Oncology

Prognosis and molecular characteristics of IBD-associated colorectal cancer: Experience from a French tertiary-care center

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ABSTRACT

Background: Little is known about the prognosis of colorectal cancer associated with inflammatory bowel disease (CRC-IBD) in a real-world cohort in France.

Methods: We conducted a retrospective observational study including all patients presenting CRC-IBD in a French tertiary center.

Results: Among 6510 patients, the rate of CRC was 0.8% with a median delay of 19.5 years after IBD diagnosis (median age 46 years, ulcerative colitis 59%, initially localized tumor 69%). There was a previous exposure to immunosuppressants (IS) in 57% and anti-TNF in 29% of the cases. A RAS mutation was observed in only 13% of metastatic patients. OS of the whole cohort was 45 months. OS and PFS of synchronous metastatic patients was 20.4 months and 8.5 months respectively. Among the patients with localized tumor those previously exposed to IS had a better PFS (39 months vs 23 months; $p = 0.05$) and OS (74 vs 44 months; $p = 0.03$). The IBD relapse rate was 4%. No unexpected chemotherapy side-effect was observed

Conclusions: OS of CRC-IBD is poor in metastatic patients although IBD is not associated with under-exposure or increased toxicity to chemotherapy. Previous IS exposure may be associated with a better prognosis.

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1. Introduction

Inflammatory bowel disease (IBD) patients are at increased risk of developing colorectal cancer (CRC) which is 2–5 times as high as the general population [1,2]. A meta-analysis of data from population-based studies found a pooled standardized incidence ratio for colorectal cancer of 1.7 in IBD population [3]. Colitis-associated CRC do not follow the typical adenoma-carcinoma sequence but results from a multi-focal genetic alterations secondary to chronic inflammation of colonic mucosa [4,5]. Endoscopic surveillance with intervals according to the presence of risk factors can detect pre-cancerous lesions and cancers at an earlier stage, thereby reducing the risk of cancer [6]. Risk factors for

advanced CRC in IBD have been widely studied. A recent meta-analysis found a strong or moderate evidence for the following parameters: extensive disease, history of low grade dysplasia, concomitant primary sclerosing cholangitis, ulcerative colitis (UC) versus Crohn's disease (CD), stricture, post-inflammatory polyps and family history of CRC [7]. More recently, the genomic landscape of IBD-associated CRC has also been explored by large genomic analysis leading to better understand molecular alterations of these tumors [8]. A specific genomic profile could be defined in CRC-IBD compared to sporadic CRC with alterations in unusual genes like IDH1 and uncommon mutation prevalence in TP53 or genes of the WNT pathway. Few data are available on characteristics, treatment, and prognosis of CRC-IBD in population-based [9,10] . IBD-CRC occur at a younger age and appear to have a worse prognosis than sporadic CRC. However studies evaluating the prognosis of CRC-IBD provide conflicting results. Thus, in a cancer registry from Ireland the treatment modalities were similar and the survival times of

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CRC patients with and without IBD did not differ significantly [11]. In France, the main data come from the Burgundy digestive cancer registry, which found a five-year relative survival of 41.3% survival in IBD patients and 51.9% in non-IBD patients [10]. The modalities of diagnosis, the precise details of IBD characteristics and cancer treatment as well as the molecular characteristics according to the initial tumor stage have been poorly reported in the literature. Our unit is both a French tertiary referral center for the management of IBD and a regional reference center for the management of digestive cancers. The objective of this study is to report the clinical and molecular characteristics as well as the prognosis and therapeutic management of all CRC-IBD patients treated in our department.

2. Patients and methods

2.1. Cohort selection

This work is a retrospective observational cohort study. Among all patients followed in our tertiary French center for IBD, all patients presenting CRC-IBD between 1990 and 2021 were included. Patients were identified either from our hospital database or from the analysis of prospectively collected records of oncologic multidisciplinary meetings. The study protocol has been declared to the CNIL (Commission Nationale de l'Informatique et des Libertés; number 2,227,992). All data were anonymously collected and, according to the Loi Jardé (French law amended by Order no. 2016–800 and its implementing decree no. 2016–1537 of 16/11/ 2016 relating to research involving the human person), no patient consent was needed, as this was an observational cohort study without any intervention.

2.2. Data collection

Clinical, biological and histological parameters were collected retrospectively. For the IBD, data collected included the type of IBD, age at diagnosis, IBD topography, associated primary sclerosing cholangitis, IBD specific treatments (including 5ASA, immunosuppressants, anti-TNF and other biotherapies) before and at the time of cancer diagnosis and the delay between IBD and cancer diagnosis. For the cancer, data collected included age at diagnosis, cancer location, modalities of cancer diagnosis, cancer extension at diagnosis (localized or metastatic, TNM status), cancer histology (level of tumor differentiation, presence of independent cells, mucinous status), molecular biology status (*RAS, BRAF* and *MSS* vs MSI status) and cancer management including primary tumor resection, irradiation of the primary tumor (for rectal lesions), chemotherapy (neoadjuvant, adjuvant or metastatic and type of chemotherapy drugs used. Patients were included in this cohort at cancer diagnosis until date of the latest news. Outcomes included cancer progression, date of death and date of the latest news.

2.3. Genomic analysis

Formalin Fixed-Paraffin Embedded (FFPE) primitive tumor sample sections (diagnostic biopsies or surgical specimen), with a minimal 30% tumor content, were used for DNA extraction with Promega Maxwell 16 Tissue Lev DNA kit (Promega) DNA was analyzed by next generation sequencing with the amplicon based Trusight Tumor 26 panel (Illumina) and sequenced on a Miseq plateform (Illumina) with a minimal 1000X coverage. Bioinformatic analysis were performed on SophiaDDM (Sophiagenetics) and pathogenic substitutions/indels on the 26 panel-covered genes (AKT1, ALK, APC, BRAF, CDH1, CTNNB1, EGFR, ERBB2, FBXW7, FGFR2, FOXL2, GNAQ, GNAS, KIT, KRAS, MAP2k1, MET,MSH6, NRAS, PDGFRA, PIK3CA, PTEN, SMAD4, SRC, STK11, TP53) were reported. In addition, IDH1 R132 status was screened using High Resolution

Melting (HRM) analysis of IDH1 exon 4 on the LightCycler 480 System (Roche) and characterized by direct sequencing as previously described [12]. Microsatellite instability was determined according to Buhard et al. [13].

2.4. Endpoints

Progression-free survival was defined by the delay between cancer diagnosis and cancer recurrence (either local or metastatic) or death for localized tumors at diagnosis. Overall survival was defined by the delay between cancer diagnosis and death.

2.5. Statistical analysis

Quantitative variables were expressed using median and interquartile range (IQR), and qualitative variables using count and percentages. Both progression-free survival and overall survival were estimated using Kaplan–Meier method. Prognostic value of several baseline characteristics were tested using log-rank test. Statistical analyses were performed using R version 4.0.3, all tests were two-tailed and a p value of less than 0.05 was considered as statistically significant.

3. Results

3.1. Patient characteristics at cancer diagnosis

Among a cohort of 6510 patients with IBD, 49 were diagnosed with colorectal cancer (IBD-CRC) during the course of their disease. The rate was hence of 0.8%. Median follow-up was of 40.1 months (13.5–66.6). Among these 49 patients, 29 (59%) had UC, 19 (39%) had CD and 1 (2%) an indeterminate Colitis. IBD location was beyond the splenic flexure in 30 cases (61%), left sided in 8 cases (16%), ileal and pancolonic in 10 cases (20%) and ileocaecal in 1 case (2%). Four patients of the cohort had an associated primary sclerosing cholangitis. In the whole population, almost three quarters were exposed to salicylates (73%), more than half (57%) to immunosuppressants and almost a third (29%) to anti-TNF. In the subgroup of initially localized cancers 56% of patients were exposed to immunosuppressants (Thiopurines 79%, Methotrexate 21%). In the sub-group of synchronous metastatic patients 60% of patients were exposed to immunosuppressants (Thiopurines 89%, Methotrexate 11%). Nine (18%) patients underwent surgery for their inflammatory bowel disease before cancer diagnosis.

3.2. Whole population: CRC characteristics and outcomes

In the 49 IBD-CRC cohort, the median age at cancer diagnosis was of 46 years (IQR 36–58) after a median IBD evolution of 19 years (IQR: 14–25). Thirty-four (69%) tumours were localized at diagnosis while 15 (31%) presented synchronous metastases (Fig. 1). Overall median survival of the whole cohort was 44.9 months (IC95%: 31–73.7) (Fig. 2*a*). As expected, overall median survival was significantly better in patients with initially localized tumours as compared to patients with synchronous metastases (median OS: 74 months vs 20 months, p = 3e-06) (Fig. 2*b*). The overall median survival of all metastatic patients was 24 months (Fig. 2*c*). More than half (53%) of the tumor were rectal cancers. Around a quarter was diagnosed on planned surveillance colonoscopy (24%), 68% secondary to intestinal symptoms or IBD complications and 8% due to inaugural symptomatic metastases. These proportions were similar for both rectal and colon cancers. Eleven (23%) tumors were mucinous, 9 (19%) poorly differentiated and 6 (12%) presented independent cells. Genomic analysis reveal deleterious TP53 mutations in more than half of the CRC (26/49, 53%) around a third
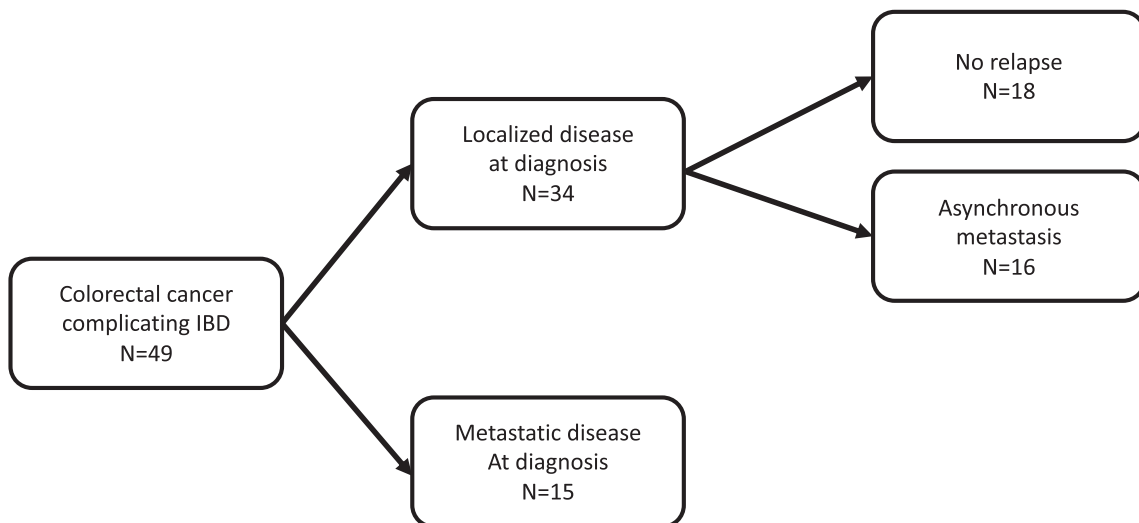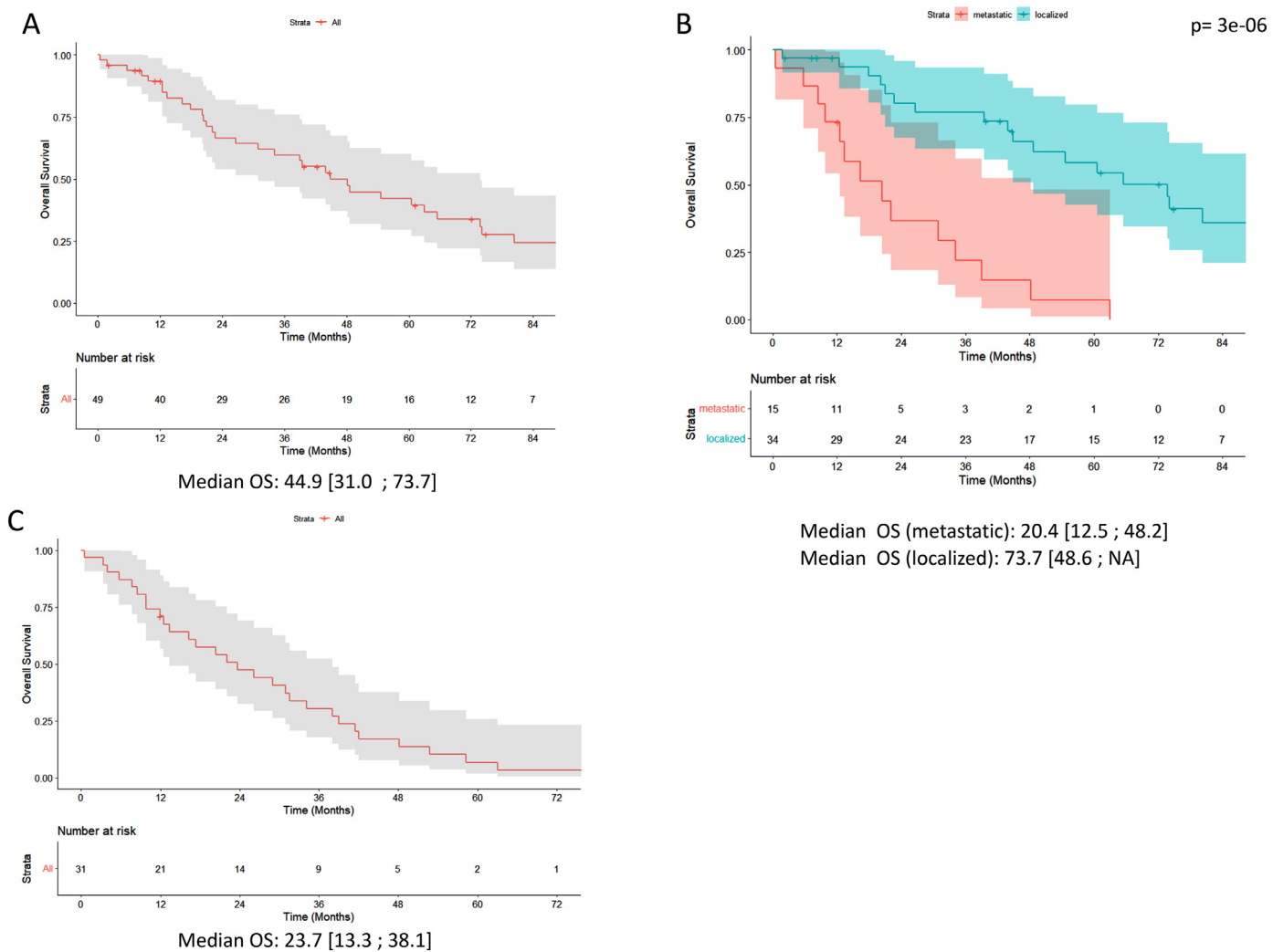
Fig. 1. Cohort Flow-charts.

Fig. 2. Overall survival. 2A: Overall survival of the whole cohort. 2B: Comparative overall survival of initially metastatic patients (red) and initially localized patients (blue) 2C: Overall survival of the metastatic patients (both synchronous and asynchronous)

Table 1a

Molecular biology in initially localized patients.

	$n = 28^*$
Molecular status (next generation sequencing)	
RAS	
Mutated	14 (50%)
Metastatic relapse	6
No Relapse	8
Wild type	14 (50%)
Metastatic relapse	8
No Relapse	6
***BRAF* V600E**	2 (7%)
MSI	1 (4%)
Other Mutations	
TP53	19 (68%)
PI3KCA	3 (11%)
CTNNB1	2 (7%)
FGFR1	0 (0%)
SMAD4	1 (4%)
IDH1	0 (0%)

Table 1b

Molecular biology in synchronous metastatic patients.

	$n = 15$
Molecular status (next generation sequencing)	
RAS	
Mutated	2 (13%)
Wild type	13 (87%)
***BRAF* V600E**	0 (0%)
MSI	0 (0%)
Other Mutation	
TP53	7 (47%)
PI3KCA	2 (13%)
CTNNB1	0 (0%)
FGFR1	1 (7%)
SMAD4	1 (7%)
IDH1	1 (7%)

*6 patients had no molecular biology available.

(16/49, 37%) RAS mutations and, only two (5%) BRAF V600E mutations. Very low mutation rates of other genes (PIK3CA, CTNNB1, FGFR1, SMAD4, IDH1) have been detected, especially, only one IDH1 R132 mutation could be identified.

3.3. Patients with initially localized disease: cancer characteristics and outcomes

Considering only the initially localized 34 IBD-CRC, half of the lesions were also of rectal location (17/34, 50%). The molecular characteristics of initially localized patients depending on whether or not a relapse has occurred are presented in (Table 1a). Almost all the tumors underwent resection except for one patient with concomitant pulmonary metastatic cancer. Preoperative treatment with either radiotherapy or radio-chemotherapy was needed in 7 (7/17, 41%) patients with rectal cancer. Grading at surgery reveled 22 (65%) were T3-T4 tumors with 17 presenting a lymph node invasion (50%). Adjuvant chemotherapy was needed in 18 patients (53%). (Table 2a). Among these initially localized IBD-CRC, 16 patients (47%) relapsed with metastasis. Fourteen of them (88%) received at least one chemotherapy regimen at relapse (Table 2a). Overall median survival was of 73.7 months (IC95%: 48.6-NR) (Fig. 2*b*). Median progression-free survival was of 38.8 months (IC95%: 22.5-NR) (Fig. 3*a*).

3.4. Factors associated with PFS and OS in patients with initially localized cancer

We try to find prognostic factors according to baseline characteristics. The following parameters were considered: tumor location, age at diagnosis of malignancy, IBD type, histological characteristics, molecular status and previous treatment exposure (*Supplementary Tables 1a and 1b*). Among them, we only found a significant association in patients with previous exposure to immunosuppressants. In this sub-group of patients, overall survival was significantly better (74 vs 44 months; $p = 0.03$) (Fig. 4). as well as progression-free survival progression-free survival (39 months vs 23 months; $p = 0.05$).

3.5. Patients with synchronous metastases at diagnosis: cancer characteristics and outcomes

As described, 15 patients presented metastasis at the diagnostic of IBD-CRC. Again, a majority of them (9/15, 60%) had a rectal cancer. Tumor management included primary tumor resection for a third of patients (5/15, 33%), irradiation of the primary tumor for 4 rectal cancers (27%) and metastasis resection for 3 (20%)

(Table 2b). All patients received at least one chemotherapy regimen. Rate of RAS mutation was low (2 patients and 13%). No BRAF mutation was found. Seven (47%) TP53 mutations were found, two PI3KCA (13%) and one FGFR1, SMAD4 and IDH1 (7%) (Table 1b). Median progression-free survival was 8.5 months (IC95%: 4.6–15.1) (Fig. 3*b*). Overall median survival was 20.4 months (IC95%: 12.5–48.2).

4. Relapse of IBD and chemotherapy toxicity

Despite the discontinuation of immunosuppressants and/or biologics in all patients at cancer diagnosis, we observed a low relapse rate of IBD in patients exposed to chemotherapy or radiotherapy. Two patients with UC experienced a clinical relapse necessitating the initiation of a 5 ASA treatment allowing remission. Only one patient underwent intestinal resection during follow-up. Surgery was motivated by the suspicion of a complicated IBD flare-up which, per-operatively, corresponded to a peritoneal cancer relapse. We did not observe a significant increase in grade 3–4 chemotherapy toxicity. Five patients treated with oxaliplatin interrupted treatment because of neurotoxicity. We did not observe any signal of increased or unusual toxicity of any grade in patients exposed to anti EGF-R and anti-VEGF agents.

5. Discussion

In this study reporting the therapeutic management of CRC-IBD in a French expert center, we found an rate of 0.8% confirming that CRC-IBD represent a important issue in IBD expert center. To our knowledge, for the first time in the literature, we found that overall survival was significantly better in patients with previous exposure to immunosuppressants. It was already shown that patients with IBD and longstanding extensive colitis receiving thiopurine therapy were at lower risk of colorectal cancer in the French CESAME cohort [14]. Several studies have suggested that exposure to an anti-TNF agent or an antimetabolite after cancer regardless of the primary site was not associated with an increased risk of de novo cancer or relapse [15,16] To date, there is no evidence suggesting that previous exposure to immunosuppressant was associated with a better prognosis in patients with CRC-IBD. The underlying mechanism is unclear. We can assume that immunosuppressant may alter the drivers of cancer by reducing chronic inflammation. The reason why anti-TNF therapy did not have the same effect remains complicated to address in our cohort. These data highlight that the role of inflammation in the development of IBD-associated CRC remains poorly understood [17]. The interaction with the host immune system, the role of the microbiota and the molecular characteristics in the initiation and development of the tumor process
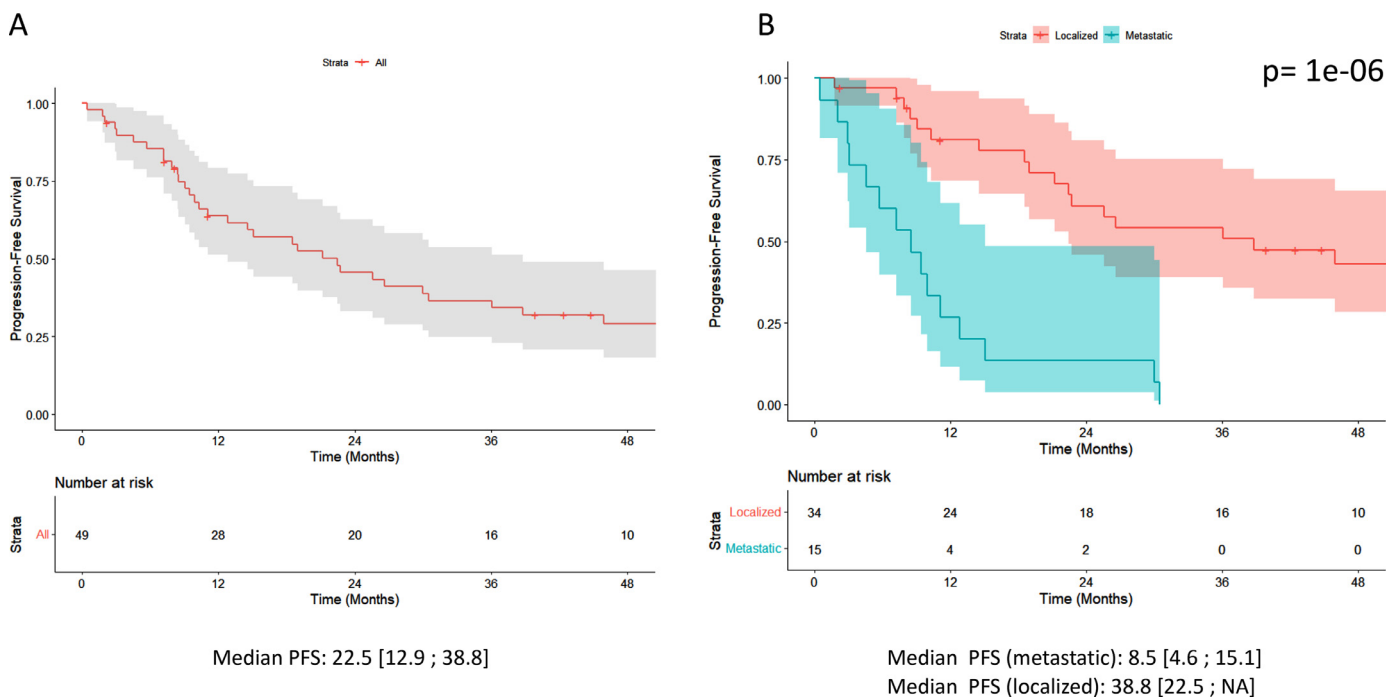
Median PFS: 22.5 [12.9 ; 38.8]

Median PFS (metastatic): 8.5 [4.6 ; 15.1]
Median PFS (localized): 38.8 [22.5 ; NA]

Fig. 3. Progression free survival. 3A: Overall survival of the whole cohort. 3B: Comparative overall survival of initially metastatic patients (red) and initially localized patients (blue).
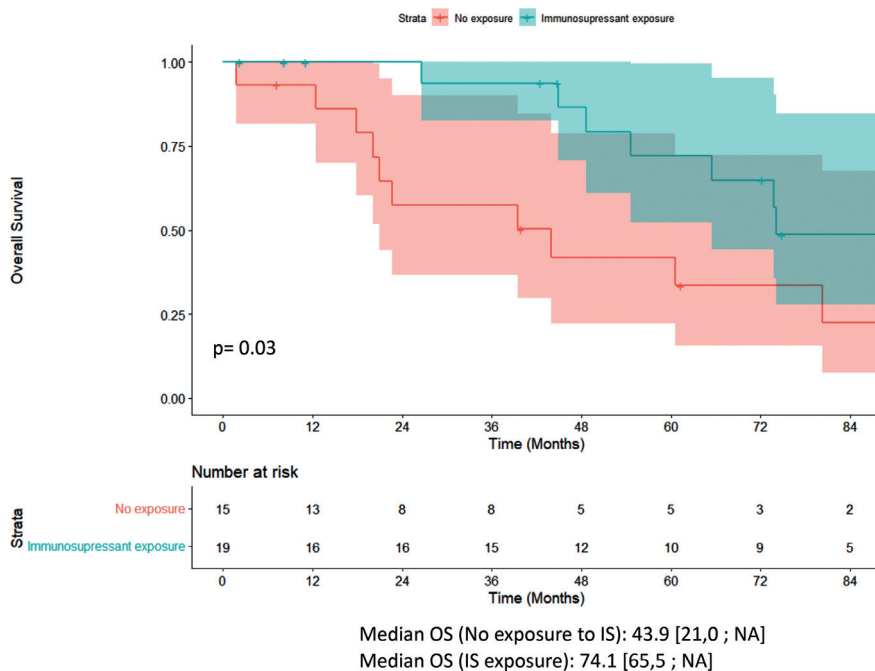

Median OS (No exposure to IS): 43.9 [21,0 ; NA]
Median OS (IS exposure): 74.1 [65,5 ; NA]

Fig. 4. Overall survival in initially localized patients according to immunosuppressant exposure.

are different in IBD-associated CRC. This may explain the difficulties in establishing a correlation between the impact of treatments controlling inflammation and the prognosis of IBD-associated CRC. The low number of patients included in this subgroup analysis which could have underpowered this evaluation might be an explanation. We also can assume than patients treated with biotherapy might have a more severe disease activity, long standing colitis and longer time since diagnosis which are known factors of CRC-IBD [14–16]. We confirm that the median age at diagnosis is lower than the one in sporadic cancers. Indeed, the median age at diag-

nosis is 46 years, whereas the median age at diagnosis of sporadic CRC is about 70 years in developed countries which is in line with other series [18]. Older studies report a later age in IBD population compared to our study. In the Irish and Danish registries, the mean age at diagnosis of CRC in IBD patients was 61.4 versus 69.1 years and 62.6 versus 71.2 years respectively [11,19]. As our data come from an expert center, they cannot be extrapolated to a national register. Thus, we manage a high proportion of patients diagnosed at a pediatric age as well as refractory patients in whom the probability of controlling IBD is lower. The long duration of the disease

Table 2a
Cancer characteristics and treatments (patients with initially localized disease).

	n = 34
Surgery	33 (97%)
Tumor location	
Rectum	17 (50%)
Radiotherapy / Radio chemotherapy	7
Immediate Surgery	10
Colon	17 (50%)
T grade at surgery	
T1-T2	11 (32%)
T3	15 (44%)
T4	7 (21%)
No surgery	1 (3%)
N grade at surgery	
N0	16 (47%)
N1	10 (29%)
N2	7 (21%)
No surgery	1 (3%)
Adjuvant chemotherapy	
Yes	18 (53%)
No	15 (44%)
No Surgery	1 (3%)
Relapse	
No	18 (53%)
Yes	16 (47%)
Histological and molecular status in patients with relapse (*n* = 16)	
Poorly differentiated	2 (13%)
Mucinous lesion	2 (13%)
Independent cell carcinoma	0
T3-T4	14 (88%)
N1-N2	8 (50%)
RAS mutation	6 (38%)
BRAF V600E mutation	2 (13%)

Table 2b
Cancer characteristics (patients with synchronous metastases).

	n = 15
Tumor location	
Rectum	9 (60%)
Colon	6 (40%)
Primary tumor resection	5 (33%)
Radiotherapy (anorectal)	4 (27%)
Metastasis resection	3 (20%)
Histological and molecular status	
Undifferentiated	6 (40%)
Independent cell carcinoma	4 (27%)
Mucinous lesion	4 (27%)
RAS mutation	2 (13%)
BRAF V600E mutation	0

and the lack of control of the inflammatory process are probably a predominant feature of our cohort that may explain the younger age at cancer diagnosis. The relationship between young age at diagnosis and the risk of developing CRC-IBD has not been found in historical series including national registers but these data cannot be extrapolated to a tertiary referral center [20]. In addition, it is likely that the recommendations concerning endoscopic screening are better applied than in a non-expert center leading to an earlier diagnosis. Nevertheless, the high percentage of synchronous metastatic cancer suggests the occurrence of interval cancers. Non-compliance with screening endoscopies, non-adherence to recommendations and differences in expertise between endoscopists may explain this finding [21].

The median delay of cancer onset after IBD diagnosis is 19.5 years. Longstanding IBD except proctitis have an approximately 2–3-fold increased risk of CRC varying according to the study period [22]. In one of the most recent meta-analysis cumulative risks of CRC were 1%, 2%, and 5% after 10, 20, and >20 years of disease duration respectively, which represents a lower excess risk than

previously reported [3]. In the Burgundy registry, the duration of IBD before the diagnosis of cancer was between 15 and 24 years in 48% of cases, and > 25 years in 37% of cases which is similar to our data [10]. In our study, 81% of patients had extensive colitis at diagnosis of cancer. This underlines the major role of disease extension in carcinogenesis of CRC-IBD. We observed a higher proportion of cancer occurring in UC representing 59% of our cohort. The over-risk of cancer has long been considered higher in UC than in CD. However, the incidence rates of CRC among individuals with CD and UC seem similar in an American database [23]. The overrepresentation of UC-associated cancers is difficult to interpret given the small number of patients in our population. We observed a surprisingly high rate of rectal cancer of 49%. This is in line with some studies that also highlighted a higher rate of distal cancers in IBD patients [24]. In a historical cohort of the SEER database, the percentage of rectal cancer was 15.6% and the percentage of rectal and rectosigmoid tumors was 34% in an Irish register [11,25]. In the only French report to date, the percentage of rectal cancer was 31.6% [10]. It is possible that a consultation for urgency or rectal bleeding is more easily accessible in an expert center, leading to early recourse to flexible sigmoidoscopy in a population of refractory patients at higher risk of cancer. This does not seem to be related to a bias linked to recruitment modalities, as the patients were not referred with a diagnosis of rectal cancer already established. Two-thirds of the cancers were initially localized in our cohort. The nationwide population-based Danish studies of CRC in UC and CD reported stage 4 disease in 17% and 23% patients, respectively, results that were not significantly different from the general CRC population in that country [19,26]. Our data therefore confirm the widespread prevalence of localized CRC-IBD at diagnosis. The proportion of patients receiving adjuvant chemotherapy is slightly higher than the number of patients with lymph node invasion suggesting that the standard of care has been applied to the majority of patients contrarily to the sporadic cancer population [27]. Nearly all patients presenting metastatic disease have received at

least one line of systemic chemotherapy (93%). In a French registry that studied the management of patients with metastatic colorectal cancer between 1999 and 2010, only 40% of patients with synchronous metastases and 42% of patients with asynchronous metastases had received chemotherapy [28]. They were, however, over 75 years old in 45% of cases reflecting the general population of patients with sporadic cancer but not that of IBD patients who are younger and have therefore a higher probability of being exposed to chemotherapy. We did observed very few relapses of IBD during chemotherapy despite the fact that all patients stopped immunosuppressants and/or biologics at the time of cancer diagnosis. We did not observe any unusual toxicity or obvious increase in the rate of severe chemotherapy toxicity, particularly digestive, regardless of the drug or targeted therapy used. IBD therefore does not appear to be a limiting factor for chemotherapy use. There are conflicting data regarding survival in the literature with one Norwegian registry reporting a worse prognosis of CRC-IBD while an Irish registry reported no difference [11,29]. Overall survival of our whole population was 45 months which seem in line with European registers of sporadic CRC [30,31]. In a French registry, the survival rate at 5 years of CCR was 93% for stage I, 78% for stage II, 56% for stage III and 8% for stage IV [32]. In our cohort of initially localized patients, progression free survival was 38.8 months and overall survival was 73.7 months which seem close to those of French randomized trial MOSAIC [33]. In our cohort of synchronous metastatic patients, progression free survival was 8.5 months and overall survival was 20.4 months, which is much lower than reported in clinical trials of sporadic metastatic colorectal cancer [34,35]. These data are in line with a recent retrospective matched cohort of 18 CRC-IBD patients which found an even lower median OS [9]. The overall survival of all metastatic patients is also poor at 24 months. This is not related to treatment under-exposure and may reflect a more severe prognosis in CRC-IBD. However, real-life studies have a lower survival rate than in clinical trials where patients are highly selected. Therefore, it cannot be formally concluded that the prognosis is worse because of IBD. CRC-IBD exhibit genomic differences when compared to sporadic CRC, suggesting different pathways of carcinogenesis [8]. As expected, mutation of the *TP53* tumor suppressor gene is the most frequent somatic genetic alteration. The rate of *BRAF* V600E mutation and MSI tumors is similar to that of sporadic tumors. The potential for treatments targeting these mutations such as encorafenib and immunotherapy is therefore limited in CRC-IBD. No *APC* mutations were found confirming that the classical APC inactivated adenoma pathway does not appear to be a mechanism of carcinogenesis in CRC-IBD. We confirm that *KRAS* mutations were significantly less common then in sporadic CRC [36,37]. Although the mechanism is unclear, this feature is of major interest allowing more frequent use of anti-EGFR agents, a major therapeutic class in metastatic patients. *IDH1* mutation has been reported as more frequent in CRC-IBD than in sporadic CRC with rates of 7% to 11% [38]. This finding was also confirmed in small bowel adenocarcinomas in patients with CD [39]. We do not confirm this data. This is not clearly related to our sample size, as the main genomic studies reported in the literature involve a smaller number of patients. Early-onset colorectal cancer younger than 50 years in non-IBD patients is an emerging topic with different features comparing to late-onset disease [40]. Those patients tend to be more often of distal location with a more advanced stage at diagnosis and associated with pejorative histological features (poor differentiation, mucinous morphology). Their molecular profile also differs with more microsatellite instability tumors, more frequent TP53 variations and are less likely to harbor KRAS, BRAF and APC mutations. Some of these characteristics are therefore different from our population.

Our work has some important limitations as this is a monocentric and retrospective analysis study with a long inclusion period which may lead to a bias in the interpretation of our data. The standards of care have changed over time with a trend to better prognosis in the more recent periods and use of new drugs and more aggressive strategies in the metastatic setting. Thus, it cannot be excluded that the prognosis might be different if we have considered only more recently treated patients. Some subgroups of interest, notably CRC associated with primary sclerosing cholangitis, could not be studied due to the small number of patients in our cohort. Our work has some strengths as well. It reports comprehensive clinical data on both IBD and cancer with a focus on molecular status in a real-life study and provides useful date in routine practice.

6. Conclusion

CRC-IBD is a frequent issue in IBD expert centers. Their prognosis is poor especially for synchronous metastatic patients. We found that previous exposure to immunosuppressants seems to be associated with a better outcome in initially localized patients. We did not observe any increased rate of severe chemotherapy toxicity or unusual toxicity. Very few IBD relapses were noted during follow-up despite immunosuppressants and/or biologics withdrawal at cancer diagnosis. A case-control matched study is currently ongoing with the present cohort to better compare this population with sporadic CRC. Improvement of endoscopic screening and new approaches for cancer diagnosis represent major issues. Further works on the mechanisms of carcinogenesis of CRC-IBD are needed to improve their prognosis.

Conflict of interest

MA received grant supports from Innate Pharma, Janssen, Takeda, Genentech/Roche, and honoraria for teaching activities or consultancy from Abbvie, Amgen, Biogen, Boehringer-Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Ferring, Genentech, Gilead, IQVIA, Janssen, Novartis, Pfizer, Roche, Takeda, Tillots. T.A. presented conferences for Shire, Ipsen, Amgen, BMS, Servier, Pfizer, Roche Sanofi and meeting grants for Ipsen, Novartis, Roche and Hospira. He also obtained research grant from Novartis and Innate Pharma. N.H. received honoraria for consultancy from Janssen and Takeda. M.L.T.M. received honoraria from Abbvie and Janssen. J.M.G. has been a speaker and/advisory board member for Abbvie, Amgen, Celltrion, Takeda, Janssen and Sanofi Genzyme. N.L. has been a speaker for Sanofi. J.L.C., J.L., M.A., L.M., C.B., N.A., B.P., and H.C. have no conflict of interest to declare.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. Additional data are available on request.

Author contributions

J.M.G. designed the study, interpreted the data and wrote the manuscript; N.H.: collected data and wrote the manuscript; J.L.C. and B.P. performed the molecular biology analysis, J.L. performed the statistical analysis; M.A.: collected the data; L.M., D.S., M.L.T.M., C.B., N.A., N.L., H.C., M.A. and T.A. included patients and reviewed the final version of the manuscript. All authors read and approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.02.011.

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