Proton Pump Inhibitor Intake During Chemoradiotherapy for Rectal Cancer: A Retrospective Study

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Abstract

Purpose: Proton pump inhibitors (PPIs) are one of the most widely used drugs worldwide and are involved in several drug interactions. Recently, several studies have suggested that PPIs may interfere with the efficacy of capecitabine. This study primarily aimed to investigate the effects of PPI intake on the pathological response rate of patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy with capecitabine.

Method: A retrospective study was conducted at a French Comprehensive Cancer Center. Patients with locally advanced rectal cancer treated with neoadjuvant radiochemotherapy followed by surgery were included in the study. Demographic parameters, treatment characteristics, survival data, and PPI intake data were collected. Survival data were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results: In total, 215 patients were included, of whom 135 (62.8%) were men. The PPI intake frequency was 16.1%. The rate of complete histological response was lower in patients on PPIs than in those not on PPIs (8.7% vs. 19%, p=0.36). PPI intake was not associated with a statistically significant decrease in recurrence-free survival (hazard ratio [HR]=1.26, 95% confidence interval [CI] 0.61–2.60, p=0.54) or overall survival (HR=0.95, 95% CI 0.33–2.76, p=0.93).

Conclusion: There is a trend to a lower complete histological response with PPI co-medication in patients treated for locally advanced rectal cancer. However, the safety of PPIs could not be confirmed. Further ancillary studies of prospective clinical trials or studies using the Health Data Hub are necessary to explore the effects of PPIs on rectal cancer more accurately.

Introduction

Colorectal cancer is the third most frequent cancer and the second leading cause of cancer-related deaths worldwide. Rectal cancer accounts for one-third of these cases. Until recently, preoperative chemoradiotherapy (CRT) followed by radical surgery was the preferred treatment for patients with locally advanced rectal cancer (LARC) [1]. In France, CRT consists of radiotherapy (RT) 50 Gy associated with capecitabine, an oral prodrug of 5-fluorouracil (5-FU), according to the CAP50 scheme [1].

Proton pump inhibitors (PPIs) are one of the most used drugs worldwide, with approximately 20% of cancer patients taking PPIs [2–4]. They inhibit H^+/K^+ adenosine triphosphatase pumps in parietal gastric cells to reduce gastric acid secretion. This reduction in gastric pH can affect drug absorption [5]. Sometimes, the increase in gastric pH may considerably impair the drug's absorption. Thus, some drug associations, such as omeprazole and nelfinavir, a human immunodeficiency virus protease inhibitor, are contraindicated [6].

Off-label prescribing has been widely reported, particularly in functional dyspepsia and in the prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced gastroduodenal lesions in non-at-risk patients [7]. In 2015, according to the French Health Data Hub, for nearly one-third of PPI users, the indication for PPI treatment could not be determined and did not seem to correspond to the recommendations (e.g., prevention of gastroduodenal lesions due to NSAIDs in patients with no identifiable risk factor, gastroesophageal reflux disease [GERD] not detected by upper gastrointestinal endoscopy) [8].

Recently, concerns have been raised regarding drug interactions between PPIs and tyrosine kinase inhibitors (TKIs). Since TKIs are weakly basic, their absorption is dependent on intragastric pH and is optimal at low intragastric pH. When the intragastric pH is increased due to concurrent PPI use, the solubility, bioavailability, and efficacy of TKIs may decrease significantly [9]. Indeed, Mir et al. [10] have found reduced progression-free survival and overall survival (OS) in advanced soft tissue sarcoma treated with pazopanib when co-administered with gastric acid-suppressive therapy (mainly PPIs).

Some authors question the existence of a similar interaction between capecitabine and PPIs. To date, contradictory findings have been reported in the literature on colorectal cancer, with some publications reporting a positive effect on tumor regression grade [11] and recurrence-free survival (RFS) [11] in contrast to other publications reporting a negative effect on RFS [12, 13].

This study primarily aimed to investigate the association between PPI use and pathological response rate in patients with rectal cancer treated with capecitabine-based CRT. Secondary endpoints included RFS, OS, severe toxicity and other histological features (tumor response grade [TRG]).

Materials And Methods

1. Study design

We retrospectively identified patients with LARC who underwent CRT followed by surgery from a comprehensive cancer center (Oscar Lambret Center, Lille, France) from January 1, 2004, to December 31, 2017.

We identified the patients from the hospital's "Programme de Médicalisation des Systèmes d'Information" database (i.e., a program for the medicalization of information systems) and from the ConSoRe data extraction from the electronic patient records. All potentially eligible patients were assessed to confirm their inclusion in the study. All consecutive patients who met the inclusion criteria were finally included in the study. Patients and treatment characteristics, outcomes, and PPI intake data were collected from electronic patient medical records.

2. Study population

The inclusion criteria were as follows: patients aged > 18 years, patients diagnosed with locally advanced rectal adenocarcinoma, patients receiving CRT including capecitabine followed by surgery with or without adjuvant chemotherapy, and patients who started receiving RT between January 1, 2004, and December 31, 2017.

The exclusion criteria were as follows: patients with metastatic disease, patients without rectal adenocarcinoma, patients not receiving RT at the cancer center, patients not receiving oral 5-FU, patients not undergoing rectal surgery, patients receiving first-line chemotherapy before CRT, or patients under tutorship or curatorship.

3. Ethical considerations

Data were collected from hospital patient files without direct interaction with patients for research purposes. Consequently, ethical approval was not required. The study complied with the "reference methodology" MR004 adopted by the French Data Protection Authority (*Commission Nationale Informatique et Libertés*, Paris, France), and we confirmed that patients did not object to the use of their health data for research purposes.

4. Definition of proton pump inhibitor exposure

Study patients were divided into the PPI intake, non-PPI intake, and unknown treatment groups. Patients belonging in the "PPI" group were on PPIs, as defined by notification in consultation report at any point in time at the beginning or during CRT treatment. We hypothesized that, unless otherwise stated, patients taking PPIs before starting the treatment continued during the treatment. Patients belonging to the "non-PPI" group were not taking PPIs according to the list of treatments of all medical visit reports. All patients for whom no treatment was mentioned belonged to the unknown treatment group. As the PPI treatment was indicated in cases of upper digestive disorder, it was deemed independent of the underlying rectal cancer and its outcome. Consequently, we did not explore propensity scores to control for a possible indication bias.

5. Treatment and follow-up

Over the study period, most patients were treated according to the CAP50 protocol, which combines rectal RT (50 Gy in 25 fractions spread over 5 weeks) and concomitant capecitabine chemotherapy (800 mg/m^2 twice daily on days of RT), followed by surgery 6 to 8 weeks later [1].

After the end of treatment, standard follow-up included clinical examination and imaging (abdominal ultrasound and chest X-ray alternated with thoraco-abdominopelvic computed tomography scan) every 3 months in the first 3 years and subsequently every 6 months up to 5 years. Colonoscopy at 3 years has been recommended [1].

6. Study outcomes

The primary endpoint of this study was complete pathological response [ypT0N0]).

Among the secondary endpoints, RFS over the first 5 years from the date of diagnosis, considering disease recurrence at any site or death from any cause was considered. Patients were censored at their last follow-up date if no recurrence was observed. Follow-up data were censored at 5 years, as patients had no regular follow-up after 5 years. Other secondary endpoints were OS over the first 5 years considering death from any cause, severe toxicity (defined as toxicity grade 3 or 4 according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0), and other histological features (tumor response grade [TRG]).

7. Statistical considerations

Descriptive statistics were used to describe the baseline characteristics of the study cohort overall and according to the PPI intake. Frequencies and percentages were reported for categorical variables and medians and interquartile ranges for continuous variables. We compared the distribution of variables according to PPI treatment (yes vs. no) using the chi-square test or Fisher's exact test as appropriate for categorical data and nonparametric Wilcoxon tests for continuous variables. We estimated RFS and OS curves using the Kaplan-Meier method with their corresponding 95% confidence intervals (95% CIs). The log-rank test was used to compare survival curves between the PPI and no-PPI groups. Cox proportional hazards regression models were used to estimate the HRs of progression or death. We performed a sensitivity analysis comparing patients with PPI intake vs. patients with no PPI intake or unknown treatment.

Statistical analysis was performed using Stata version 15.0, and a significance level of $p<0.05$ was used for statistical testing.

Results

1. Population characteristics

A total of 1008 patients were preselected from hospital databases, of whom 215 met the inclusion criteria for the study. A flowchart is shown in Figure 1.

Of these 215 patients, 25 (11.6%) took a PPI, and 130 (60.5%) did not during CRT. Drug status was unknown in 60 patients (27.9%). In patients with known drug status, the frequency of PPI use was 16.1%. The most commonly used PPI was esomeprazole (Supplementary Table S1), and the median daily dose was 20 mg. The main indications were treatment of GERD, ulcers, and hiatal hernia.

The details of patient demographics are presented in Table 1. The two groups were balanced for sex distribution, age, stage, and location of the primary tumor. Of the 215 patients, 135 (62.8%) were men. The median age at diagnosis was 61 (range, 54–69 years). Rectal tumors were located in the middle rectum and lower rectum in 94 (43.7%) and 107

(49.8%) patients, respectively. They were mostly locally advanced stages: T3, T4, and N1 or N2 in 165 (77%), 17 (8%), and 181 (84.2%) patients, respectively, leading to 26 patients with stage II and 181 patients with stage III according to the Thésaurus National de Cancérologie Digestive classification [1].

Table 1: Baseline characteristics of selected patients, overall and according to proton pump inhibitor (PPI) intake.

Characteristics	Overall (N=215)	PPI intake		P-value (1)
		Yes (N=25)	No (N=130)	Unknown (N=60)
sex, n (%)				0.54
Male	135 (62.8)	17 (68)	80 (61.5)	38 (63.3)
Female	80 (37.2)	8 (32)	50 (38.5)	22 (36.7)
Age in years, median (range)	61 (54–69)	61 (56–71)	62 (54–69)	61 (53.5–65.5)	0.52
Rectal cancer location, n (%)				0.67
High	14 (6.5)	2 (8)	7 (5.4)	5 (8.3)
Middle	94 (43.7)	13 (52)	61 (46.9)	20 (33.3)
Lower	107 (49.8)	10 (40)	62 (47.7)	35 (58.3)
Stage of cancer according to TNCD(2), (MD=2) n (%)				0.11
I	7 (3.3)	0 (0)	4 (3.1)	3 (5.2)
II	25 (11.7)	7 (28)	16 (12.3)	2 (3.4)
III	181 (85)	18 (72)	110 (84.6)	53 (91.4)

MD: number of missing data

(1)Tests comparing PPI intake vs. no PPI intake

(2)TNCD: Thésaurus National de Cancérologie Digestive [1]

Treatment characteristics are summarized in Table 2. The characteristics of CRT were well balanced between patients with and without PPI intake. CRT combined a median RT dose of 50 Gy and a median capecitabine dose of 1600 mg/m^2.

Table 2: Treatment characteristics and complications according to proton pump inhibitor (PPI) intake.

Treatment characteristics and safety data	Overall (N=215)	Yes (N=25)	PPI INTAKE No (N=130)	Unknown (N=60)	P-value[1]
Radiotherapy					
Dose (Gray)	50	50	50	50	
Fractions	25	25	25	25	
Duration (days)	36	36	36	36	
Chemotherapy					
Capecitabine (dose in mg/m^2)	1600	1600	1600	1600	
Oxaliplatine combination (MD=5) n (%)					1
Yes	40 (19)	3 (12.5)	18 (13.8)	19 (33.9)	
No	170 (81)	21 (87.5)	112 (86.2)	37 (66.1)	
Safety of chemoradiotherapy					
Severe toxicity, (MD=3) n (%)					0.58
Yes	36 (17)	6 (24)	23 (17.8)	7 (12.1)	
No	176 (83)	19 (76)	106 (82.2)	51 (87.9)	
Toxicities, n					
Diarrhea	19	12	3	4	
Radiodermitis	5	0	5	0	
Rectal syndrome	3	0	2	1	
Hematologic	3	1	2	0	
Others[2]	5	2	2	1	
Toxicity leading to treatment interruption, (MD=3) n (%)					0.54
Yes (CESSATION of RT)	2 (0.9)	0 (0)	1 (0.8)	1 (1.7)	
Yes (CESSATION of CT)	16 (7.5)	5 (20)	10 (7.8)	1 (1.7)	
Yes (CRT)	9 (4.2)	0 (0)	6 (4.7)	3 (5.2)	
No	185 (87.3)	20 (80)	112 (86.8)	53 (91.4)	
Surgery					
Time interval from RT (days), median (range)	56 (48-68)	55 (47–64)	57 (50–69)	55 (46–67)	
Surgical procedure, (MD=3) n (%)					
Colorectal exerisis	104 (49.1)	8 (33.3)	64 (49.6)	32 (54.2)	
Proctectomy	55 (25.9)	9 (37.5)	36 (27.9)	10 (16.9)	
Abdominal amputation	48 (22.6)	5 (20.8)	28 (21.7)	15 (25.4)	

Local excision	4 (1.9)	2 (8.3)	0 (0)	2 (3.4)	
Total pelvectomy	1 (0.5)	0 (0)	1 (0.8)	0 (0)	
Postoperative complications, (MD=7) n(%)					0.18
Yes	58 (27.9)	10 (41.7)	36 (28.1)	12 (21.4)	
No	150 (72.1)	14 (58.3)	92 (71.9)	44 (78.6)	
Type of complications, n					0.94
Parietal	4	1	2	1	
Infection	15	2	9	4	
Fistula	6	2	4	0	
Bowel obstruction	21	3	13	5	
Others[3]	12	2	8	2	
Adjuvant chemotherapy, (MD=4) n (%)					0.69
Yes	87 (41.2)	11 (45.8)	53 (41.4)	23 (39)	
No	124 (58.8)	13 (54.2)	75 (58.6)	36 (61)	
Chemotherapy[4]**, (MD=4) n (%)**					0.62
5-FU	1 (1.1)	0 (0)	1 (1.9)	0 (0)	
Capecitabine	21 (24.1)	4 (36.3)	12 (22.6)	5 (21.7)	
CAPOX	13 (14.9)	0 (0)	8 (15.1)	5 (21.7)	
FOLFOX	51 (58.6)	7 (63.6)	31 (58.5)	13 (56.5)	
FOLFOX-bevacizumab	1 (1.1)	0 (0)	1 (1.9)	0 (0)	

CRT: chemoradiotherapy

CT: chemotherapy

MD: number of missing data

RT: radiotherapy

[1]Tests comparing PPI intake vs. no-PPI intake

[2]Others: acute urinary retention, allergy, and hand-foot syndrome

[3]Others: colic necrosis, acute urinary retention, and delayed healing

[4]Chemotherapy protocols according to Thésaurus National de Cancérologie Digestive [1]:

a. 5-FU or LV5FU2 (day [D] 1 equal to day 14): folinic acid 400 mg/m^2, 5-FU bolus 400 mg/m2, 5-FU 2400 mg/m^2 over 46 hours
b. Capecitabine (D1 equal to D21): 1250 mg/m^2 twice daily from D1 to D14

c. CAPOX (D1 equal to D21): on D1 oxaliplatin 130 mg/m^2, and from D1 to D14, capecitabine 1000 mg/m^2 twice daily

d.

FOLFOX (D1 equal to D14): folinic acid 400 mg/m^2, oxaliplatin 85 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU 2400 mg/m^2 over 46 hours

e. FOLFOX-bevacizumab (D1 equal to D14): bevacizumab 5 mg/kg, folinic acid 400 mg/m^2, oxaliplatin 85 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU 2400 mg/m^2 over 46 hours

The median time between surgery and the end of RT was 56 days (8 weeks). A total of 194 (95.6%) surgical resections were complete (R0 resection). Fifty-eight patients (27.9%) had postoperative complications, mainly occlusive syndrome (n=21) or infectious complications (n=15). The rate of postoperative complications was higher in the PPI group than in the non-PPI group (41.7% vs. 28.1%, p=0.18), but the difference was not significant.

2. Pathological features

Overall, among the 204 patients evaluated for this criterion, the proportion of complete pathological response (ypT0N0) was 18% (Table 3). It seems lower in the PPI group than in the non-PPI group (8.7% vs. 19%), but the difference was not significant (p=0.36).

Table 3
Pathological features of patients taking proton pump inhibitors (PPIs) vs no PPIs.

	TOTAL	PPI USE			P-VALUE
		YES	NO	UNKNOWN	
COMPLETE RESPONSE (YPT0N0), (MD=11) N (%)					**0.36**
YES	37 (18.1)	2 (8.7)	24 (19)	11 (20)	
NO	167 (81.9)	21 (91.3)	102 (81)	44 (80)	
COMPLETE RESECTION (R0), (MD=12) N (%)					**0.59**
YES	194 (95.6)	23 (100)	119 (95.2)	52 (94.5)	
NO	9 (4.4)	0 (0)	6 (4.8)	3 (5.5)	

3. Recurrence-free survival

The survival analysis results are presented in Table 4. Relapse was reported in seven patients in the PPI group and in 33 patients in the non-PPI group.

Table 4
Survival analyses.

Survival outcome	Overall	PPI intake		Unknown	P-value
		Yes	No		
Relapse-free survival					
Numbers of events, n					
Relapse	61	7	33	21	
Local	6	0	5	1	
Metastatic	37	6	21	15	
Combined	18	1	7	5	
Death without prior relapse	9	2	5	2	
Recurrence-free survival, (95% CI)					
36-month RFS	71.1 (64.2–76.8)	61.5 (38.9-77.8)	71.6 (62.5–78.8)	74.0 (60.5–83.4)	
60-month RFS	63.4 (56.0–69.9)	61.5 (38.9-77.8)	66.9 (57.3–74.9)	58.7 (44.6–70.4)	
Hazard ratio (relapse or death), (95% CI)					
HR (PPI/no PPI)	-	1.26 (0.61–2.60)	Ref [1]	-	0.54
HR (PPI/no PPI or unknown)	-	1.20 (0.60–2.42)	Ref [1]		0.60
Overall survival					
Number of deaths, n					
Death	35	4	22	9	
Related to disease progression	20	3	13	6	
Unrelated to disease progression	15	1	9	3	
Overall survival, (95% CI)					
36-month OS	91.9 (87.2–95.0)	87.4 (65.9–95.8)	90.6 (83.7–94.7)	96.5 (86.7–99.1)	
60-month OS	80.3 (73.5–85.5)	81.2 (56.5–92.7)	79.0 (69.7–85.8)	82.7 (69.3–90.6)	
Hazard ratio (death), (95% CI)					
HR (PPI/no PPI)	-	0.95 (0.33–2.76)	Ref [1]	-	0.93

Survival outcome	Overall	Yes	PPI intake No	Unknown	P-value
HR (PPI/no PPI or unknown)	-	1.05 (0.37–2.97)	Ref [1]		0.93

Patients who took a PPI while on CRT did not have a statistically significant decrease in RFS over the first 5 years compared to patients who did not take a PPI. Indeed, 5-year RFS rates were 61.5% vs. 66.9% (HR=1.26, 95% CI, 0.61–2.60, p=0.54) (Figure 2). The results were stable when comparing patients with PPI intake to patients with no PPI intake or unknown treatment (HR=1.20, 95% CI, 0.60–2.42, p=0.60).

Overall, the 3-year RFS rate was 71.1% (95% CI 64.2–76.8), with 61.5% (95% CI 38.9–77.8) in the PPI group and 71.6% (95% CI 62.5–78.8) in the non-PPI group.

4. Overall survival

The 3-year OS rate was 91.9% (95% CI 87.2–95): 87.4% (95% CI 65.9–95.8) in the PPI group and 90.6% (95% CI 83.7–94.7) in the non-PPI group (Table 4, Figure 3, and Supplementary Figure S2). Co-medication with PPIs was not associated with a decrease in 5-year OS (81.2 vs. 79% [HR=0.95, 95% CI 0.33–2.76, p=0.93]).

5. Safety

Of the 215 patients included in the study, 36 experienced severe toxicity (the most common was diarrhea). The addition of oxaliplatin was associated with a significant increase in the risk of severe toxicity (13/40 [33%] vs. 23/170 [14%], p=0.004). Treatment was discontinued in 27 patients (12.7%), mostly chemotherapy (n=16) and mainly due to diarrhea (41% of reasons for discontinuation). The rate of severe toxicities during CRT was similar in both groups (24% in the PPI group vs. 17.8% in the non-PPI group, p=0.58), but gastrointestinal toxicities such as diarrhea were more frequent in the PPI group than in the non-PPI group (12/25 and 48% vs. 3/130 and 2.3%, p<10-5). The rate of chemotherapy discontinuation during treatment was higher in patients on PPIs than in patients not on PPIs (20% vs. 7.8%, p=0.07). On the contrary, PPI use did not affect the safety of RT. In the PPI group, interruption of RT and/or CRT and severe RT-related toxicities were not observed.

Discussion

We aimed to investigate the association between PPIs and CRT in LARC in a large cohort in France. In our study, we observed a nonsignificant reduction in the complete pathological response rate, recurrence-free rate and overall survival in the PPI group. As already mentioned, contradictory findings have been reported in the literature regarding the effect of PPIs on oncological outcomes in this setting. Indeed, Sun et al. [12] have found reduced 5-year RFS rates between early-stage colorectal cancer patients treated with capecitabine monotherapy and taking PPIs (HR=1.89, 95% CI 1.07–3.35, p=0.03). Similar results were found by Wong et al. [13] among early-stage colorectal cancer patients who received concurrent CAPOX and PPIs (HR=2.03, 95% CI 1.06–3.38, p=0.03), but not among patients who received FOLFOX and PPIs (HR=0.51, 95% CI 0.25–1.06, p=0.071). However, opposite results were found by Zhang et al. [11] in LARC treated with CRT (chemotherapy with CAPOX, associated with a three-dimensional conformal RT total dose of 46 Gy). Concomitant use of PPI omeprazole was associated with improved tumor regression grade (p=0.02) and reduced recurrence rate (HR=0.25, 95% CI 0.07–0.90, p=0.025) [11].

In addition to interfering with the efficacy of capecitabine, PPI use appears to be associated with decreased chemotherapy safety. Indeed, it seems to increase capecitabine toxicities, such as severe digestive disorders, and lead to capecitabine discontinuation.

The present study has several limitations. The main limitations are related to its retrospective design; PPI drug status was determined from patients' electronic medical records, and data on PPI status were lacking in 28% of patients. As we could not verify PPI delivery and PPI intake, there might be inaccuracies in PPI drug status, possibly leading to underreporting of PPI use. This may partially explain the low frequency of PPI intake (approximately 16% in patients with known drug status and 11% of all patients), which is lower than that usually found in the literature (20–25%) [2, 3]. Another limitation is the lack of information about patients' comorbidities, which may be a confounding factor. Moreover, the pathological response was difficult to assess. Less than a quarter of the pathology reports evaluated the histological response using TRG (Supplementary Table S2).

Considering these limitations, a large sample size is important in future studies, and the study was stopped after analysis of the data of the first 215 patients. Considering the relatively small sample size of our study and the low frequency of PPI intake, our findings must be interpreted with caution. Although we did not observe any significant association between PPI intake and oncological outcomes, we cannot assert the safety of PPI use.

If the interaction between PPIs and capecitabine is confirmed, the biological mechanism of its interaction is not clearly established. Decreased gastric absorption may be involved in this interaction. Other mechanisms could be implied, such as single nucleotide polymorphisms of genes related to drug efflux transport (such as *ABCB1*) [14].

In addition, currently, there are significantly few data available concerning the interaction between PPIs and RT.

To limit inaccuracies about PPI drug status, more accurate information about patients' co-medications should be obtained. Analysis of co-medications prospectively collected in clinical trials could be helpful, although it focuses on relatively limited samples in the setting of experimental studies. Another source of data available in the near future in France could be shared medical records. This is an electronic service collecting patients' medical information, such as treatments, accessible to physicians and pharmacists who manage patients, with a formalized process of medication reconciliation.

On a larger scale, the Health Data Hub provides information on the entire population. These data, obtained based on health insurance reimbursements, make it possible to compile information on treatments dispensed in drugstores. For example, in 2015, according to the French Health Data Hub, nearly a quarter of the French population (15.8 million patients, 24%) used at least one PPI medication [8].

Moreover, PPIs have other adverse effects on patients with cancer and cancer-related treatments. The reduction of gastric acidity secondary to PPIs leads to a decrease in the gastric bactericidal effect and, therefore, to a change in the gut microbiome [15]. There is growing evidence reporting that the gut microbiome plays a central role in controlling the antitumor immune response of digestive organs and in the host immune system response to anticancer therapies [16]. Further studies are required to better identify the role of drug-induced dysbiosis in the effectiveness and safety of antineoplastic treatment.

Conclusion

There is a trend to a lower complete histological response with PPI co-medication in patients treated for locally advanced rectal cancer. Despite these inconclusive results and some limitations, oncologists should consider the pathophysiological consequences of PPI use. PPIs have several adverse events and may interact with cancer, the microbiome, and the efficacy of antineoplastic agents. Further ancillary studies of prospective clinical trials or studies using the Health Data Hub are necessary to explore the effects of PPIs on rectal cancer more accurately.

Declarations

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Conflicts of interest

The authors have no conflict of interest to declare.

Availability of data and material Yes

Data are available upon request from the study sponsor (University Hospital, Lille) and from the principal investigator Anthony Turpin.

Code availability not applicable

Authors' contributions

Marie- Bridoux: Conceptualization, Investigation, Writing, Reviewing, and Editing.

Anthony Turpin: Conceptualization, Supervision, Writing, Reviewing, and Editing.

Marie-Cécile Le Deley: Methodology, Formal analysis, Writing, Reviewing, and Editing.

Dienabou Sylla: Methodology, Formal analysis

Nicolas Simon, Nicolas Bertrand and Xavier Mirabel: Writing, Reviewing, and Editing.

Ethics approval: The ethics committee of the participating center approved the study and follow-up protocol.

Consent to participate: Alive patients were given a no opposition letter according to French regulations. A derogation was allowed for deceased patients.

Consent for publication: not applicable

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Figures

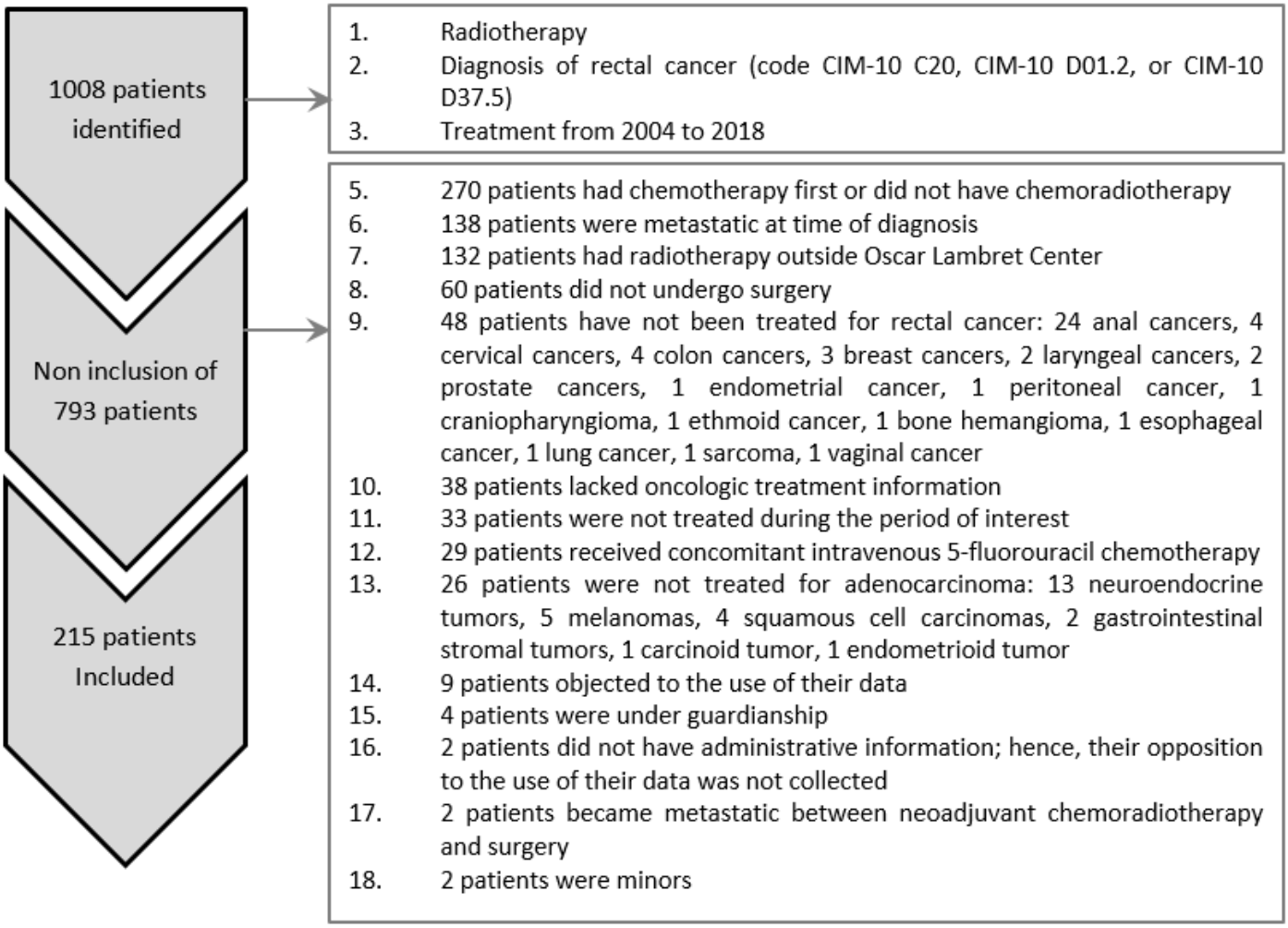

Figure 1

Flowchart

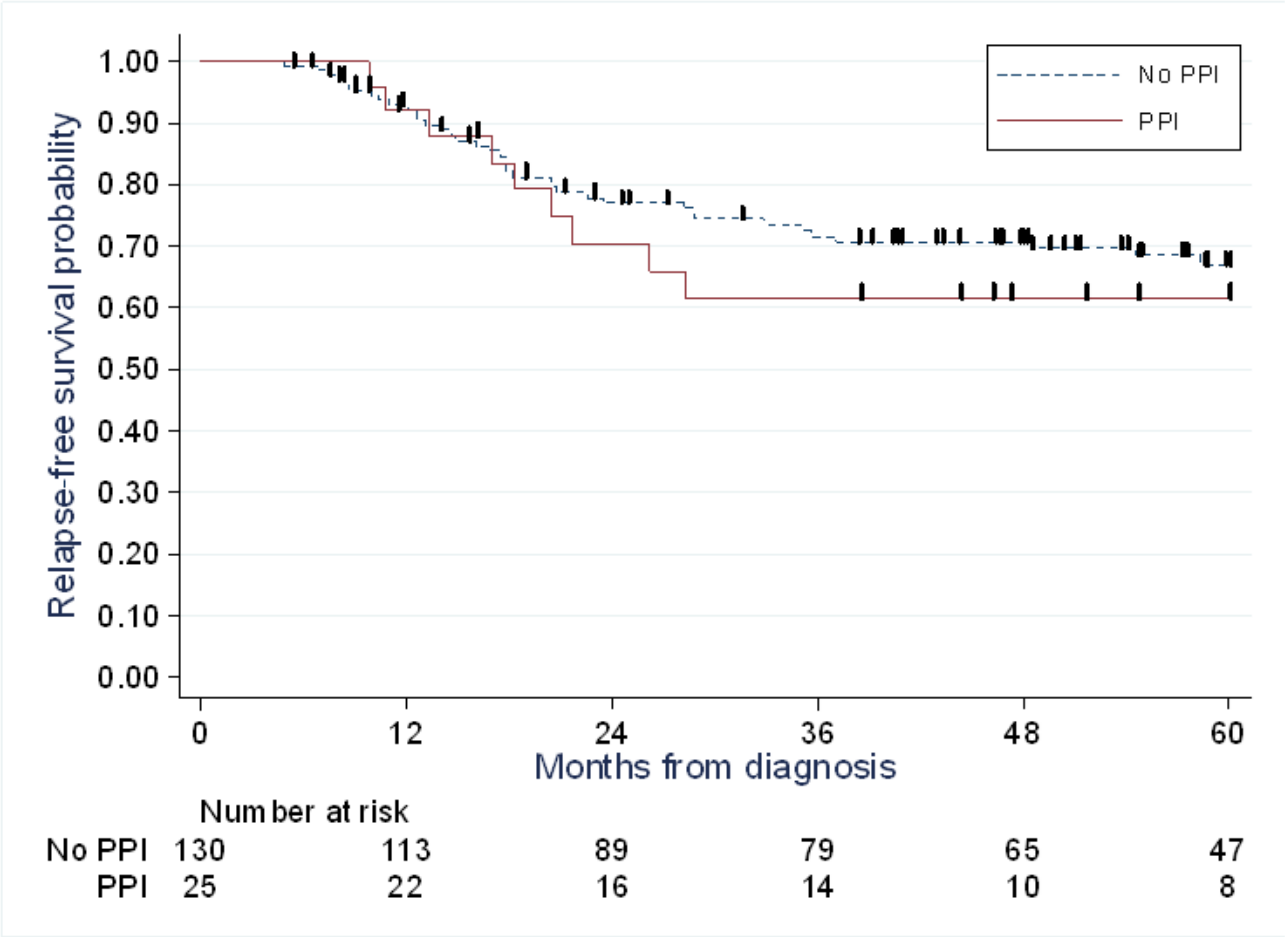

Figure 2

Five-year recurrence-free survival of patients according to proton pump inhibitor intake

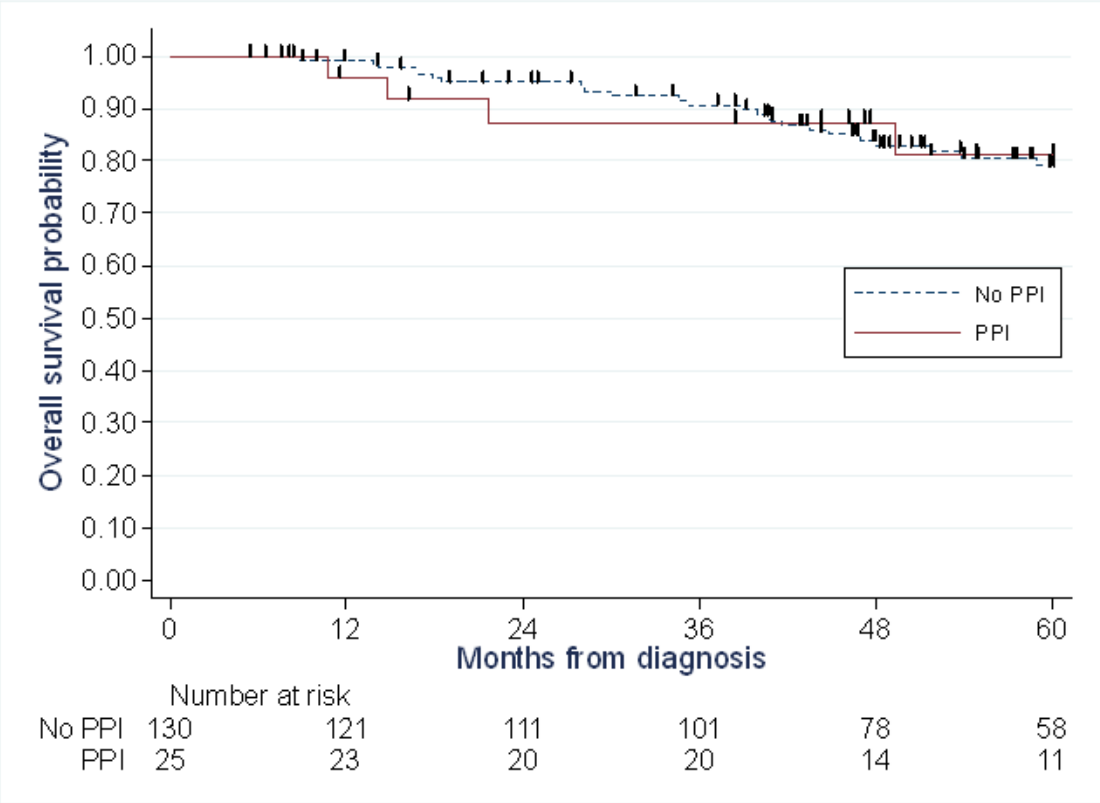

Figure 3

Five-year overall survival of patients according to proton pump inhibi

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