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Enhanced recovery and survival after elective surgery for colorectal cancer - propensity score weighting analysis of 2,865 prospective patients

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ABSTRACT

Background: The impact of enhanced recovery pathway (ERP) on survival after colorectal cancer surgery (CCS) remains controversial.
Materials and methods: A total of 2865 adults enrolled in a multicenter cohort study (iCral3 study) after CCS were followed up. The percentage adherence to the ERP was recorded, and the patients were grouped according to their quartiles. Other patient-, center-, disease-, and treatment-related factors were considered in a machine learning generalized boosted model (GBM) to estimate the 22 covariates propensity score weights for the binary comparisons between the reference treatment (1st quartile, ERP adherence rates <57.7 %) and the other treatment arms (2nd, 3rd, and 4th quartile). The primary endpoint was overall survival (OS). A GBM-weighted Cox model balanced on the same covariates was used to estimate the hazard ratio (HR) and 95 % confidence interval (95 %CI).
Results: Patients in the 4th quartile (ERP adherence rates ≥80.8 %) showed a significant lower risk of death from any cause (HR, 0.69; 95 %CI 0.49–0.96; p = 0.026).
Conclusions: High adherence to ERP was associated to a significant impact on long-term overall survival, supporting the efforts towards proper ERP implementation after CCS.

1. Introduction

The enhanced recovery pathway (ERP) is a multifaceted approach to optimizing perioperative management [1] designed to modify and enhance the response to surgery-induced trauma, based on a series of evidence-based elements related to perioperative care [2]. Numerous meta-analyses have indicated a notable decrease in morbidity rates and duration of hospitalization following colorectal surgery (CRS) [3–5]. It has not yet been definitively proven that ERP may also confer a substantial benefit concerning long-term survival after CRS for malignancy. Contemporary evidence, mainly derived from retrospective analyses, is still controversial, with great heterogeneity among studies regarding the type and number of ERP items, thresholds of ERP adherence, study populations, and methodological issues [6–18]. More recent studies on large cohorts showed that only high adherence to the ERP can influence early outcomes [19–22]. Consequently, any inference regarding ERP as a treatment variable should consider the effective rate of adherence to the pathway.

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To evaluate the impact of ERP adherence rates on survival, the Italian ColoRectal Anastomotic Leakage (iCral) study group planned a long-term follow-up of all cancer patients enrolled in the recent iCral3 study [23] with data analysis based on propensity score weighting algorithms.

2. Methods

2.1. Study design, participants, and setting

This was a planned post-hoc analysis based on long-term follow-up of a prospective multicenter study conducted in Italy from October 2020 to September 2021 at 76 surgical centers that voluntarily participated in the iCral3 study [23]. All adult patients who underwent elective or delayed urgency (≥24 h from admission) CRS with anastomosis were assessed for inclusion according to explicit inclusion and exclusion criteria. The inclusion criteria were as follows: a) patients who underwent laparoscopic/robotic/open/converted colon and rectal resection with anastomosis, including planned Hartmann's reversals; b) American Society of Anesthesiologists (ASA) class I, II, or III; c) elective or delayed urgency (≥24 h from admission) surgery; and d) patients' written acceptance to be included in the study. The exclusion criteria were as follows: a) ASA class IV-V; b) emergent surgery (≤24 h from admission); c) pregnancy; and d) hyperthermic intraperitoneal chemotherapy for carcinomatosis. Any case involving the creation of a proximal diverting stoma at the index operation was submitted per protocol (NCT04397627) to routine check of anastomotic integrity through an intraluminal contrast exam (standard x-rays or CT scan), MRI, or direct endoscopic evaluation three to six weeks after the operation.

Finally, 4529 patients were enrolled in the study. Prospective follow-up of all enrolled patients who underwent colorectal cancer surgery (CCS) was planned for 3283 patients (72.5 %), of whom 158 (4.8 %) with delayed urgent admission were excluded. At the established censor, 143 patients (4.3 %) treated in five centers that did not complete the planned follow-up were excluded, as were 117 (3.6 %) lost to follow-up. The remaining 2865 (87.3 %) patients were included in the analysis (Fig. 1).

2.2. Clinical and ERP adherence data

Quality control of the data for consistency, plausibility, and completeness was performed for each record by local investigators, and subsequently validated by the study coordinator, resolving any discrepancies through strict cooperation and excluding any record with incoherent or missing data. During the perioperative period, patients were examined daily by local investigators who were left free to decide on any complementary imaging and any further action according to their local criteria. The percentage adherence to the 26 items of the ERP [24,25] was measured in every case using explicit criteria. Patients were grouped according to quartiles (Fig. 1): The 1st quartile (Q1) included patients with ERP adherence rates <57.7 % (compliance up to 14 out of 26 items), 2nd quartile (Q2) ≥ 57.7 % to < 69.2 % (15–17 out of 26 items), 3rd quartile (Q3) ≥ 69.2 % to < 80.8 % (18–20 out of 26 items), and 4th quartile (Q4) ≥ 80.8 % (more than 20 out of 26 items). The list of ERP items, adherence criteria, and the standardized effect size of the 4th quartile of ERP adherence compared to the whole population are shown in Table 1.

Patient-, center-, disease-, and treatment-related factors were recorded (Table 2). Continuous variables such as age, Body Mass Index, and operation length were categorized according to their median values. The Mini Nutritional Assessment – Short Form (MNA-SF) was categorized as < 12, indicating potential malnutrition, or ≥ 12, indicating a normal nutritional status [26]. Potential clustering bias was addressed by defining each participating center as a Metropolitan/Academic or Local/Regional hospital, specialized Colorectal/Oncologic or General surgical unit, or high-volume (>4) or low-volume (≤4), according to the median number of cases enrolled per month of recruitment. Surgical procedures were categorized as standard (anterior resection, right colectomy, and left colectomy) or nonstandard (splenic flexure resection, transverse colectomy, subtotal and total colectomy, and other) resections. The location of the tumor (sidedness) was categorized as "right" (up to the transverse colon) or "left" (from the splenic flexure to the lower rectum). Pathologic stage grouping was performed according to the eighth edition of the American Joint Committee on Cancer [27], and was considered in the analysis as a dichotomous variable for each stage. Neoadjuvant treatments were administered mostly for locally

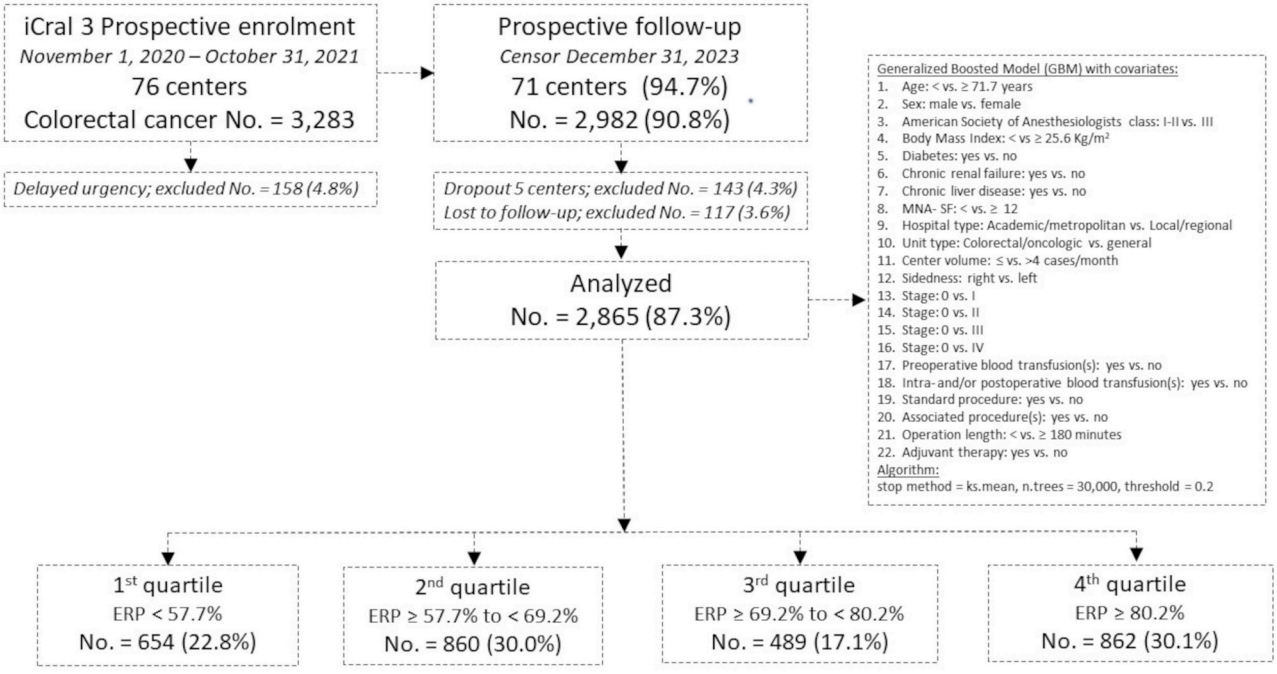

Fig. 1. Study flowchart.

Table 1
Definitions, adherence criteria, and percentage of adherence to the ERP items with comparison between the whole population and the 4th quartile of adherence (≥80.8 %).

ITEM		Adherence criteria	% (No.) of adherence in 2865 patients	% (No.) of adherence in 4th quartile of ERAS adherence rates (≥80.8 %; 862 patients)	[a]p	[b]SES
Preoperative	Nutritional status screening	Patient submitted to nutritional screening through Mini Nutritional Assessment Short Form (MNA-SF) (ref)	90.8 (2602/2865 pts. adhered)	99.8 (860/862 pts. adhered)	.000	15.9
	Nutritional Prehabilitation	All patients showing MNA-SF < 12 (malnourished or suspect malnutrition) and body mass index (BMI) > 30 (obesity) receive specific nutritional consultation	36.1 (1033/2865 pts. adhered)	79.0 (681/862 pts. adhered)	.000	26.4
	Physical Prehabilitation	Patients receive a standard protocol of physical activity to be accomplished in the preoperative period; frail and limited motility patients are submitted to specific geriatrician/ physiatrist consultation and personalized activity program	25.6 (732/2865 pts. adhered)	61.3 (528/862 pts. adhered)	.000	19.3
	Psychologic Prehabilitation	Patient and his familiars/caregivers are screened by the cases-manager; in case of anxiety/depression concerning diagnosis and related procedure for psychological consultation is warranted	20.1 (575/2865 pts. adhered)	45.9 (396/862 pts. adhered)	.000	13.9
	Counseling	Patient and his familiars/caregivers receive full information and suggestions regarding perioperative program from surgeon, anesthesiologist and case-manager	73.5 (2107/2865 pts. adhered)	95.2 (821/862 pts. adhered)	.000	19.8
	Preoperative Immunonutrition	Patient is administered Impact Oral ™ (Nestlè Health Science, Italy) 330 ml per os, three bricks per day during the 5 days preceding surgery or two bricks per day during the 7 days preceding surgery	36.0 (1032/2865 pts. adhered)	67.3 (580/862 pts. adhered)	.000	17.1
	Management of anemia	Patient with hemoglobin (Hb) concentration <130 g/L receive correction of anemia before surgery preferably through intravenous iron preparations (ferric carboxymaltose) and blood transfusion(s) in strictly necessary cases	14.5 (416/2865 pts. adhered)	25.2 (217/862 pts. adhered)	.000	6.6
	Antithrombotic prophylaxis	Patient receives compression stockings and/or pneumatic compression device, together with prophylaxis with low molecular weight heparin during the perioperative period, to be extended up to 28 days after surgery in case of malignancy	93.1 (2668/2865 pts. adhered)	97.6 (841/862 pts. adhered)	.000	6.3
	Antibiotic prophylaxis	Patients are administered i.v. antibiotic 30–60 min before incision, according to local protocols	97.6 (2797/2865 pts. adhered)	100.0 (862/862 pts. adhered)	.000	3.3
	No bowel preparation	No routine bowel preparation is used, except in case of anticipated need for covering stoma	63.3 (1812/2865 pts. adhered)	91.5 (789/862 pts. adhered)	.000	21.6
	Oral carbohydrates load	Carbohydrates rich beverage (12.5 % maltrodextrins, PreOp™, Nutricia Italy) is given preoperatively (800 ml on the evening before surgery and 400 ml 2–3 h before surgery)	60.8 (1741/2865 pts. adhered)	95.1 (820/862 pts. adhered)	.000	29.3
	Preoperative fasting	Preoperative fasting is limited to 2 h for clear liquids (water, coffee, tea) and to 6 h for milk and solid food	76.6 (2194/2865 pts. adhered)	99.8 (860/862 pts. adhered)	.000	28.7
Intraoperative	No premedication	No long- or medium-action sedatives. Short and ultra-short acting sedatives (e.g. Lorazepam, Midazolam, Methohexital, Dexmedetomidine, Ketamine) are allowed before performing spinal, epidural or loco-regional anesthesia	77.7 (2226/2865 pts. adhered)	99.7 (859/862 pts. adhered)	.000	27.3
	PONV prophylaxis	Postoperative nausea/vomiting (PONV) prophylaxis is administered according to individual risk assessment (Apfel score) through a multimodal approach	91.3 (2617/2865 pts. adhered)	99.5 (858/862 pts. adhered)	.000	14.3
	Normothermia	Body temperature is monitored during surgery, utilizing fluid warmers and/or thermic blankets as necessary	93.0 (2664/2865 pts. adhered)	99.7 (859/862 pts. adhered)	.000	12.9
	Standard anesthetic protocol	General anesthesia through short-acting anesthetics, cerebral activity monitoring to enhance recovery and to reduce postoperative delirium, anesthesia level monitoring and complete reversal of neuromuscular blockade	85.7 (2455/2865 pts. adhered)	99.2 (855/862 pts. adhered)	.000	18.7
	Intraoperative fluid management	Restrictive fluid therapy (defined as maintenance fluids at <2 ml/kg/h) or goal-oriented fluid therapy (stroke volume)	76.6 (2194/2865 pts. adhered)	97.0 (836/862 pts. adhered)	.000	20.8
	Multimodal analgesia	Use of more than two drugs or analgesia strategies (transversus abdominis plane (TAP) block or spinal anesthesia for minimally invasive surgery; thoracic epidural anesthesia for open surgery) in order to reduce the use of opiates	90.9 (2604/2865 pts. adhered)	99.0 (853/862 pts. adhered)	.000	12.6
	Minimally invasive surgery	Patient submitted to laparoscopic, robotic or video-assisted surgery (conversions to open surgery included on an intention-to-treat basis)	88.2 (2526/2865 pts. adhered)	96.2 (829/862 pts. adhered)	.000	9.0
	No nasogastric tube	Nasogastric tube, if used, is removed at the end of surgery	82.7 (2369/2865 pts. adhered)	99.2 (855/862 pts. adhered)	.000	21.4
	No drain	No drain is placed in the abdominal cavity (pelvic drain allowed for pelvic surgery with low colorectal anastomosis)	34.3 (983/2865 pts. adhered)	58.7 (506/862 pts. adhered)	.000	12.8
Postoperative	No major opiates	Patient receives no major opiates in the postoperative period	75.1 (2152/2865 pts. adhered)	98.1 (846/862 pts. adhered)	.000	24.8
	Bladdder catheter	Urinary catheter removed on postoperative day after surgery (POD) 1 (up to POD 2 in case of pelvic surgery)	76.3 (2185/2865 pts. adhered)	96.1 (828/862 pts. adhered)	.000	19.1
	Early mobilization	Patient receives passive mobilization on POD 0, active mobilization on POD 1	58.3 (1671/2865 pts. adhered)	90.7 (782/862 pts. adhered)	.000	24.0
	Early oral feeding	Patient receives liquid oral diet starting 6 h after surgery and semisolid diet starting on POD 1	56.6 (1622/2865 pts. adhered)	89.1 (768/862 pts. adhered)	.000	23.0

(*continued on next page*)

Table 1 (*continued*)

ITEM		Adherence criteria	% (No.) of adherence in 2865 patients	% (No.) of adherence in 4th quartile of ERAS adherence rates (≥80.8 %; 862 patients)	[a]p	[b]SES
	Pre-discharge check	Patients are checked just before discharge at home concerning adequate oral intake, bowel function, adequate pain control, active mobilization, no clinical/serological evidence of any postoperative complication, full agreement to go home	82.1 (2352/2865 pts. adhered)	99.1 (854/862 pts. adhered)	.000	21.6

[a] T test between proportions.
[b] SES: the standardized effect size is the difference between the percentage of adherence to the single enhanced recovery pathway item in the whole population and in the 4th quartile of adherence (≥80.8 %), divided by the standard error.

advanced low rectal cancer according to national guidelines [28]. The return to intended oncologic therapy (RIOT) was defined as the administration of adjuvant therapy within 8 weeks of the index operation, calculated in a subgroup of 1267 patients in whom adjuvant therapy was indicated according to the stage and national guidelines for colorectal cancer [29]. A proximal diverting stoma was performed at index operation in 263 (9.2 %) cases; it was closed in all but 5 (2.0 %) cases after a median (IQR; range) of 77 (54–154; 8–351) days. Any adverse events occurring within 8 weeks of surgery were recorded and graded according to Clavien-Dindo [30] and the Japanese Clinical Oncology Group-extended criteria [31], as were any readmissions, reoperations, and deaths. Anastomotic leakage (AL) was defined according to international consensus [32]. The Comprehensive Complication Index (CCI) was calculated [33].

2.3. Outcomes

The primary endpoint at the established censor (December 31, 2023) was overall survival (OS, time from surgery to death due to any cause). Secondary endpoints were cancer-specific survival (CSS, time from surgery to death for cancer) and disease-free survival (DFS, time from surgery to evidence of disease recurrence or death).

2.4. Ethics

The study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice E6 (R2) principles. After approval from the coordinating center ethics committee (Comitato Etico Regionale Marche, C.E.R.M. #2020/192, approved on 07/30/2020), the study protocol was registered (ClinicalTrials.gov #NCT04397627). All other participating centers obtained authorization from the local institutional review board. Individual participant-level anonymized datasets were made available upon explicit request from the study coordinator.

2.5. Statistical analysis

The sample size was calculated as previously reported [23]. Events per variable guideline was followed [34]. There were no missing data in the database of 2865 patients. The target of estimands was represented by the average treatment effect in the true population of interest (Average Treatment Effect on the Treated; ATT) answering the question "How would the average outcome(s) change if anyone receiving the reference treatment (Q1) had received another treatment (Q2, Q3, and Q4)?". A machine learning technique called the Generalized Boosted Model (GBM) [35] was used to estimate the propensity score weights for the binary comparisons between the reference treatment and the other treatment arms. GBM estimation involves an iterative process with multiple regression trees to capture complex and nonlinear relationships between treatment assignments and covariates without overfitting the data. In other words, GBM estimates weights that are higher or lower than 1 associated with each single record based on the selected covariates. During each iteration, the algorithm calculates the residuals, which are the differences between actual and predicted values.

The choice of GBM was due to a better balance of the covariates [35] and an enhanced bias reduction [36] compared to other multinomial logistic regression models such as inverse probability weighting (IPWT). The analysis was performed using the "twang library" (Toolkit for Weighting and Analysis of Nonequivalent Groups) of the software "R©" (Version 4.2.2, The R Foundation© for Statistical Computing, Vienna, Austria, 2022). GBM worked iteratively to estimate the propensity scores according to the minimization of the distance of the weighted distributions of the covariates given the baseline treatment (Supplemental Fig. 1). The balance comparisons were estimated by calculating 30,000 iterations and using the Kolmogorov-Smirnov (KS.mean) metrics with a threshold of 0.2 (a difference less than 0.2 typically indicates a negligible difference between the groups) [35]. The KS.mean was preferred because the availability of a large sample size allowed the comparison of the entire distribution rather than just the mean. The learning rate was set to 0.01 (this is the "shrinkage parameter"of the command "mnps"). The maximum depth of the individual trees used in the model was set to 3. To optimize the balance statistics of interest, the number of trees was set at 30.000 so that the KS.mean measure of balance did not decrease after these iterations were performed. Other parametric settings followed the default provided by the library "twang"; in particular, the regularization parameters were provided by the "gbm" library used by "twang". Twenty-two covariates potentially affecting the four treatment variable assignments were included (Fig. 1) and balanced in the model (Supplemental Fig. 1). A reasoned exclusion [37] of four covariates was performed: "mini-invasive surgery" because it was one of the ERP items and consequently part of the treatment variable, "neo-adjuvant therapy" because it was highly colinear with "adjuvant therapy", "diverting stoma" because it was highly colinear with "sidedness", and "RIOT" because it was calculated in a subgroup of 1267 patients in which adjuvant therapy was indicated according to stage and national guidelines for colorectal cancer. The estimation of the effective sample size of the four treatment groups, required to achieve the same level of precision as would be expected to be obtained by a simple random sample, was calculated using the command "summary (mnps.data)", confirming the adequate size of the weighted samples.

Survival was calculated using the Kaplan-Meier method. For the outcome analysis, a GBM-weighted Cox model was used to estimate the Hazard Ratio (HR) and 95 % confidence intervals (95 % CI) of the survival endpoints at censor, and the GBM-weighted survival curves were compared using the Log-rank test, based on the "R©" Survey library and the commands "svycoxph" and "svylogrank". All weighted models were adjusted considering the same 22 covariates used in the weight estimation using a "doubly robust" estimation of the treatment effects [35].

All the instructions used with the software "R©" were made available upon explicit request from the study coordinator.

3. Results

After a median (IQR) follow-up of 31.6 (28.3–34.8) months, 2486 patients were alive (OS rate 86.8 %). There were 379 (13.2 %) deaths, of which 207 (7.2 %) were due to cancer (CSS rate, 92.8 %) and 172 (6.0 %) were due to any other cause. Cancer recurrence occurred in 569 patients (19.9 %), of whom 362 (63.6 %) were alive with the disease

Table 2
Descriptive analysis of the study variables in the whole population and according to the quartiles of ERP adherence rates.

Descriptive variables		Whole population		[a]1st quartile of ERP adherence		[a]2nd quartile of ERP adherence		[a]3rd quartile of ERP adherence		[a]4th quartile of ERP adherence		
		No. 2865		No. 654		No. 860		No. 489		No. 862		
Patient-related	**Pattern**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**[b]p**
Age (years)	<71.7	1432	50.0	322	49.2	449	52.2	228	46.6	433	50.2	.253
	≥71.7	1433	50.0	332	50.8	411	47.8	261	53.4	429	49.8	
Sex	Male	1605	56.0	386	59.0	480	55.8	269	55.0	470	54.5	.335
	Female	1260	44.0	268	41.0	380	44.2	220	45.0	392	45.5	
[c]ASA class	I-II	1730	60.4	362	55.4	518	60.2	281	57.5	569	66.0	.000
	III	1135	39.6	292	44.6	342	39.8	208	42.5	293	34.0	
Body Mass Index (Kg/m^2)	<25.6	1419	49.5	319	48.8	445	51.7	224	45.8	431	50.0	.202
	≥25.6	1446	50.5	335	51.2	415	48.3	265	54.2	431	50.0	
Diabetes	Yes	464	16.2	120	18.4	128	14.9	77	15.3	139	16.1	.334
	No	2401	83.8	534	81.2	732	85.1	412	84.3	723	83.9	
Chronic renal failure	Yes	149	5.2	39	6.0	38	4.4	26	5.3	46	5.3	.597
	No	2716	94.8	615	94.0	822	95.6	463	94.7	816	94.7	
Chronic liver disease	Yes	39	1.4	13	2.0	12	1.4	5	1.0	9	1.0	.394
	No	2826	98.6	641	98.0	848	98.6	484	99.0	853	99.0	
[d]MNA-SF	<12	1013	35.4	242	37.0	292	34.0	198	40.5	281	32.6	.018
	≥12	1852	64.6	412	63.0	568	66.0	291	59.5	581	67.4	
Center-related	**Pattern**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**[b]p**
Hospital type	[e]Met./Ac.	2142	74.8	489	74.8	735	85.5	349	71.4	569	66.0	<.001
	Local/Regional	723	25.2	165	25.2	125	14.5	140	28.6	293	34.0	
Unit type	Colorectal/Oncologic	529	18.5	36	5.5	259	30.1	112	22.9	122	14.2	<.001
	General	2336	81.5	618	94.5	601	69.9	377	77.1	740	85.9	
Center volume	≤4 cases/month	644	22.5	244	37.3	168	19.5	64	13.1	168	19.5	<.001
	>4 cases/month	2221	77.5	410	62.7	692	80.5	425	86.9	694	80.5	
Disease-related	**Pattern**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**[b]p**
Sidedness[f]	Right	1290	45.0	298	45.6	360	41.9	231	47.2	401	46.5	.151
	Left	1575	55.0	356	54.4	500	58.1	258	52.8	461	53.5	
Stage	0	127	4.4	24	3.7	49	5.7	23	4.7	31	3.6	.130
	I	717	25.0	142	21.7	230	26.7	122	25.0	223	25.9	.138
	II	899	31.4	223	34.1	248	28.8	150	30.7	278	32.3	.155
	III	887	31.0	194	29.7	269	31.3	150	30.7	274	31.8	.838
	IV	235	8.2	71	10.9	64	7.4	44	9.0	56	6.5	.015
Treatment-related	**Pattern**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**[b]p**
Neoadjuvant therapy	Yes	303	10.6	62	9.5	111	12.9	42	8.6	88	10.2	.047
	No	2562	89.4	592	90.5	749	87.1	447	91.4	774	89.8	
Diverting stoma	Yes	263	9.2	72	11.0	74	8.6	42	8.6	75	8.7	.335
	No	2602	90.8	582	89.0	786	91.4	447	91.4	785	91.3	
Preoperative [g]BT(s)	Yes	200	7.0	45	6.9	53	6.2	36	7.4	66	7.7	.657
	No	2665	93.0	609	93.1	807	93.8	453	92.6	796	92.3	
Intra/postoperative [g]BT(s)	Yes	214	7.5	51	7.8	88	10.2	34	6.9	41	4.8	<.001
	No	2651	92.5	603	92.2	772	89.8	455	93.1	821	95.2	
Mini-invasive surgery	No	339	11.8	165	25.2	103	12.0	38	7.8	33	3.8	<.001
	Yes	2526	88.2	489	74.8	757	88.0	451	92.2	829	96.2	
	Laparoscopic	1967	68.7	322	49.2	569	66.2	364	74.4	712	82.6	
	Robotic	395	13.8	111	17.0	131	15.2	63	12.9	90	10.4	
	Converted	164	5.7	56	8.6	57	6.6	24	4.9	27	3.1	
Standard procedures	Yes	2530	88.3	567	86.7	755	87.8	438	89.6	770	89.3	.322
	Right colectomy	1197	41.7	270	41.2	328	38.1	217	44.3	382	44.3	
	Left colectomy	624	21.8	139	21.3	184	21.4	122	25.0	179	20.8	
	Anterior resection	709	24.8	158	24.1	243	28.3	99	20.3	209	24.3	
	No	335	11.7	87	13.3	105	12.2	51	10.4	92	10.7	
	Transverse colectomy	65	2.3	19	2.9	24	2.8	8	1.6	14	1.6	
	Splenic flexure colectomy	105	3.7	18	2.8	33	3.8	20	4.1	34	3.9	
	(Sub) total colectomy	34	1.2	7	1.1	13	1.5	4	0.8	10	1.2	
	[h]TaTME	49	1.7	9	1.4	13	1.5	7	1.4	20	2.3	
	Other	82	2.8	34	5.1	22	2.6	12	2.5	14	1.7	
Associated procedures	Yes	421	14.7	113	17.3	119	13.8	86	17.6	103	11.9	.006
	No	2444	85.3	541	82.7	741	86.2	403	82.4	759	88.1	
Operation length (minutes)	<180	1286	44.9	305	46.6	369	42.9	219	44.8	393	45.6	.504
	≥180	1579	55.1	349	53.4	491	57.1	270	55.2	496	54.4	
Adjuvant therapy	No	1811	63.2	433	66.2	543	63.1	315	64.2	520	60.3	.115
	Yes	1054	36.8	221	33.8	317	36.9	174	35.6	342	39.7	
[i]RIOT	No	551	43.5	155	54.2	181	46.1	71	34.6	144	37.6	<.001
	Yes	716	56.5	131	45.8	212	53.9	134	65.4	239	62.4	
60-day Adverse events	**Pattern**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**[b]p**
Anastomotic leakage	Yes	122	4.3	38	5.8	34	3.9	17	3.5	33	3.8	.159
	No	2743	95.7	616	94.2	826	96.1	472	96.5	829	96.2	

(*continued on next page*)

Table 2 (*continued*)

Descriptive variables		Whole population		[a]1st quartile of ERP adherence		[a]2nd quartile of ERP adherence		[a]3rd quartile of ERP adherence		[a]4th quartile of ERP adherence		
		No. 2865		No. 654		No. 860		No. 489		No. 862		
Overall morbidity	Yes	770	26.9	175	26.8	226	26.3	136	27.8	233	27.0	.943
	No	2095	73.1	479	73.2	634	73.7	353	72.2	629	73.0	
Major morbidity	Yes	207	7.2	50	7.6	57	6.6	32	6.5	68	7.9	.674
	No	2658	92.8	604	92.4	803	93.4	457	93.5	794	92.1	
Mortality	Yes	21	0.7	4	0.6	3	0.3	2	0.4	12	1.4	.052
	No	2844	99.3	650	99.4	857	99.7	487	99.6	850	98.6	

[a] ERP: enhanced recovery pathway.
[b] Chi square independence test with three degrees of freedom.
[c] ASA: American Society of Anesthesiologists.
[d] MNA-SF: Mini Nutritional Assessment—Short Form.
[e] Met./Ac.: Metropolitan/Academic.
[f] Right: from cecum to the distal transverse colon; Left: from the left flexure to the distal rectum and/or multiple sites.
[g] BT: blood transfusion(s).
[h] TaTME: Transanal total mesorectal excision.
[i] RIOT: return to intended oncologic therapy administered within 8 weeks after surgery, calculated in 1267 patients with adjuvant therapy indicated according to disease stage and national guidelines.

(DFS rate 80.1 %). The mean ± SD OS time was 32.5 ± 3.4, CSS time 31.3 ± 6.3, and DFS time 30.9 ± 6.8 months. The rates of death from causes other than cancer were significantly different (p = 0.047) in the four treatment arms (8.7 % in Q1, 4.8 % in Q2, 6.1 % in Q3, and 5.1 % in Q4). No significant differences were recorded concerning disease recurrence and RIOT rates in the four treatment arms.

The survival rates at the censor according to the quartiles of ERP adherence rates before and after GBM weighting are shown in Table 3. After GBM weighting, patients in Q4 showed a 31 % lower risk of death for any cause (HR 0.69; 95 %CI 0.49–0.96; p = 0.026) compared to patients in Q1. No significant differences were observed in CSS or DFS. Similarly, the log-rank test of the survival curves according to the quartiles of ERP adherence rates (Fig. 2) showed significant differences (p = 0.043) in OS and no significant differences in CSS and DFS. The other independent determinants of primary endpoint are shown in Fig. 3.

At 60-day follow-up, one or more adverse event was observed in 770 patients (OM = 26.9 %). Major adverse events were observed in 207 (MM = 7.2 %), AL in 127 (4.4 %), and death in 21 (0.7 %) patients. The median (IQR; range) CCI score was 0 (0–8.7; 0–100). After GBM weighting, the AL rates were significantly lower in Q4 vs Q1 (OR 0.52; 95 %CI 0.28–0.96; p = 0.036), whereas no significant differences were observed regarding the other outcomes (Supplemental Table 1).

Table 3
Overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) according to the quartiles of ERP adherence rates before and after Generalized Boosted Model (GBM) weighting.

Survival	[a]ERP adherence rates (%) quartiles	Before [b]GBM weighting (2865 patients)				After [b]GBM weighting (2865 patients)			
		Survival rate at censor (%)	[c]Mean survival time (95 % CI) in months	HR (95 % CI)	p	Survival rate at censor (%)	[c]Mean survival time (95 % CI) in months	HR (95 % CI)	p
Primary endpoint									
OS	Q1; <57.7	82.6	29.6 (29.0–30.3)	reference	–	82.6	29.6 (29.0–30.3)	reference	–
	Q2; ≥57.7 to <69.2	87.9	30.0 (29.5–30.5)	0.86 (0.65–1.13)	.288	89.8	29.5 (28.8–30.2)	0.90 (0.66–1.23)	.518
	Q3; ≥69.2 to <80.8	87.5	30.1 (29.5–30.8)	0.72 (0.52–1.00)	.047	80.5	30.1 (29.1–31.0)	0.90 (0.63–1.30)	.580
	Q4; ≥80.8	88.4	30.8 (30.3–31.3)	0.78 (0.59–1.03)	.076	92.1	30.9 (30.3–31.5)	0.69 (0.49–0.96)	.026
Secondary endpoints									
CSS	Q1; <57.7	91.3	37.4 (36.8–38.0)	reference	–	91.2	30.9 (30.3–31.5)	reference	–
	Q2; ≥57.7 to <69.2	92.7	37.7 (37.2–38.2)	1.11 (0.76–1.61)	.586	93.6	31.0 (30.5–31.5)	1.15 (0.74–1.77)	.529
	Q3; ≥69.2 to <80.8	93.7	38.1 (37.6–38.6)	0.74 (0.47–1.18)	.209	87.7	31.5 (30.7–32.2)	1.13 (0.67–1.92)	.636
	Q4; ≥80.8	93.5	38.1 (37.7–38.5)	0.98 (0.66–1.45)	.914	95.3	31.9 (31.5–32.4)	0.85 (0.53–1.37)	.508
DFS	Q1; <57.7	78.6	32.7 (31.6–33.8)	reference	–	78.6	30.4 (29.8–31.1)	reference	
	Q2; ≥57.7 to <69.2	80.6	33.7 (32.9–34.5)	0.83 (0.65–1.01)	.120	84.4	30.5 (29.9–31.2)	0.87 (0.67–1.14)	.321
	Q3; ≥69.2 to <80.8	80.4	33.7 (32.6–34.8)	0.80 (0.61–1.06)	.123	74.5	31.1 (30.2–32.0)	0.85 (0.61–1.19)	.350
	Q4; ≥80.8	80.7	34.1 (33.3–34.9)	0.92 (0.73–1.17)	.517	85.8	31.7 (31.2–32.3)	0.92 (0.68–1.25)	.607

[a] ERP: enhanced recovery pathway.
[b] GBM: Generalized Boosted Model.
[c] Mean survival times are used instead of median survival times because the last-ones are not estimable (patients experiencing death did not reach 50 % of the sample); HR (95 % CI): hazard ratio (95 % confidence interval.

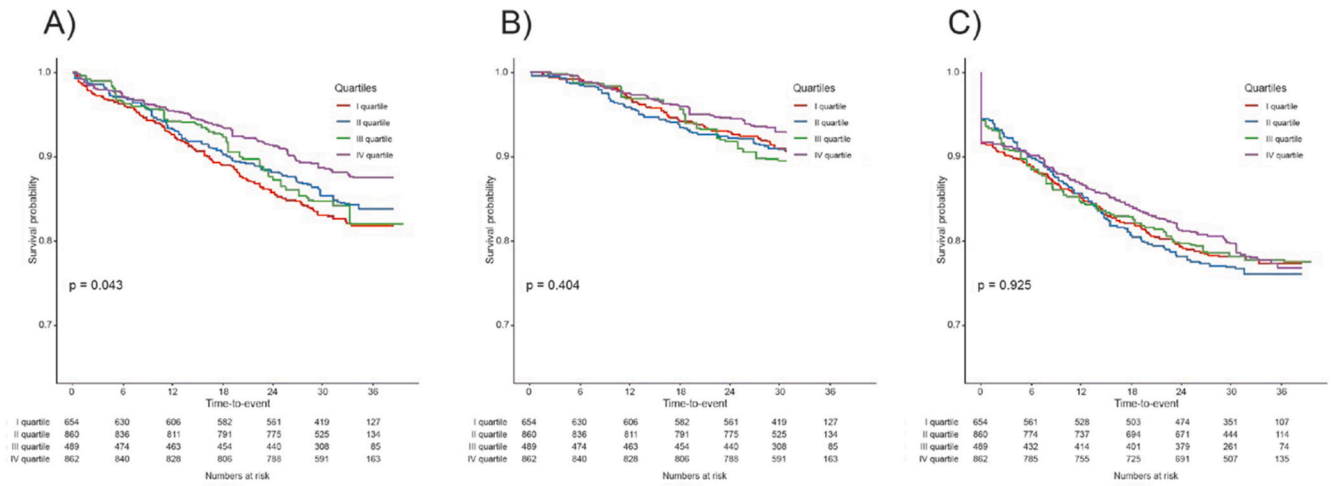

Fig. 2. Kaplan-Meier survival curves after GBM weighting: A) overall survival; B) cancer-specific survival; C) disease-free survival. Log-rank test: time-to-event = months.

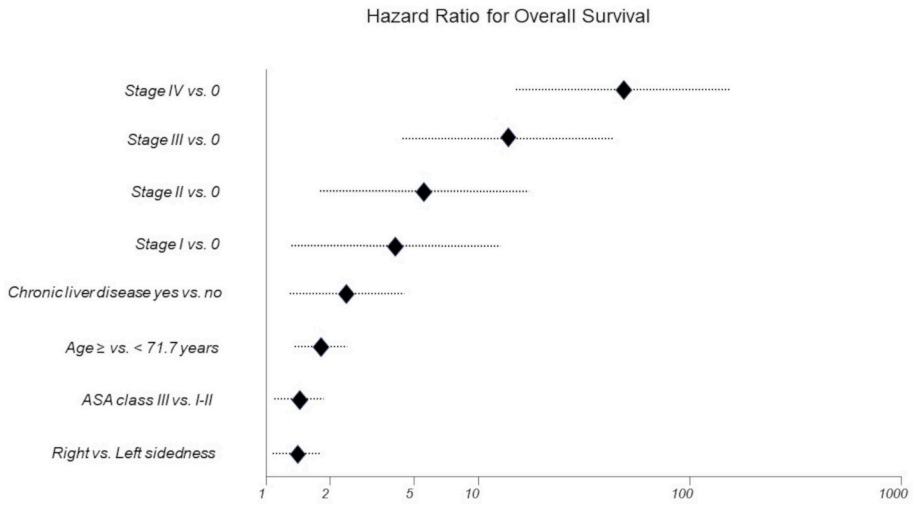

Fig. 3. Forest plot (log scale) of independent variables for overall survival after the weighted Cox model; diamonds show HR, dotted lines show 95 %CI.

4. Discussion

Controversial results regarding the influence of ERP on long-term survival after CCS have been reported to date in either retrospective or prospective observational studies, considering either ERP vs. no ERP [8,12,14,15,17,18] or high vs. low ERP adherence based on varying thresholds (70–80 %) [6,9–11] as treatment variables. All of these studies used different numbers and types of ERP items, different definitions of ERP adherence, and non-homogeneous patient populations, making them difficult to compare. The long-term follow-up of a multicenter Spanish observational study is still ongoing [38], and the planned long-term follow-up of a largely underpowered randomized controlled trial (RCT) designed for other endpoints showed significantly higher CSS rates in the arm treated with ERP than in those without ERP [16], but no differences in OS and DFS rates. The great heterogeneity of the above reported definitions of ERP as a treatment variable makes any new RCT hardly foreseeable [13]. When conclusive evidence from RCTs is lacking, or when researchers need to assess treatment effects on the basis of real-life data outside any intervention implemented by randomized assignment rules, multiple-treatment propensity score-weighting analysis based on machine learning methods performed on data from prospective observational studies offers an alternative approach for estimating treatment effects. To the best of our knowledge, this is the first machine learning analysis of prospective data that explores the impact of ERP adherence on long-term survival after CCS. According to McCaffrey's studies [35], an automatic prediction (machine learning) model (GBM-weighting), balancing and estimating the weights of the 22 selected confounders for each patient, was used to reduce the selection bias, confounding bias, clustering bias, and variance in the estimates. According to the propensity score methods [35], the resulting inference estimates were intended to approximate those of a RCT.

This prospective "quasi-experimental" study showed (Table 3) that adherence to at least 21 out of 26 ERP items (≥80.8 %) was independently associated with higher OS rates compared to adherence up to 14 out of 26 items (<57.7 %), without any significant effect on CSS and DFS, suggesting that this association could be related to deaths due to causes other than cancer.

Patients in Q4 showed a significantly higher adherence to all ERP items compared to the whole population (Table 1), but a significant standardized effect size (i.e.: higher than 25) was limited to some preoperative items (nutritional prehabilitation, oral carbohydrates load, short preoperative fasting, no premedication), suggesting that the independently higher overall survival in this subgroup, in which 80 % of patients have been treated in high volume centers, may be also related to preoperative measures that tend to correct nutritional deficiencies and could act on the metabolic state of the immediate postoperative period

improving the insulin sensitivity and reducing the use of muscle proteins as an energy source [39,40]. However, without objective baseline metrics, this interpretation, that supports the original idea that pre- and intraoperative ERP items are the main determinants of postoperative outcomes [41], remains only speculative.

In contrast to previous studies on unweighted prospective data [20–22], that failed to show any effect of ERP adherence on AL, GBM-weighted data in the present study showed that ERP adherence rate ≥80.8 % was significantly associated with a lower risk of AL.

These findings suggest that the recorded higher OS rates in Q4 compared with Q1 could be related not only to a lower risk of death other than cancer but also, speculatively, to the adoption of items that impact on the postoperative patient's metabolic status and early outcomes.

Finally, the finding that OS rates were independently associated with other prognostic factors (Fig. 3) such as age, ASA class, disease stage, and tumor location [27,42,43] confirmed the internal validity of the study.

The strengths of the present study are its large sample size, well-defined time-lapse in a large number of centers in Italy, approximating a population-based study, and analysis based on machine learning techniques (GBM), including and balancing 22 potential confounders and limiting selection, confounding, and clustering bias. The main limitation is that both observational and quasi-experimental studies are prone to unobserved confounders, which may affect the outcomes estimation. In conclusion, every effort should be made towards proper ERP implementation to achieve high adherence rates and improved overall survival rates after CCS.

Credit author statement

Marco Catarci: Conceptualization, Methodology, Data curation, Investigation, Validation, Writing- Original draft preparation, Writing-Reviewing and Editing, Supervision, Visualization **Stefano Guadagni**: Conceptualization, Methodology, Data curation, Investigation, Validation, Writing- Original draft preparation, Writing- Reviewing and Editing, Supervision, Visualization **Marco Scatizzi**: Investigation, Validation **Raffaele De Luca**: Investigation, Validation **Paolo Delrio**: Investigation, Validation **Giacomo Ruffo**: Investigation, Validation **Felice Borghi**: Investigation, Validation **Francesco Masedu**: Conceptualization, Formal analysis, Software, Writing- Original draft preparation, Writing- Reviewing and Editing.

Data sharing statement

Individual participant-level anonymized datasets and all instructions used with the software "R©" were made available upon explicit request from the study coordinator.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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