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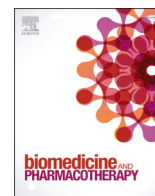
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The association of benzodiazepine and benzodiazepine-related drugs with outcomes after surgery for colorectal cancer

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ABSTRACT

Benzodiazepines increase plasma brain-derived neurotrophic factor (BDNF) level which, in turn, may improve survival in colorectal cancer (CRC) patients. This study aimed to evaluate the associations between benzodiazepine and benzodiazepine-related drugs (BZRD) use and outcomes of patients operated for CRC. This is a retrospective cohort study including patients operated for CRC at Limoges' University Hospital between 2010 and 2019. Data were collected from two sources: medical records of patients in the digestive, general and endocrine surgery department at Limoges University Hospital and from the Haute-Vienne general cancer registry. Patients were divided into benzodiazepine users and non-users. Outcomes were overall survival (OS) and recurrence-free survival (RFS). Among 504 patients who underwent surgery for CRC, 125 (24.8%) patients were treated with benzodiazepine/BZRD drugs. Users and non-users of benzodiazepine/BZRD showed no statistically significant differences in 5-year OS ($45.5 \pm 1.9\%$ vs. $46.5 \pm 1.1\%$ $p = 0.25$) and 5-year RFS ($41.0 \pm 2.1\%$ vs. $39.6 \pm 1.3\%$, $p = 0.94$), even after adjustment for confounders and propensity score (OS: aHR=1.02, 95%CI: 0.71–1.48; RFS: aHR=1.00, 95%CI: 0.72–1.40). Subgroup analysis on CRC patients with psychiatric disorders revealed that benzodiazepine users had better RFS (aHR=0.58, 95%CI: 0.35–0.96) compared with non-users, particularly, patients with stages III or IV of CRC had better OS (aHR=0.27; 95%CI: 0.12–0.59) and RFS (aHR=0.30, 95%CI: 0.15–0.62). OS and RFS was significantly better in patients taking benzodiazepines classified as anxiolytics, having longer half-life, and producing active metabolites. In conclusion, benzodiazepine use was not associated with outcomes in CRC patients. Nevertheless, in subgroup of patients with psychiatric disorders and advanced CRC stage, benzodiazepine could improve survival.

1. Introduction

Colorectal cancer (CRC) corresponds to a malignant tumor from the mucosa of the colon or the rectum [1]. CRC is the second most deadly cancer worldwide (9.4%), and the third most diagnosed form of cancer globally (10.0%) for both sexes combined [2].

The survival of patients with CRC depends on a variety of prognostic factors including the cancer stage at diagnosis, histological factors (tumor grade, tumor perforation, vascular invasion, perineural infiltration) and post-therapy follow-up [3].

Due to the life-threatening nature of the disease, the need for regular follow-up, the adverse effects of adjuvant treatment, and the life changes

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that occur after diagnosis, patients with cancer are more likely to suffer from psychiatric disorders such as anxiety, depression, and sleep disorders [4,5]. In this regard, the prevalence of depression in colon cancer is estimated to be high, between 13.0% and 25.0% [6].

Benzodiazepines are among the most commonly prescribed psychotropic drugs in the high income countries [7–9]. They are generally used to treat anxiety and/or insomnia and may be prescribed in specific cases such as epilepsy, dementia-related agitation and acute alcohol withdrawal symptoms [7–9].

Benzodiazepines share a common molecular structure, and their effects in humans are primarily produced by allosteric modification of a the Gamma amino butyric acid (GABA) receptor, which increases the overall conductance of these inhibitory channels; resulting in the various therapeutic effects of benzodiazepines [10].

The latest research on the effect of benzodiazepine use on survival was conducted by Oh et al. in 2023 among non-cancer patients with chronic musculoskeletal pain who found that benzodiazepine increased 10-year all-cause mortality [11]. Findings regarding the association between benzodiazepine use and cancer risk have been controversial. Although a previous meta-analysis has suggested a positive association between benzodiazepine use and cancer risk [12], a more recent meta-analysis found that the use of lower dose hypnotics and shorter durations of exposure to benzodiazepines was not associated with an increased risk of cancer [13]. An updated review on adverse effects of benzodiazepine and BZRD found that there is currently a lack of conclusive, high-quality epidemiological and experimental evidence to confirm an association between benzodiazepine use and cancer risk [14].

When it comes to cancer survival, data from existing research on the effects of benzodiazepine use are limited. From a mechanistic point of view, Sarabi et al. found that CRC patients receiving benzodiazepines had better survival and higher serum levels of brain-derived neurotrophic factor (BDNF) compared with those not treated with these drugs [15]. Nonetheless, a recent study on the effect of propofol, benzodiazepines, and opioids on the survival of cancer patients in intensive care unit found that benzodiazepines were associated with an increased risk of 28-day mortality [16]. Another study found that benzodiazepine use was not associated with 5-year cancer mortality, but did increase mortality in patients with nervous system disease [17].

There is a lack of clear and comprehensive studies examining the relationship between benzodiazepine use and survival outcomes in patients with CRC, and previous studies have yielded inconsistent findings. Further research is needed to study the effect of benzodiazepine on CRC survival, as this directly impacts CRC patients who are at a high risk of developing psychiatric disorders and be treated with these drugs [18, 19].

The primary objective of this study was to evaluate the effect of benzodiazepine and benzodiazepine-related drugs (BZRD) use on overall survival (OS) and recurrence-free survival (RFS) in patients undergoing surgery for CRC, with a particular focus on assessing the effect in patients diagnosed with psychiatric disorders.

2. Materials and methods

2.1. Study design

This was a retrospective cohort study conducted at the University Hospital of Limoges-France using the “General Cancer Registry of Haute-Vienne, France” and medical records of the “Digestive, General and Endocrine Surgery” department. It included patients recorded by the general cancer registry and operated for CRC in the digestive, general and endocrine surgery department of Limoges University Hospital-France.

2.2. Inclusion and exclusion criteria

Patients over 18 years of age were included if they had undergone a surgery for CRC at Limoges University hospital between January 01, 2010 and April 30, 2019. Patients were excluded according to the following criteria: (1) non-resection of the colorectal tumor at surgery, (2) non-CRC after anatomopathological examination (e.g. ischemic injury, inflammatory lesion, appendiceal cancer, colonic and rectal metastases from another primary cancer), (3) benign colorectal tumor, (4) patients for whom the report of post-surgical anatomic pathology or the list of daily medications were not available in their medical records.

2.3. Benzodiazepine drug exposure

Benzodiazepines were defined as any drug within the Anatomical Therapeutic Chemical (ATC) groups N05BA (anxiolytics), N05CD (hypnotics and sedatives), N03AE (antiseizures medications, clonazepam). In addition, benzodiazepine-related drugs (BZRD) were defined as any drug within the ATC group N05CF (zopiclone, zolpidem).

In the present study, long-term benzodiazepine/BZRD use was defined as prescription of such drug for more than three months after the surgery for CRC. This same definition was used in previous studies [20–22]. Patients with prescription less than 3-month were considered as short-term benzodiazepine users [20–22].

The effect of benzodiazepine was first examined in long-term benzodiazepine/BZRD users. Subsequently, a subgroup analysis was also carried out to compare survival between subgroups of:

- Long-term and short-term benzodiazepine/BZRD users
- ATC classification of benzodiazepine: anxiolytics (bromazepam, diazepam, clobazam, prazepam, clorazepate, clotiazepam, oxazepam, lorazepam, alprazolam) vs. hypnotics (zolpidem, zopiclone, lormetazepam)
- Long half-life (≥ 20 h: bromazepam, diazepam, clobazam, prazepam, clorazepate) vs. short half-life of benzodiazepine (< 20 h: zolpidem, zopiclone, lormetazepam, clotiazepam, oxazepam, lorazepam, alprazolam)
- Molecules producing active metabolites (clobazam, diazepam, prazepam, clorazepate) or not (alprazolam, bromazepam, clotiazepam, lorazepam, oxazepam, lormetazepam)

2.4. Endpoints

The overall survival (OS) was the primary endpoint and was compared between benzodiazepine/BZRD users and non-users. The OS was defined as the time from CRC surgery to death from any cause. Data on the date of death were collected from the general cancer registry of the Haute-Vienne and from the death certificate in patient's computerized medical record at Limoges University hospital. When the information was not available in either source, it was verified by consulting the files of deceased person available on the website of the National Institute of Statistics and Economic Studies (INSEE) [23].

The secondary endpoint was recurrence-free survival (RFS), defined as the time between CRC surgery and the first documented local or distant (metastasis) CRC recurrence or death.

Recurrence of CRC was defined as recurrence at the site of anastomosis, pelvic cavity structure, systemic lymph nodes, liver, lungs, peritoneum, bones, and brain [24]. All cases of CRC recurrence were confirmed by computed tomography scan or magnetic resonance imaging and verified by biopsy. An expert (NC) reviewed suspected cases to confirm the presence or absence of CRC recurrence.

2.5. Follow-up time

The date of CRC surgery was the date of patient entry into this cohort. Patients were followed for five years after surgery, and follow-up

ended upon death for overall survival endpoint and upon death or recurrence for recurrence-free survival endpoint.

2.6. Data collection

Data collection was based on patients' electronic medical records from two sources:

- Medical records of CRC patients from the digestive, general and endocrine surgery department of Limoges University Hospital using the hospital systems.
- Patients records from the Haute-Vienne general cancer registry in France. The sources used for data collection in the cancer registry were as follows:

- Medical Information Departments of public and private facilities,
- The medical services of the health insurance of the Haute-Vienne,
- The public and private anatomical pathology, hematology, molecular biology and cytogenetics laboratories and cytogenetic laboratories of the Haute-Vienne,
- Summaries of Multidisciplinary Consultation Meetings, organized by the Limousin Regional Cancer Network, Limousin Hematology Oncology Network and the Haute Vienne Cancer Coordination Center,
- General physicians and specialists, and other cancer registries.

A double-check on the data collected from both sources (Cancer registry and department of digestive surgery) was performed for each patient. Data were coded anonymously and entered manually into a database stored on a secure server at the hospital.

2.7. Variables

The following variables were collected:

- Sociodemographic parameters and lifestyle: age, sex, body mass index (BMI: classified as underweight <18.5, normal 18.5–24.9, overweight 25–29.9 and obese ≥30), family history of cancer and CRC, alcohol consumption.
- Cancer treatment: surgery alone, neoadjuvant treatment and surgery, surgery and adjuvant chemotherapy.
- Clinical parameters for CRC: site (right colon (consists of caecum, ascending colon, and right hepatic flexure), transverse colon (encompasses the segment of colon between right hepatic flexure and left hepatic flexure as it is described by anatomists), left colon (consists of descending colon, left hepatic flexure and sigmoid colon), rectosigmoid junction and rectum), CRC stage at diagnosis (in situ, I, II, III, IV) according to American Joint Committee on Cancer (AJCC) 8th edition [25], type of CRC (Lieberkühn adenocarcinoma, mucinous adenocarcinoma, medullary carcinoma, neuroendocrine carcinoma, signet-ring cell carcinoma), tumor histology (well differentiated, moderately differentiated, poorly differentiated, undifferentiated), tumor size (<4, ≥4 cm), microsatellite status (microsatellite instability (MSI) or microsatellite stable tumor (MSS)), type of mutation (KRAS, BRAF, NRAS, no mutations).
- Medication use: benzodiazepine, benzodiazepine-related drugs, antidepressant drugs, antipsychotic drugs, anti-seizures drugs, antihypertensive drugs, hypolipidemic drugs and thyroid hormones.
- Psychiatric disorder: diagnosed by a psychiatrist according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), which may include depression, anxiety, schizophrenia, bipolar disorder, eating disorder and post-traumatic stress disorder [26].
- Other comorbidities: epilepsy and dementia

- Charlson comorbidity index (CCI score): used to assess the patients' comorbidities. It comprises 19 items in which each disease is assigned a score according to its influence on mortality [27,28].
- Tumor markers: carcinoembryonic antigen levels (CEA positive ≥5 ng/mL) and carbohydrate antigen levels (CA 19-9 positive > 39 U/mL).

2.8. Statistical analyses

Normality of quantitative variables was checked using the Kolmogorov-Smirnov test. Continuous variables were summarized using means and standard deviations (SD) or median and interquartile (IQR). Frequency and percentages were reported for qualitative variables. Comparative analysis between groups (i.e. benzodiazepine/BZRD users versus non-users) was performed using Pearson's chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney test for quantitative variables. Survival curves were obtained using the Kaplan-Meier method and compared using a log-rank test. Multivariable Cox regression models were performed to estimate the adjusted hazard ratios (HR) and their corresponding 95% confidence intervals (95%CI) for the association between benzodiazepine/BZRD use and the survival outcomes (OS, RFS). The enter method was used for all analyses of this association.

The covariates used for adjustment in the multivariable analysis were age at surgery, sex, BMI, CRC stage, Charlson comorbidity index, tumor site, antipsychotics, antidepressant treatment and alcohol consumption. Variables with a p-value < 0.25 in the univariable analysis were tested in a multivariable analysis with a significance level set at 0.05. These factors were validated by the authors' clinical experience, in accordance with the literature, and selected due to their clinical relevance [27]. In addition, a propensity score, defined as the probability to be treated with benzodiazepine/BZRD, was calculated using logistic regression [29].

The variables included in the propensity score for benzodiazepine use were age, sex, country of birth, depression, bipolar disorder, dementia, epilepsy, stroke, high blood pressure, and alcohol consumption. The discrimination of the model used to calculate the propensity score was tested using receiver operative characteristics. The area under the curve of the model was 0.81, suggesting good discrimination. The calibration of the model was visually inspected, and a goodness-of-fit test was used (Hosmer-Lemeshow p-value=0.35 suggesting good calibration).

A p-value ≤ 0.05 was considered statistically significant and all analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 software.

2.9. Ethical considerations

This study has received the validation and approval of the Ethics Committee of Limoges University Hospital (N0 479–2021–135). In Limoges, the cancer registry is authorized by the French Data Protection Authority (CNIL) to collect data for epidemiological surveillance purposes. For the present study, which corresponds to a re-use of data, data collection and analysis were performed in accordance with reference methodology MR004. In addition, patients at Limoges University Hospital were informed of the potential use of their data for research purposes when they were admitted.

3. Results

3.1. Descriptive analyses: patients' characteristics

After exclusion of 12 patients who did not meet the eligibility criteria for this study, 504 patients undergoing CRC surgery were included in this study. 125 (24.8%) patients were treated with benzodiazepine/BZRD drugs of which 86 (68.8%) were treated with benzodiazepine

alone, 23 (18.4%) were treated with BZRD alone, and 16 (12.8%) were treated with benzodiazepine in association with BZRD (Fig. 1). The benzodiazepine types most frequently used were alprazolam (22.4%), zolpidem (19.2%) and bromazepam (18.4%) while the least frequently used were clobazam (1.6%), diazepam (4%) and clonazepam (4%).

Tables 1 and 2 present the demographic and clinical data as well as CRC characteristics of the patients. The median age of patients was 73.4 [63.9–81.8] years; 58.7% were males and 44.9% were obese or overweight. Half the patients (52.5%) were diagnosed with early-stage CRC (in situ, stage I and II), 21.2% had rectal cancer and 28.4% were diagnosed with a psychiatric disorder.

3.2. Bivariate analyses

As compared with non-users, benzodiazepine/BZRD use was significantly higher among females ($p = 0.002$) and older patients ($p = 0.005$, Table 1). The stage and site of CRC were statistically similar in benzodiazepine/BZRD users and non-users ($p = 0.84$ and 0.41 respectively). Benzodiazepine/BZRD users had more comorbidities according to the Charlson comorbidity index, as well as psychiatric and neurological disorders (depression: $p < 0.001$, bipolar disorder: $p < 0.001$, dementia: $p = 0.01$), compared to non-users.

The use of other drugs was more frequent among benzodiazepine/BZRD users, such as antidepressants ($p < 0.001$), antipsychotics ($p = 0.001$) and antiepileptic medication ($p = 0.02$) compared with non-users.

3.3. Association between benzodiazepine/BZRD use and survival outcomes

During a mean follow-up of 46 months, 204 (40.5%) deaths and 134 (26.6%) recurrences were recorded, resulting in 5-year OS and RFS of $46.2 \pm 0.9\%$ and $39.9 \pm 1.1\%$ respectively.

Benzodiazepine/BZRD users and non-users showed no statistically significant differences in 5-year OS ($45.5 \pm 1.9\%$ vs. $46.5 \pm 1.1\%$ respectively, $p = 0.25$, Fig. 2.a), or 5-year RFS ($41.0 \pm 2.1\%$ vs. $39.6 \pm 1.3\%$ respectively, $p = 0.94$, Fig. 2.b).

3.4. Multivariable analyses: Cox regression model

3.4.1. Overall survival (OS)

After adjustment for confounding factors, benzodiazepine use was not associated with OS (aHR=1.04, 95%CI: 0.74–1.47). Further

adjustment for propensity score provided similar results (aHR=1.02, 95%CI: 0.71–1.48, Table 3).

The independent determinants of OS were age (aHR=1.04, 95%CI: 1.02–1.05), being underweight (BMI<18.5; aHR=2.89; 95%CI: 1.91–4.38), CRC stage III (aHR=1.48; 95%CI: 1.08–2.03) and stage IV (aHR=5.29; 95%CI: 3.60–7.76), Charlson comorbidity index (aHR=1.20, 95%CI: 1.07–1.35), and alcohol consumption (aHR=1.66; 95%CI: 1.16–2.38).

3.4.2. Recurrence-free survival (RFS)

In multivariable analysis, benzodiazepine use was not associated with RFS (aHR=0.98, 95%CI: 0.72–1.34). With further adjustment for propensity score, multivariable analysis provides similar results (aHR=1.00, 95%CI: 0.72–1.40, Table 4).

The independent determinants of RFS were age (aHR=1.03, 95%CI: 1.02–1.04), being underweight (aHR=2.82, 95%CI: 1.89–4.22), CRC stage III (aHR=1.73, 95%CI: 1.30–2.32), stage IV (aHR=6.83, 95%CI: 4.75–9.80) and Charlson comorbidity index (aHR=1.14, 95%CI: 1.02–1.26).

3.5. Subgroup analysis

3.5.1. Effect of benzodiazepine/BZRD in subgroups of psychiatric disorders, CRC stages and tumor site

Among CRC patients with psychiatric disorders ($n = 143$), benzodiazepine users had better RFS (aHR=0.58, 95%CI: 0.35–0.96) compared with non-users (Fig. 3b).

A subgroup analyses including only CRC patients diagnosed with a psychiatric disorder showed that the effect of benzodiazepine use varied according to CRC stage. Benzodiazepines showed a protective effect on OS and RFS only in stages III and IV (aHR=0.27; 95%CI: 0.12–0.59 and aHR=0.30, 95%CI: 0.15–0.62 respectively) (Figs. 3a, 3b).

3.5.2. Effect of benzodiazepine vs. BZRD use, duration of use, corresponding ATC classification, and pharmacokinetic/pharmacodynamics benzodiazepine properties on survival outcomes

When comparing benzodiazepine users to BZRD users, improved RFS was found only in benzodiazepine users (aHR=0.47, 95%CI: 0.26–0.83; $p = 0.01$), but not in BZRD users (aHR=0.71; 95%CI: 0.27–1.83; $p = 0.48$).

Patients with long-term benzodiazepine use had better RFS (aHR=0.65; 95%CI: 0.43–0.98; $p = 0.04$) compared to patients with short-term benzodiazepine use.

Subgroup analysis according to ATC classification showed that users of benzodiazepines classified as anxiolytics (ATC classification N05BA) had improved OS and RFS compared to non-users (OS: aHR=0.53; 95%CI: 0.30–0.91; $p = 0.02$; RFS: aHR=0.54; 95%CI: 0.32–0.92; $p = 0.02$, respectively). Use of benzodiazepines/BZRDs classified as hypnotics (ATC classification N05C) had no significant effect on OS and RFS (OS: aHR=1.39; 95%CI: 0.75–2.58; $p = 0.30$ and RFS: aHR=1.33; 95%CI: 0.73–2.42; $p = 0.35$ respectively).

The effect of benzodiazepines was influenced by the pharmacokinetic and pharmacodynamics properties of the molecules. Benzodiazepines with long half-lives improved OS and RFS compared with benzodiazepines with short half-lives (aHR=0.40; 95%CI: 0.19–0.84; $p = 0.02$ and aHR=0.42; 95%CI: 0.20–0.85; $p = 0.02$ respectively). Furthermore, benzodiazepines producing active metabolites improved OS and RFS compared with molecules with non-active metabolites (aHR=0.21; 95%CI: 0.05–0.86; $p = 0.03$ and aHR=0.19; 95%CI: 0.05–0.76; $p = 0.02$ respectively).

Benzodiazepines molecules having both a long-half-life and active metabolites also improved OS and RFS (aHR=0.21; 95%CI: 0.05–0.86; $p = 0.03$ and aHR=0.19; 95%CI: 0.05–0.76; $p = 0.02$ respectively).

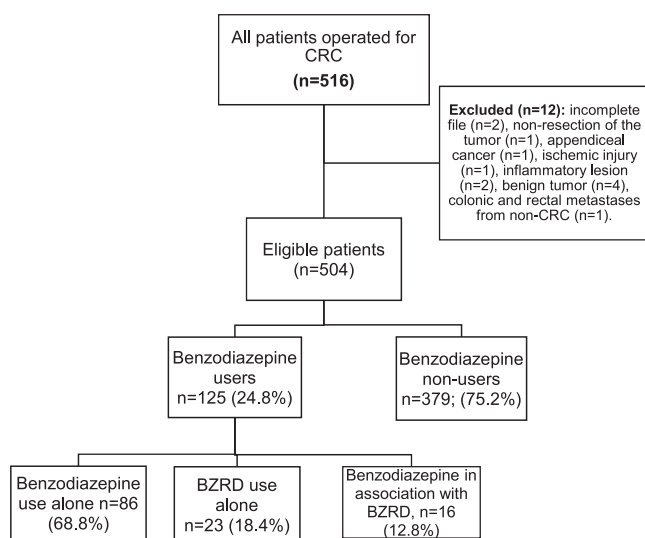


Fig. 1. Flowchart showing the process of enrollment of colorectal cancer patients.

Table 1
Demographic characteristics, clinical data and medications by benzodiazepine/benzodiazepine-related drugs (BZRD) use.

Variables	All patients (n = 504)	Benzodiazepine/BZRD non- users, (n = 379, 75%)	Benzodiazepine /BZRD users (n = 125, 25%)	p-value
Age, years	73.4 [63.9–81.8]	72.24 [63.4–80.7]	77.70 [66.4–84.7]	0.005
Female sex, n (%)	208 (41.3)	141 (37.2)	67 (53.6)	0.002
BMI, kg/m ²	25.0 [22.5–28.5]	25.0 [22.7–28.7]	24.9 [22.0–27.7]	0.32
Alcohol consumption	90 (17.9)	69 (18.2)	21 (16.8)	0.79
Family history of cancer, n (%)	104 (20.6)	77 (20.3)	27 (21.6)	0.80
Family history of CRC, n (%)	67 (13.3)	52 (13.7)	15 (12.0)	0.65
Charlson comorbidity index	0.0 [0.0–1.0]	0.0 [0.0–1.0]	1.0 [0.0–1.0]	0.03
Psychiatric disorder, n (%)	143 (28.4)	55 (14.5)	88 (70.4)	< 0.001
Depression	121 (24.0)	46 (12.1)	75 (60.0)	< 0.001
Anxiety	57 (11.3)	21 (5.5)	36 (28.8)	< 0.001
Bipolar disorder	10 (2.0)	2 (0.5)	8 (6.4)	< 0.001
Other comorbidities, n (%)				
Dementia	19 (3.8)	9 (2.4)	10 (8.0)	0.01
Epilepsy	20 (4.0)	12 (3.2)	8 (6.4)	0.12
Number of drugs/day	5.0 [2.0–7.0]	4.0 [2.0–6.0]	7.0 [5.0–9.0]	< 0.001
Medications, n (%)				
Anti-depressants	133 (26.4)	63 (16.6)	70 (56.0)	< 0.001
Thyroid hormones	45 (8.9)	34 (9.0)	11 (8.8)	0.99
Anti-seizures drugs	51 (10.1)	31 (8.2)	20 (16.0)	0.02
Antihypertensive drugs	285 (56.5)	204 (53.8)	81 (64.8)	0.04
Antipsychotic drugs	29 (5.8)	14 (3.7)	15 (12.0)	0.001
Hypolipidemic drugs	133 (26.4)	101 (26.6)	32 (25.6)	0.91
Adjuvant chemotherapy	188 (37.3)	149 (39.3)	39 (31.2)	0.11
Neoadjuvant treatment	56 (11.1)	46 (12.1)	10 (8.0)	0.25

Abbreviations: BMI=body mass index

4. Discussion

The results of the present study show that benzodiazepines/BZRDs do not seem to improve OS and RFS in patients operated for CRC. However, benzodiazepine use may improve RFS in subgroups of CRC patients with psychiatric disorders.

Studies on the effect of benzodiazepines on cancer survival are controversial. Some studies have shown a protective effect of benzodiazepines [15], while others have demonstrated a cancer risk associated with benzodiazepine use [16], however these studies had limitations. One study showed that benzodiazepines and opioid use were associated with an increased risk of 28-day mortality, but this study only included patients in the intensive care unit and is subject to a selection bias [16]. Another systematic review showed that there was no statistically significant association between benzodiazepine use and decreased survival in cancer patients, but all of the included studies were of poor methodological quality and assessed benzodiazepine use and survival time only in the last days and weeks of life [30]. No study was done to specifically assess the effect of benzodiazepines on survival as a primary outcome.

This was the first epidemiologic study to assess the effect of benzodiazepine use on OS or RFS in patients with CRC. It is well established that cancer and chemotherapy treatment have long term psychiatric effects [31], and that these symptoms are negatively associated with the survival rate of CRC patients [32]. In our study, 24% of CRC patients were diagnosed with depression, and a quarter of patients were long-term benzodiazepine/BZRD users.

The hypothesis behind the protective effect of benzodiazepines on survival could be attributed to its effect on BDNF level. Patients with psychiatric disorders are found to have lower serum BDNF levels compared to individuals without such disorders [33]. Previous studies also revealed that stressful experiences are common in cancer patients and are found to decrease the protein levels of BDNF [34,35]. Fortunately, this decrease in serum BDNF levels could be reversed after a period of treatment with psychoactive drugs [33]. This was validated in a study that showed benzodiazepine use increases plasma BDNF levels which may, in turn, improve survival in CRC patients treated with these drugs [15]. Our study explored this association and found that benzodiazepine use may have positive effects on CRC survival but only in

patients having psychiatric disorders and treated with benzodiazepines.

This study further explored the effects of pharmacokinetic/pharmacodynamic properties of benzodiazepines on CRC survival. Benzodiazepines with a longer half-life and that produce active metabolites improved OS and RFS compared with benzodiazepine molecules with a shorter half-life and that don't produce active metabolites. This is probably due to the higher levels of BDNF expressed in patients using these drugs. These results are in line with the study of Sarabi et al. which demonstrated that higher BDNF expression related to benzodiazepine use was significantly associated with better survival [15]. Molecules with longer half-life and that produce active metabolites remain longer in the body and contribute to a greater increase in BDNF and subsequently improved survival [15]. This finding is concordant with the subgroup results obtained in this study, whereby patients having a longer duration of treatment with benzodiazepines/BZRDs had better survival compared to patients treated with a shorter duration. This also may be attributed to the higher BDNF levels associated with longer term use. To date, the specific and precise dosage of benzodiazepines needed to trigger a fluctuation in BDNF levels, potentially influencing CRC survival, remains unknown, warranting further research in this area.

The effect of benzodiazepines/BZRDs on CRC survival also varied according to the Anatomical Therapeutic Chemical (ATC) classification (anxiolytics vs. hypnotics) of the molecule. We found that only benzodiazepine molecules classified as anxiolytics improved survival in CRC patients. Hypnotics such as zolpidem and zopiclone have a shorter half-life, which may not allow them to exert a sufficient effect on BDNF levels and improve survival in CRC patients [15]. This was further validated by our subgroup analysis, whereby only CRC patients suffering from a psychiatric disorder and using benzodiazepines had significantly improved survival. This association was not observed among BZRD (zolpidem, zopiclone) users.

The strengths of this study include the integration of multiple sources for data collection using the general cancer registry at Limoges University Hospital and medical records of the digestive, general and endocrine surgery department at Limoges University Hospital, which reduces information bias by enhancing the accuracy of the data collected. In addition, cross-validation and comparison of data from different sources can help identify discrepancies or inconsistencies, further improving data quality and reducing bias in our study.

Table 2
Colorectal cancer characteristics of patients by benzodiazepine/benzodiazepine-related drugs (BZRD) use.

Variables	All patients n = 504	Benzodiazepine/ BZRD non- users, n = 379	Benzodiazepine /BZRD users n = 125	p-value
Tumor site, n (%)				0.41
Right colon	193 (38.3)	136 (35.9)	57 (45.6)	
Colon	28 (5.6)	21 (5.5)	7 (5.6)	
Transverse				
Left colon	134 (26.6)	104 (27.4)	30 (24.0)	
Rectum	107 (21.2)	85 (22.4)	22 (17.6)	
Rectosigmoid junction	42 (8.3)	33 (8.7)	9 (7.2)	
CRC stage, n (%)				0.84
In situ	18 (3.6)	13 (3.4)	5 (4.0)	
I	89 (17.7)	69 (18.2)	20 (16.0)	
II	157 (31.2)	117 (30.9)	40 (32.0)	
III	180 (35.7)	132 (34.8)	48 (38.4)	
IV	60 (11.9)	48 (12.7)	12 (9.6)	
Type of cancer, n (%)				0.97
Lieberkühn adenocarcinoma	453 (89.9)	338 (89.2)	115 (92.0)	
Mucinous adenocarcinoma	41 (8.1)	32 (8.4)	9 (7.2)	
Medullary carcinoma	5 (1.0)	5 (1.3)	0 (0.0)	
Neuroendocrine carcinoma	1 (0.2)	1 (0.3)	0 (0.0)	
Signet-ring cell carcinoma	4 (0.8)	3 (0.8)	1 (0.8)	
Tumor size, n (%)				0.75
≥4 cm	260 (53.9)	193 (53.5)	67 (55.4)	
Histological type, n (%)				0.46
Well differentiated	54 (12.7)	44 (14.0)	10 (9.1)	
Moderately differentiated	325 (76.7)	239 (76.1)	86 (78.2)	
Poorly differentiated	44 (10.4)	30 (9.6)	14 (12.7)	
Undifferentiated	1 (0.2)	1 (0.3)	0 (0.0)	
Type of mutation, n (%)				0.60
KRAS	92 (48.4)	70 (49.3)	22 (45.8)	
BRAF	31 (16.3)	24 (16.9)	7 (14.6)	
NRAS	5 (2.6)	5 (3.5)	0 (0.0)	
No mutations	62 (32.7)	43 (30.3)	19 (39.6)	
Microsatellite status, n (%)				0.17
MSI	32 (18.5)	21 (16.0)	11 (26.2)	
MSS	141 (81.5)	110 (84.0)	31 (73.8)	
CEA positive, ng/mL	139 (34.8)	102 (34.0)	37 (37.0)	0.63
CA 19-9 positive, U/mL	56 (15.3)	47 (16.9)	9 (10.1)	0.13

CEA: carcinoembryonic antigen levels, CA 19-9: carbohydrate antigen levels

To our knowledge, this is the first epidemiological cohort study to assess the effect of benzodiazepine use on survival in CRC patients with or without psychiatric disorder. It included a high number of patients (504 patients) operated for CRC at the same hospital.

This study however has some limitations. The study was a retrospective cohort in which patients were not randomized. Consequently, the presence of residual confounding due to unmeasured confounders cannot be totally excluded. However, to address this issue, we used the propensity score and adjustment for several important confounding factors in multivariable analysis.

The presence of immortal time bias could misclassify unexposed time as exposed [36,37]. In addition, the effects of cumulative benzodiazepine doses by molecule have not been evaluated. An accurate estimate of true exposure to this class of drugs is difficult to obtain, given the considerable and heterogeneous patient non-compliance, which was not

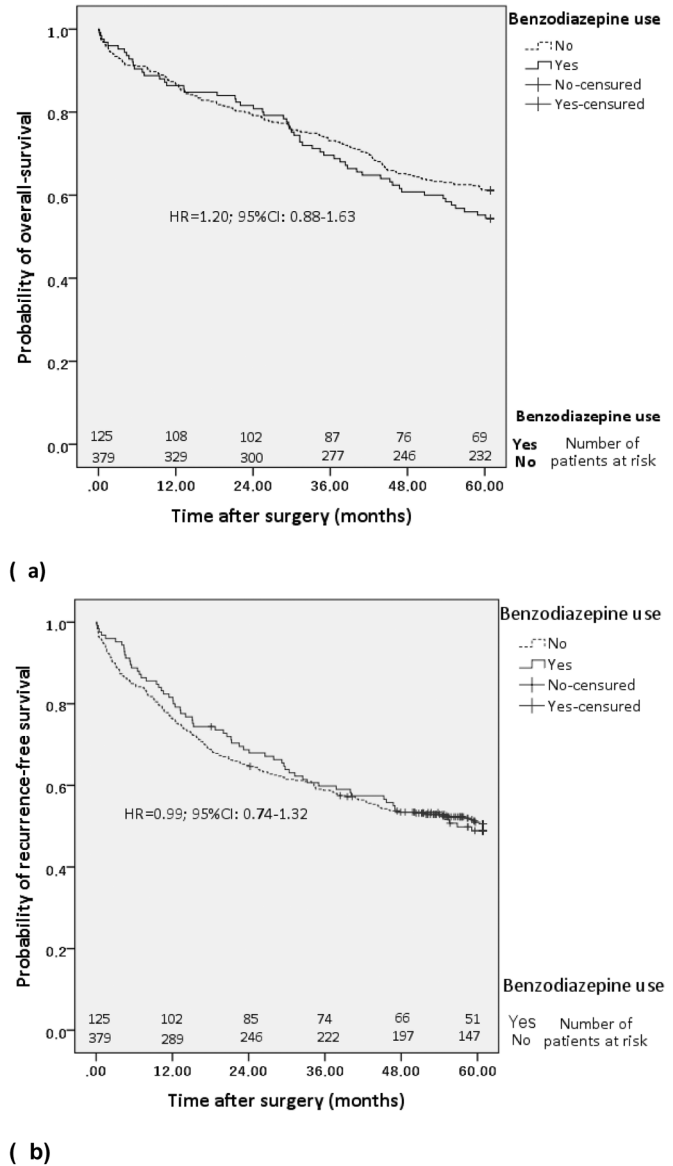


Fig. 2. Comparison of survival between benzodiazepine/benzodiazepine-related drugs users and non-users. **(2a)** overall survival; **(2b)** recurrence-free survival.

controlled for in this study. In line with other pharmacoepidemiological studies, we recognize the possibility of non-adherence to treatment.

Due to the retrospective design of the study, which relies solely on patients' medical records as data sources, a possible information bias may be present. Consequently, certain variables such as alcohol consumption and diagnosis of psychiatric disorders may have been underestimated.

This cohort included patients living in France who may be ethnically diverse and have genetic variability influencing CRC survival, response to cancer treatment, as well as drug metabolism and individual responses to benzodiazepines. However, these patients shared the same environment in the same geographical area and underwent the same surgical procedure in the same hospital. This reduces potential variations in treatment protocols and minimizes potential biases that could be introduced by environmental conditions between patients [38,39].

Prospective trials are warranted to assess the effects of benzodiazepine on CRC cancer outcomes, particularly in people with psychiatric disorders, taking into account the effect of the type of molecule, dosing regimen, and the duration of treatment.

Table 3
Overall survival assessed by the Cox regression model.

Overall-survival						
Variables	HR	95%CI	p-value	aHR ^a	95%CI	p-value
Age at surgery, per year	1.04	1.02–1.05	< 0.001	1.04	1.02–1.05	< 0.001
Sex (female/male)	0.83	0.63–1.11	0.21	0.73	0.53–1.01	0.054
BMI, per kg/m ²	0.95	0.90–0.99	0.02			
Normal (reference)						
Underweight	3.70	2.49–5.48	< 0.001	2.89	1.91–4.38	< 0.001
Overweight/Obese	0.81	0.60–1.10	0.18	0.75	0.55–1.03	0.08
Tumor site						
Colon (reference)						
Rectum	0.75	0.53–1.08	0.12	0.94	0.65–1.37	0.75
CRC stage						
In situ, I, II (reference)						
III	1.45	1.06–1.98	0.02	1.48	1.08–2.03	0.02
IV	4.09	2.84–5.89	< 0.001	5.29	3.60–7.76	< 0.001
Charlson comorbidity index	1.24	1.12–1.38	< 0.001	1.20	1.07–1.35	0.001
Alcohol consumption	1.40	1.00–1.96	0.05	1.66	1.16–2.38	0.006
Benzodiazepine use	1.20	0.88–1.63	0.25	1.02	0.71–1.48	0.91
Propensity score	1.76	0.99–3.12	0.052	1.11	0.48–2.57	0.80
Antidepressant drugs	1.41	1.05–1.90	0.02	1.19	0.81–1.75	0.37
Antipsychotic drugs	1.26	0.72–2.21	0.42	1.12	0.62–2.04	0.71

Abbreviations: BMI=body mass index; HR=hazard ratio; CI=confidence interval.
a Adjusted for age at surgery, sex, BMI, tumor site, cancer stage at diagnosis, Charlson comorbidity index, benzodiazepine/BZRD use, propensity score, alcohol consumption, antipsychotics, antidepressants.

Table 4
Recurrence-free survival assessed by the Cox regression model.

Recurrence-free survival						
Variables	HR	95%CI	p-value	aHR ^a	95%CI	p-value
Age at surgery, years	1.02	1.01–1.03	< 0.001	1.03	1.02–1.04	< 0.001
Sex, female/male	0.82	0.63–1.06	0.12	0.77	0.58–1.04	0.09
BMI, kg/m ²						
Normal (reference)						
Underweight	3.54	2.41–5.19	< 0.001	2.82	1.89–4.22	< 0.001
Overweight/Obese	1.00	0.76–1.31	0.99	0.98	0.74–1.29	0.86
Tumor site						
Colon (reference)						
Rectum	0.73	0.52–1.01	0.06	0.81	0.58–1.14	0.23
Cancer stage at diagnosis						
In situ, I, II (reference)						
III	1.75	1.32–2.33	< 0.001	1.73	1.30–2.32	< 0.001
IV	6.01	4.27–8.47	< 0.001	6.83	4.75–9.80	< 0.001
Alcohol consumption	1.42	1.05–1.92	0.02	1.51	0.99–2.30	0.052
Charlson comorbidity index	0.92	0.77–1.08	0.31	1.14	1.02–1.26	0.02
Benzodiazepine use	0.99	0.74–1.32	0.94	1.00	0.72–1.40	0.99
Propensity score	1.00	0.58–1.74	0.99	0.88	0.41–1.89	0.74
Antipsychotic drugs	1.08	0.64–1.82	0.77	1.17	0.67–2.05	0.58
Antidepressant drugs	1.02	0.77–1.35	0.90	0.90	0.63–1.27	0.54

Abbreviations: BMI=body mass index; HR=hazard ratio; CI=confidence interval.
a Adjusted for age at surgery, sex, BMI, tumor site, cancer stage at diagnosis, Charlson comorbidity index, benzodiazepine/BZRD use, propensity score, alcohol consumption, antipsychotic drugs, antidepressant drugs.

5. Conclusions

In conclusion, the use of benzodiazepines does not seem to be associated with OS and RFS in patients operated for CRC. However, in patients with psychiatric disorders and with advanced CRC stage, benzodiazepine use may have better RFS. This beneficial effect is particular for benzodiazepines classified as anxiolytics, having longer half-life, and producing active metabolites. Long-term use of benzodiazepines may lead to better survival in those patients as compared to short-term use.

Consequently, it is recommended to early screen cancer patients for psychiatric disorders and promptly consider benzodiazepine treatment. Further studies and warranted to determine the optimal use, dosage, duration, and long-term effects of benzodiazepine treatment in CRC patients with psychiatric disorders.

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CRediT authorship contribution statement

Zeinab Tarhini: Conceptualization, methodology, validation, formal analysis, investigation, data curation, original draft preparation, writing-review and editing, visualization, project administration. **Julien Magne:** methodology, writing—review and editing, validation. **Pierre-Marie Preux:** methodology, writing—review and editing, validation. **Alexis Parenté :** validation, writing—review and editing. **Muriel Mathonnet:** validation, writing—review and editing. **Niki Christou:** Conceptualization, methodology, validation, writing—review and editing, supervision, project administration. **Jeremy Jost:**

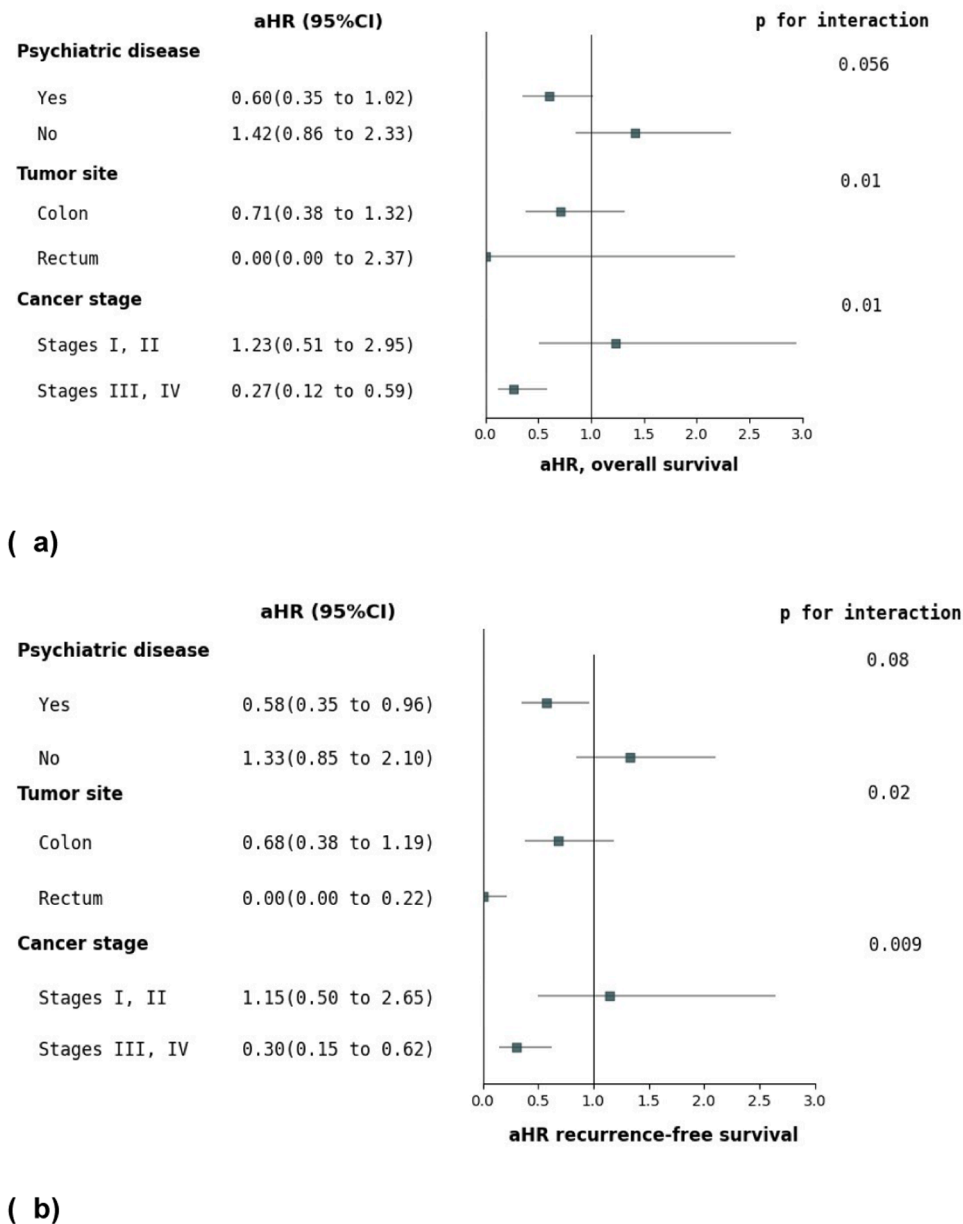


Fig. 3. Forest plot for subgroup analysis: effect of benzodiazepine on (3a): overall-survival, (3b): recurrence-free survival. aHR: adjusted hazard ratio.

Conceptualization, methodology, validation, writing—review and editing, supervision, project administration. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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