II colon cancer remains controversial but should be considered in patients with high-risk characteristics. The objective of our study is to report clinical characteristics, poor prognostic factors and compare the Overall Survival (OS) and Recurrence Free Survival (RFS) according to the number of poor prognostic factors. This is a retrospective study which included 191 patients with colon cancer treated at the medical oncology department of Fez over a period from June 2010 to June 2023. Kaplan Meier method was used to evaluate median survival. 54 patients were diagnosed between the year 2010/2014 *vs.* 65 patients between 2015/2018 and 72 new patients between 2019/2023. The average age at the time of diagnosis was 58 years. The main clinical symptoms were occlusion, abdominal pain and transit disorders objectified in 33%, 28% and 26% of patients respectively. 53 patients (28%) had a stable Microsatellite Status (MSS), while only 16 patients (8%) were MSI. The most common poor prognostic factors were occlusion, pT4 status, vascular emboli and perforation found in 33%, 29%, 23.5% and 23% respectively. 41 patients (21.6%) had a single poor prognostic factor vs. 59 patients (31.1%) had 2 prognostic factors. The presence of 3 or more risk factors was reported in 68 patients (35.8%). Median Overall Survival (OS) and Recurrence Free Survival (RFS) was 88.5 months and 36.3 months respectively. We found significant variations in survival related to poor prognostic factors. Our study showed a decrease in the median OS and RFS with the increase of poor prognostic factors from 2 risk factors or more.

Keywords: colorectal cancer, stage II, poor prognostic factor, overall survival

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INTRODUCTION

Colorectal Cancer (CRC) is a major public health problem in Morocco and around the world. In Morocco, it ranks 3rd in men in terms of incidence of tumors after lung and prostate cancer, and 4th in women after breast, cervical and thyroid cancers with an incidence of 8.8% and 7.5% respectively [1-3]. CRC is staged by extent of primary organ involvement and metastatic spread to lymph nodes or distant organs [4, 5]. Patients with stage II CRC have a 5 years survival of 75% to 80% when treated surgically. Although surgical resection is very effective for localized disease, a significant proportion of stage II patients (20%-25%) develop disease recurrence. CRC can be distinguished into two main subgroups: Microsatellite Stable Cancers (MSS) and Microsatellite Instable Cancers (MSI) respectively. Histologically, the two molecular subgroups are similar, but clinically they behave differently. MSI cancers have a better prognosis, however they respond less well to chemotherapy [6, 7]. Adjuvant treatment for stage II colon cancer remains controversial but may be considered for patients with high-risk characteristics.

The aim of this work is to describe the various prognostic and clinicopathologic factors and to analyze Overall Survival (OS) and Recurrence Free Survival (RFS) in patients with stage II colon cancer with poor prognostic characteristics.

MATERIALS AND METHODS

This is a retrospective study which included 191 patients with stage II colon cancer, collected at the medical oncology department of the Hassan II university hospital center in Fez, during a 13 years period from June 2010 until to June 2023. Epidemiological, clinical, paraclinical and therapeutic data were collected from medical records in their computerized form (available in the hosix software). Statistical analysis of data was performed using Microsoft Office Excel and SPSS software. Kaplan-Meier analysis was used to determine overall and recurrence free survival rates. Comparisons of survival curves were calculated using the Log Rank test. The statistical significance threshold was set at $p<0.05$. The elements collected were: age at diagnosis, sex, personal and family history of cancer, tumor location, Tumour Node Metastasis (TNM) Classification, histological subtype, poor prognostic factors, date and type of surgery, type of systemic treatment, date of relapse, mutational status (MSI, RAS, and BRAF), disease-free survival and overall survival.

RESULT

From June 2010 to June 2023, 191 patients with stage II colon cancer according to the TNM classification were admitted to the medical oncology department of Fez. 54 patients were diagnosed between the year 2010/2014 *vs.* 65 patients between 2015/2018 and 72 new patients between 2019/2023 (Figure 1). The average age at the time of diagnosis was 58 years with extremes ranging from 20 years to 103 years. In our series, we noted a slight male predominance with a sex ratio (M/F) of 1/2. The main personal histories observed in our study are tobacco and excessive consumption of meat found in 20 patients and 25 patients respectively. Alcohol consumption, history of adenoma, Crohn's disease and obesity were objectified in 11 patients, 10 patients, 5 patients and 6 patients respectively. In our study, we did not observe several family histories of cancers in our patients. No Hereditary Non-Polyposis Colorectal Cancers (HNPCC) or familial adenomatous polyposis syndrome was detected. The clinical symptomatology was dominated by occlusion, abdominal pain and transit disorders objectified in 33%, 28% and 26% of patients respectively.

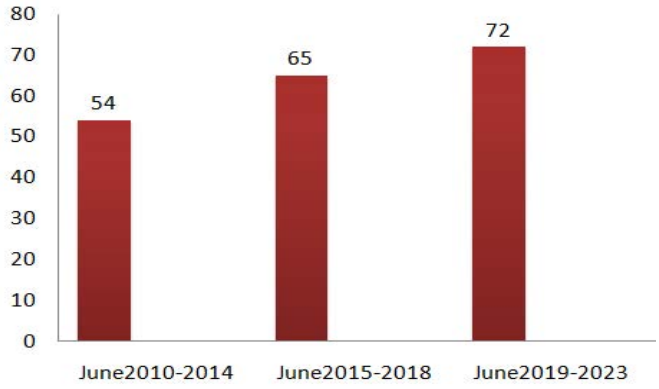

Fig. 1. Distribution of patients with stage II colon cancer over the years

The most common poor prognostic factors are occlusion, pT4 status, vascular emboli and perforation found in 33%, 29%, 23.5% and 23% respectively (Figure 2). 122 patients (64%) had an unavailable MSI status, 53 patients (28%) had a stable microsatellite status, while only 16 patients (8%) were MSI. 41 patients (2.6%) had a single poor prognostic factor *vs.* 59 patients (31.1%) had 2 prognostic factors. The presence of 3 or more risk factors was reported in 68 patients (35.8%) (Table 1). It was observed that 48% patients (N=92) were put under surveillance only and 52% patients (N=99) received adjuvant chemotherapy.

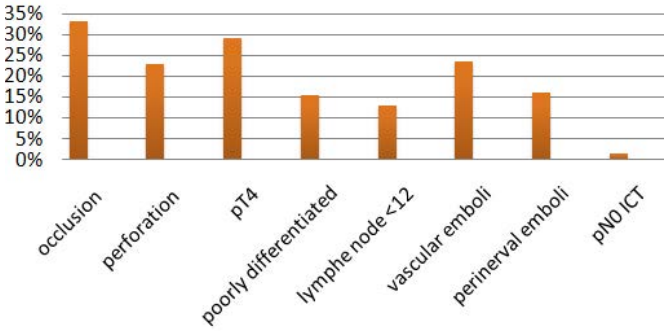

Fig. 2. Factors of poor prognosis in our population

Abbreviation: (pN0 ICT: Isolated Tumor cells in lymph nodes)

Tab. 1. Distribution of patients according to the number of prognostic factors

Number of prognostic factors					
		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0	22	11.6%	11.6%	11.6%
	1	41	21.6%	21.6%	33.2%
	2	59	31.1%	31.1%	64.2%
	3	43	22.6%	22.6%	86.8%
	4	25	13.2%	13.2%	100.0%
	Total	190	100.0%	100.0%	-

Coding:
0: No poor prognosis factor
1: One poor prognosis factor
2: Two poor prognosis factors
3: Three poor prognosis factors
4: More than three factors

Median OS and RFS were 88.5 months and 36.3 months respectively in the whole population. Stratification according to poor prognostic factors, showed a decrease in OS and RFS associated with an increase in the number of risk factors with a very significant p<0.001. No difference is objectified between OS and RFS in patients without or with only one poor prognostic factor (Figure 3 and 4).

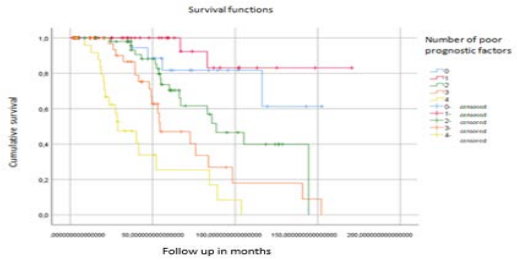

Fig. 3. Overall survival of patients according to the number of poor prognostic factors

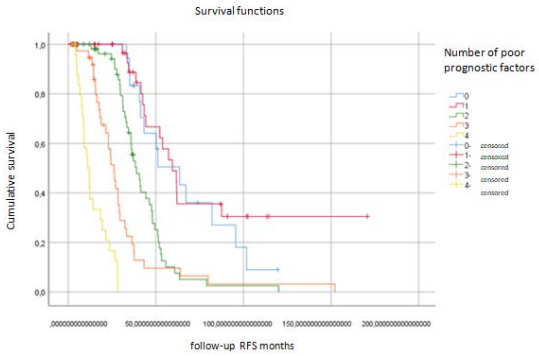

Fig. 4. Recurrence free survival of patients according to the number of prognostic factors

DISCUSSION

Stage II colon cancer is characterized by a very heterogeneous prognosis associated with 5 years overall survival rates of 87.5% in stage IIa and 58.4% in stage IIc [8]. Thus certain stages II with a high "relative" risk of recurrence have a poorer prognosis than certain stage III with low risk [9, 10]. The demonstration of the potential interest of adjuvant chemotherapy for stage II cancers was reported through the results of the QUASAR study which compared adjuvant chemotherapy with FOLFOX to an arm without adjuvant chemotherapy in patients with CRC mostly stage II (91%). In subgroup analysis, for stage II colon cancers, the relative risk of recurrence at 2 years was reduced by 29% with a Hazard Ratio (HR) of 0.71 with a non-significant trend towards improvement in overall survival [11].

In our study, median recurrence-free survival was 36 months, and we found significant association between the time to relapse and the number of poor prognostic factors.

The determination of MSI or Deficit in Mis-match Repair (dMMR) status is recommended to discuss the indication of adjuvant chemotherapy for a patient operated for stage II colon cancer with poor prognostic factors. The good prognosis of patients operated for stage II colon cancer with a molecular MSI and/or dMMR phenotype is an argument for not offering adjuvant chemotherapy.

Stage II tumors should be stratified according to their "relative" risk of recurrence: low or moderate "relative" risk of recurrence: for patients with proficient MMR (pMMR)/MSS tumor with the following good prognostic factors: T3, analysis of more than 12 nodes, absence of venous, perineural and/or lymphatic emboli, well or moderately differentiated tumor, and absence of tumor perforation or for patient with dMMR/MSI tumor.

High "relative" risk of recurrence (pMMR/MSS tumors with one or more of the following poor prognostic factors): T4, analysis of less than 12 nodes, presence of venous, perineural and/or lymphatic emboli, poorly differentiated tumor, tumor perforation and for some revealing occlusion and presence of isolated neoplastic cells in a N_0 node (pN0 INC).

In our study, the most common poor prognostic factors are occlusion, pT4 status, vascular emboli and perforation found in 33%, 29%, 23.5% and 23% respectively.

For some experts, the presence of perineural or lymphatic emboli cannot be considered as a high risk when it is a single risk factor. Also the occlusive nature of the tumor in endoscopy is not a factor of poor prognosis, unlike the clinical and radiological occlusive syndrome treated by stoma or emergency colectomy [12].

The poorly differentiated nature of the tumor is associated with a high risk only in the case of an MSS tumor (MSI tumors are very often poorly differentiated and have a good prognosis). The presence of isolated neoplastic cells in a ganglion is a rare situation that is considered by some to be a high risk factor [13].

Another approach is currently being studied, which is the monitoring of residual disease through circulating DNA of Tumoral origin (ctDNA) in the blood. The detection of ctDNA postoperatively in patients with localized colon cancer is very promising as a biomarker associated with disease-free survival and overall survival and for monitoring adjuvant chemotherapy. Prospective studies are currently underway to validate it as future factor in the strategy of adjuvant treatment of localized colon cancer, such as the CIRCULATE-PRODIGE 70 study in stages II [14].

An immunoscore for in situ quantification of lymphocyte infiltrate has been evaluated within the framework of an international consortium with the aim of standardizing this score in clinical

practice [15]. The reproducibility of the standardized score has been validated in a series of 2681 patients with stage I, II or III colon cancer and its prognostic value in localized colon cancers has been confirmed.

In the near future, a more precise molecular classification of colon cancers will make it possible to stratify the therapeutic manage-ment of patients with localized colon cancer with perhaps differ-ent treatments for BRAF mutated, dMMR/MSI, HER2 ampli-fied, KRAS G12C mutated [16].

In the end, in the adjuvant setting, no biological factor predicting the efficacy of adjuvant chemotherapy has been identified to date with a sufficient level of evidence, but studies are currently under-way to assess their place as a decision-making factor in therapeutic strategies for the management of localized colon cancers.

CONCLUSION

The indication of adjuvant chemotherapy for patients with stage II colon cancer should be discussed based on poor prognostic factors with knowledge of the MMR/MSI status. A significant impact of the number of poor prognostic factors on overall survival and recurrence free survival was demonstrated.

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