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"Ultra" E.R.A.S. in laparoscopic colectomy for cancer: discharge after the first flatus? A prospective, randomized trial

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Abstract
Background Enhanced Recovery After Surgery (E.R.A.S.) programs are now widely accepted in colonic laparoscopic resections because of faster recovery and less perioperative complications. The aim of this study was to assess safety and feasibility of discharging patients operated on by laparoscopic colectomy on postoperative day 2, so long as the first flatus has passed and in the absence of complication-related symptoms.
Methods This study was a non-inferiority, open-label, single-center, prospective, randomized study comparing "Ultra" to Classic E.R.A.S. with discharge on POD 2 and 4, respectively. Seven hundred and sixty-five patients with resectable non-metastatic colonic cancer were analyzed: 384 patients were assigned to "Ultra" E.R.A.S. and 381 to Classic E.R.A.S. Primary end-point was mortality; secondary end-points were morbidity, readmission and reoperation rate. Limitations are: it is a single-center experience; it is not double-blind, with the intrinsic risk of intentional or unconscious bias; exclusion criteria because of "non-compliance" may be considered arbitrary.
Results Mortality was 0.89 % in "Ultra" E.R.A.S. group and 0.59 % in Classic E.R.A.S. ($p = 0.571$). Morbidity was 34.1 % for "Ultra" E.R.A.S. arm and 35.4 % for Classic E.R.A.S. ($p = 0.753$). Readmissions were 5.6 % for "Ultra" E.R.A.S. and 5.9 % for Classic E.R.A.S. ($p = 0.359$). Reoperation rate was 3.8 % for "Ultra" ERAS and 4.7 % for Classic E.R.A.S. ($p = 0.713$). Multivariate regression analyses using Cox's proportional hazard model showed that mortality (primary end-point), morbidity, reoperation and readmission (secondary end-points) were not significantly influenced by the two different perioperative regimens; conversely, the global cost of "Ultra" E.R.A.S. regimen was more economically effective.
Conclusion "Ultra" E.R.A.S. showed to be safe, actual and effective; discharge on postoperative day 2 after the first flatus passage, in the absence of complication-related symptoms, should be actively considered in a modern, multidisciplinary, multimodal laparoscopic management of colonic cancer.

Keywords E.R.A.S. · Laparoscopy · Colonic cancer · Safety · Early discharge

The concept of E.R.A.S. (Enhanced Recovery After Surgery) programs in colorectal surgery was firstly introduced by Kehlet in the late 1990 [1], with the aim to reduce postoperative complications, leading to shorter hospital stays and convalescence [2, 3].

E.R.A.S. goes beyond the traditional concept of perioperative care based on the use of nasogastric and drainage tubes, starvation until passage of gas or feces and bed rest until the second postoperative day, and affirms a multidisciplinary, multimodal strategy: extensive preoperative counseling, no mechanical bowel preparation, no sedative pre-medication, 400 mg complex carbohydrate load (mainly maltodextrins) 2 h before surgery, restrictive perioperative fluid treatment to prevent liquid overload, multimodal pain management with epidural anesthesia and short acting anesthetics trying to avoid opiates; minimally invasive surgery with no routine use of drains and nasogastric tubes; early oral feeding, precocious mobilization

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and early Foley catheter removal [4–20]. Proper integration of all these methodologies is cardinal in reducing surgical stress, with the ultimate goal of minimizing any procedure-related risk of complications [6, 7].

Even with E.R.A.S. programs applied, patients treated with laparoscopic colonic resections are usually discharged on the 3rd/4th postoperative day (POD); the aim of this prospective randomized trial was to demonstrate that discharging patients operated on by laparoscopic colectomy on POD 2 ("Ultra" E.R.A.S.) is safe and feasible, so long as the flatus has passed and in the absence of signs or symptoms suggestive of possible complications.

Materials and methods

Study design

Our study was a non-inferiority, open-label, prospective, randomized trial, performed in a single-center, regional referral center for advanced laparoscopic surgery. The study was conducted in accordance with the principles of the Declaration of Helsinki and the independent medical ethics review board of the hospital approved the study protocol.

The trial was registered at ClinicalTrials.gov (US National Institutes of Health, NIH) with I.D. NCT-02727153.

Patients

Patients with solitary non-metastatic adenocarcinoma of the colon candidates for elective surgery were eligible for inclusion. In addition to metastatic patients, exclusion criteria were T4b tumors, urgent operations (because of obstruction, perforation or bleeding refractory to conservative treatment), positive cytology in peritoneal lavage or frank carcinosis, inability to tolerate pneumoperitoneum, ASA class 4 and severe portal hypertension.

All patients gave their informed consent, being fully aware of the advantages and risks of both treatment regimens.

Randomization

Randomization was performed at the patient level; eligible patients were randomly assigned in a 1:1 ratio; the list was computer generated, with stratification according to sex, age (two groups: <65 and >65 years), tumor location (left/right sided), comorbidities (3 groups: no comorbidity, 1 comorbidity, 2 or more comorbidities) and ASA class.

Protocol

All patients were scheduled for laparoscopic approach primarily and were operated on by the same surgical group. The protocol of "Ultra" E.R.A.S. was the same of Classic E.R.A.S., differing only in discharge on POD 2 (Table 1): normal diet until 8 h before surgery; glucose load 2 h before surgery; thromboprophylaxis; antibiotic prophylaxis; continuous thoracic epidural opiate-sparing anesthesia, exclusively for left hemicolectomy; prevention of hypothermia and fluid overload; minimally invasive colonic surgery; no drainage; early removal of NGT and urinary catheter just after the procedure; early oral feeding (chewing gum just the patient is awake, water after 12 h and light diet on POD 1) and mobilization (2 h on day of surgery, 6 h on POD 1 and 2 h of walk around the ward on POD 2); regular pain control with opiate-sparing multimodal analgesia; fluid restriction to 1500 ml/die on POD 0.

Surgical techniques

Both laparoscopic right and left hemicolectomy were approached following a standardized method: primary vascular approach (ileocolic vessels, right colic vessels when present, right branch of middle colic vessels for right hemicolectomy; inferior mesenteric vein and artery for left hemicolectomy); mobilization of the specimen along the avascular planes between the mesocolon and the Gerota's fascia, according to the principles of complete mesocolic excision and central vascular ligation; transection of the distal and proximal side of the specimen with linear staplers; totally laparoscopic intra-corporeal, iso-peristaltic, side to side anastomosis for right hemicolectomy, and laparoscopic Knight–Griffen anastomosis for left hemicolectomy with intra-corporeal section of the mesocolon.

Follow-up

Follow-up was at 3 months for all patients. Mortality, morbidity, reoperation and readmission rate were recorded for both groups.

End-points

Primary end-point was 90-day mortality. Secondary end-points were 90-day morbidity (both major and minor), readmission, reoperation rate and global costs.

Statistical method

Using a 5 % significance level, 5 % of type I error, 95 % power with a follow-up loss of 5 %, a sample size of 700 patients was required to detect significant differences

Table 1 "Ultra" and Classic E.R.A.S. protocol

Time	"Ultra" E.R.A.S.	Classic E.R.A.S.
Preoperative	Counseling	
	Informed consent	
	No bowel preparation	
	Glucose load 2 h before	
	Antibiotic prophylaxis	
	Thromboprophylaxis	
Intraoperative	Prevention of hypothermia	
	Prevention of fluid overload	
	Minimally invasive surgery	
	Removal of NGT at the end of procedure	
Day of surgery	Sit in chair for >1 h	
	Chewing gum	
	Sips of water <1 l	
	The and Marmellade at dinner	
POD 1	Removal of urinary catheter	
	Sit in chair for >4 h	
	Ward ambulation for >400 m	
	Semifluid diet >1 l	
POD 2	Liberal ward ambulation	
	Soft diet	
	Discharged late afternoon (after flatus passage)	No discharge
POD 3–4	Discharged	Discharge
POD 3–6	Daily telephone contact	
POD 7	Outpatient control	
POD 30	Outpatient control	
POD 90	End of follow-up	

POD postoperative day

between the "Ultra" and Classic E.R.A.S. in respect of mortality, morbidity, readmission and reoperation rates.

Data are expressed as a mean ± standard deviation. The Student t-test was used to analyze quantitative variables, while the Chi-squared test was used for the qualitative ones. Multivariate regression analyses using Cox's proportional hazard model were performed to analyze the effect of both regimens on mortality, minor and major morbidity, readmission and reoperation. A $p < 0.05$ was considered statistically significant (Table 2).

Table 2 "Conditional" discharge criteria for "Ultra" E.R.A.S

1. Patient with no or minimal complaints
2. No fever
3. No tachycardia (pulse rate >100 bpm)
4. No abdominal tenderness
5. No complaint with a soft diet
6. Normal or decreasing WBC count

WBC white blood cells

All statistical analyses were performer using dedicated software (SPSS 19 ®) on Windows Vista®.

Results

From January 2008 to December 2015, 765 patients were prospectively randomized for early discharge after laparoscopic colectomy: after obtained informed consent, 384 patients were randomly assigned to the "Ultra" E.R.A.S. group and 381 to Classic E.R.A.S. group.

Fifty-two patients on the "Ultra" E.R.A.S. group (31 for no passage of flatus within POD 2; 18 for conversion to laparotomy and 3 for feeding intolerance) and 40 on the Classic E.R.A.S. group (22 for no passage of flatus within POD 3, 16 for conversion to laparotomy and 2 for feeding intolerance) were excluded from the study (symptoms associated with complications and thus patients not amendable for any E.R.A.S. program; conversion put patients outside the aim of the study), resulting in 337

patients allocated to "Ultra" E.R.A.S. arm, and 336 to Classic E.R.A.S. arm (see Fig. 1).

There were 60.8 % men and 39.2 % women for "Ultra" E.R.A.S. and 58.9 % men and 41.1 % women for Classic E.R.A.S. ($p = 0.737$ and 0.853, respectively), with a mean age of 73 ± 13 for "Ultra" E.R.A.S. and 71 ± 14 for Classic E.R.A.S. ($p = 0.531$)—see Table 3.

Right sided lesions treated with right hemicolectomy were 32.9 % for "Ultra" E.R.A.S. and 31.8 % for Classic E.R.A.S. ($p = 0.357$), while left sided treated with left hemicolectomy were 67.1 % for "Ultra" E.R.A.S. and 68.2 % for Classic E.R.A.S. ($p = 0.397$).

TNM stage was I for 25.2 and 27 % ($p = 0.593$), II for 40 and 41 % ($p = 0.575$), III for 34.8 and 32 % ($p = 0.751$) for "Ultra" and Classic E.R.A.S., respectively—see Table 3.

ASA class was I in 40.4 and 37.7 % ($p = 0.735$), II in 41.5 and 44.6 % ($p = 0.651$) and III in 18.1 and 17.7 % ($p = 0.579$) of cases for "Ultra" and Classic E.R.A.S. group, respectively.

There were 18 and 16 laparotomic conversion in "Ultra" and Classic E.R.A.S. arm, respectively (4.6 vs. 4.1 %; $p = 0.973$), and these patients were excluded because beyond the aim of the study. Length of surgery was 171 ± 25 min for "Ultra" E.R.A.S. and 175 ± 21 for Classic E.R.A.S. ($p = 0.125$), with a mean estimated blood loss of 75 ± 25 cc for "Ultra" E.R.A.S. and 83 ± 15 cc for Classic E.R.A.S. ($p = 0.395$).

There was no loss on follow-up. Mortality was 0.89 % in "Ultra" E.R.A.S. group and 0.59 % in Classic E.R.A.S., without statistical significance ($p = 0.571$). Morbidity was 34.1 % for "Ultra" E.R.A.S. arm and 35.4 % for Classic E.R.A.S. ($p = 0.753$; not significant), and it is specifically reported in Table 4.

Readmissions were 5.6 % for "Ultra" E.R.A.S. and 5.9 % for Classic E.R.A.S. ($p = 0.359$), mainly for Clavien–Dindo [21] grade I–II complications (4.7 vs. 5.3 % for "Ultra" E.R.A.S. and Classic E.R.A.S., respectively, $p = 0495$), intestinal obstruction (0.6 vs. 0.5 %; $p = 0.135$; all 4 patients were managed laparoscopically) and for anastomotic leakage (0.29 % for "Ultra" E.R.A.S. versus 0 % for Classic E.R.A.S.; $p = 0.223$; the single anastomotic leakage was managed laparoscopically), as shown in Table 3. Readmissions were after POD 5 in 73.6 % of cases for "Ultra" E.R.A.S. and 75 % for Classic E.R.A.S. ($p = 0.223$); in both arms, no life-threatening condition (severe sepsis, hemodynamic instability, severe respiratory distress, APACHE II score >8) was recorded in any readmission. Reoperation rate was 3.8 % for "Ultra" E.R.A.S. and 4.7 % for Classic E.R.A.S., not reaching statistical significance ($p = 0.713$).

Global hospitalization costs, calculated by summing up the costs of the operatory room per hour stratified for laparoscopic right and left colectomy, the energy devices employed (radiofrequency or harmonic scalpel), the number of staplers used for each type of operation (usually a linear stapler with 3 tri-stapled technology cartridges for laparoscopic right colectomy; a linear stapler with 2 tri-stapled technology cartridges and a circular stapler for laparoscopic left colectomy), the cost of hospital stay (including the cost of intensive care unit per day, when needed), were 8.595€ per patient in the "Ultra" E.R.A.S. group versus 12.295€ per patient in the Classic E.R.A.S. group, reaching statistical significance ($p < 0.05$).

Multivariate regression analyses using Cox's proportional hazard model showed that mortality (primary end-point), morbidity (both minor and major), reoperation and readmission rates (secondary end-points) were not

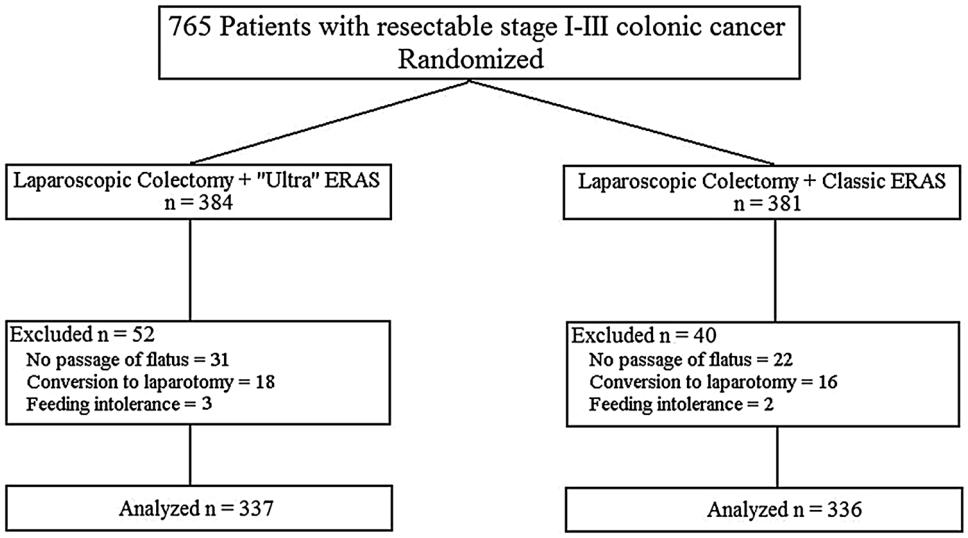

Fig. 1 Study design

Table 3 Demographics, clinicopathological data

Variable	U-ERAS % (*n*)	C-ERAS % (*n*)	*p* value
Sex			
Males	60.8 % (205)	58.9 % (198)	0.737
Females	39.2 % (132)	41.1 % (138)	0.853
Age (years)	73 ± 13	71 ± 14	0.531
Operative technique			
Right colectomy	32.9 % (111)	31.8 % (107)	0.357
Left colectomy	67.1 % (226)	68.2 % (229)	0.397
Length of surgery (min)	171 ± 25	175 ± 21	0.125
Estimated blood loss (cc)	75 ± 25	83 ± 15	0.395
Stage of disease			
I	25.2 % (85)	27 % (91)	0.593
II	40.1 % (135)	41 % (138)	0.575
III	34.7 % (117)	32 % (107)	0.751
ASA class			
I	40.3 % (136)	37.8 % (127)	0.315
II	41.5 % (140)	44.6 % (150)	0.239
III	18.1 % (61)	17.6 % (59)	0.451

U-ERAS "Ultra" E.R.A.S., *C-ERAS* Classic E.R.A.S

Table 4 Postoperative data

Variable	"Ultra" ERAS % (*n*)	Classic ERAS % (*n*)	*p* value
Mortality	0.89 % (3)	0.59 % (2)	0.571
Morbidity	34.1 % (115)	35.4 % (119)	0.551
Anastomotic leakage	3.2 % (11)	3.5 % (12)	0.573
Intestinal obstruction	6.8 % (23)	7.4 % (25)	0.135
Wound infection	13.3 % (45)	14.5 % (49)	0.335
Pneumonia	4.4 % (15)	4.1 % (14)	0.315
UTI	3.5 % (12)	2.9 % (10)	0.779
DVT	1.7 % (6)	2.0 % (7)	0.643
PE	0.8 % (3)	0.5 % (2)	0.225
Reoperation rate	3.8 % (13)	4.7 % (16)	0.713
Readmission rate	5.6 % (19)	5.9 % (20)	0.359
Clavien–Dindo grade I–II	4.7 % (16)	5.3 % (18)	0.495
Intestinal obstruction	0.6 % (2)	0.5 % (2)	0.135
Anastomotic leakage	0.29 % (1)	0 %	0.223
Reoperation after	0.89 % (3)	0.59 % (2)	0.125
Readmission			
Bowel obstruction	0.59 % (2)	0.59 % (2)	0.295
Anastomotic leakage	0.29 % (1)	0 %	0.359

UTI urinary tract infection, *DVT* deep venous thrombosis, *PE* pulmonary embolism

significantly influenced by the two different perioperative regimens; conversely, the global costs (secondary endpoint) were more convenient for the "Ultra" E.R.A.S. regimen. The hazard ratios, 95 % Confidence Intervals and *p* values are specifically shown in Table 5.

Discussion

E.R.A.S. programs are based on surgical stress mitigation by reducing the neurohormonal response to the operation, with consequent less organ dysfunction and complications

Table 5 Logistic regression analyses on "Ultra" E.R.A.S. regimen

Variable	Hazard ratio	95 % CI	*p* value
Mortality	1.039	0.913–1.135	0.571
Minor morbidity (Clavien–Dindo grade I–II)	1.007	0.995–1.101	0.449
Major morbidity (Clavien–Dindo grade III–IV)	0.995	0.991–1.002	0.559
Reoperation	1.009	1.001–1.018	0.595
Readmission	1.051	1.020–1.093	0.557
Global costs	0.715	0.479–0.853	<0.05

Classic E.R.A.S. is the reference

95 % CI 95 % confidence interval

rates [6, 7]. Factors related to stress reduction are multiple and require a multimodal-coordinated approach to be managed properly [8–21].

Several well-structured trials and four meta-analyses [22–24] have shown safety and efficacy of E.R.A.S. methods, reducing major colorectal surgery morbidity by up to 50 % [25]: in addition to precocious discharge, the real revolution of any E.R.A.S. program is in fact the significant reduction in postoperative complications when compared to traditional perioperative care management.

Our prospective randomized trial in laparoscopic colonic surgery aimed to compare Classic E.R.A.S. to a more precocious discharge, on postoperative day 2, so long as the first flatus has passed (main herald of a uneventful recovery and "necessary" for very early discharge), and no complication-related symptoms present: our goal was to demonstrate that passage of the first flatus without "conditional" signs of possible complications (Table 2) is comparable to later discharge on POD 4 (Classic E.R.A.S.) in respect of safety and efficacy. We set discharge on POD 2 because we consider 48 h of hospital stay the adequate length for a safe discharge: within 48 h, if no serious complication has occurred and recovery is uneventful, the flatus has passed and no conditional signs (Table 2) are present. The passage of flatus (main sign) and the "conditional signs" (Table 2) must not be considered independently, but as a whole: the first is the most important because there are the sign of an active peristalsis and herald of improbable endo-abdominal complications in most cases; the second strengthens the first, because, if absent, an uneventful recovery has been confirmed in almost all cases, or, if altered, further investigations have been warranted (Chest X-rays; abdominal CT scan; urine analysis; according to the clinical picture), without precluding a very early discharge if the latter were negative.

Both the "Ultra" and Classic E.R.A.S. groups showed to be homogeneous in respect of gender, age, colonic lesion side, TNM stage and ASA class.

Mortality (primary end-point) was 0.89 % in "Ultra" E.R.A.S. group and 0.59 % in Classic E.R.A.S., without statistical significance ($p = 0.571$). Overall complications rate was 34.1 % for "Ultra" E.R.A.S. versus 35.4 % for traditional E.R.A.S. ($p = 0.551$); particularly, no statistical differences were recorded in anastomotic leakage (3.2 vs. 3.5 % for "Ultra" and Classic E.R.A.S., respectively), pulmonary infections (4.4 vs. 4.1 %), wound infections (13.3 vs. 14.5 %) and intestinal obstruction rates (6.8 vs. 7.4 %), as shown in Table 3.

The critical topic of the higher readmission rate in E.R.A.S. programs when compared to traditional postoperative management is still crucial, but it must be stressed that, in our experience, over 70 % of readmissions (73.6 % for "Ultra" and 75 % for Classic E.R.A.S., not statistically significant) are usually late, after POD 5, not preventable by a longer hospital stay, but only with traditional care program based on late discharge (8th–9th POD). In our study, we had 5.6 % of readmission with "Ultra" and 5.9 % with traditional E.R.A.S., not reaching statistical significance, with uni- and multivariate analyses demonstrating that early discharge on POD 2 is independent in altering morbidity, reoperation and readmission rate (secondary end-points); interestingly, readmissions were mainly for Clavien–Dindo grade I and II complications, and rarely for grade III and IV, with a reoperation rate after discharge of only 3 cases (0.89 %) in "Ultra" E.R.A.S. (2 bowel obstructions and 1 anastomotic leakage; all managed laparoscopically) and 2 cases (0.59 %) in Classic E.R.A.S. (2 bowel obstructions; managed laparoscopically), without statistical significance.

With particularly regard to the anastomotic leakage occurring after discharge, we had only 1 readmission due to an anastomotic failure on POD 8, with an overall incidence of 0.29 % in the "Ultra" E.R.A.S. group: we are strongly convinced that this complication is a pathophysiologically "precocious" adverse event which usually takes place within the first 48 h; events which occur later are usually related not to a *"late failure"* but to a late diagnosis; in our experience, in fact, all patients with leakage had a troublesome postoperative progress from the 1st POD, characterized by suggestive clinical signs and symptoms (no passage of flatus, fever, abdominal tenderness, increased or increasing WBC), confirmed by a prompt abdominal CT

scan with endo-luminal contrast media and immediately managed.

Both in "Ultra" and in Classic E.R.A.S., no readmission was connected to acute, severe, life-threatening condition (peritonitis with severe sepsis or septic shock, intestinal obstruction with hemodynamic instability, severe respiratory distress, APACHE score >8).

Collectively, our data suggests that "Ultra" E.R.A.S. is as equally safe and effective as Classic E.R.A.S.: no statistical difference was recorded in terms of mortality (primary end-point), complications, reoperation and readmission rates (secondary end-points). Considering nosocomial infections, responsible for morbi-mortality and enhanced costs for medical care systems, earlier discharge becomes essential, especially in elderly people, reducing the risk of infective complications and optimizing short-term outcomes and costs: particularly, the total cost of hospitalization (we calculated summing up the costs of the operatory room per hour, the energy devices and the number of staplers used for each operation, the hospital staying per day and the cost of intensive care unit per day when needed) is quantifiable in 8.595€ per patient in the "Ultra" E.R.A.S. group versus 12.295€ in the Classic E.R.A.S. group, a difference reaching statistical significance ($p < 0.05$), as shown in Table 5; this outcome stresses the benefit of "Ultra" E.R.A.S. regimen in reducing costs, maximizing the economical management of laparoscopic colectomy. This aspect, especially in this historical period of global economical crisis which unavoidably involves also the national health systems, is another important argument favoring a more efficacious exploitation of E.R.A.S regimens, particularly in terms of more proper timing of discharging patients, avoiding unjustifiable infectious risks of the patients and disproportionate costs for the community.

We are strongly convinced that laparoscopic colectomy for cancer is a real revolution only when "embedded" into an E.R.A.S. program aimed to minimize surgical stress, with the ultimate goal of a "stress-free, pain-free and risk-free" surgery [26]. We demonstrated that precocious discharge on POD 2, so long as the patient has passed the first flatus (herald sign) and in the absence of signs of possible complications, is feasible, safe and absolutely effective.

In addition, we trust in "totally" minimally invasive surgery: in right hemicolectomy, the anastomosis should be intra-corporeal, in fact, even in the lack of evidence, extra-corporeal anastomoses inevitably stretch the mesocolon, and may determine a delay in recovery of peristalsis, with obvious hindrance to any enhanced recovery program; similarly, intra-corporeal section of the left mesocolon reduces traction on the mesocolon itself when the proximal colon is externalized through the mini-Pfannenstiel to insert the anvil. These technical details are crucial, optimizing both recovery and outcome, and should be methodically pursued. In addition, we like to stress the importance of strict selection criteria in laparoscopic indications and methodical step-by-step procedures, involving not only the surgical but also the anesthesiological team, for high-level multidisciplinary management of colonic cancer.

Yet, our study, even if randomized with stratification and sufficiently powered to minimize type I error, has at least three significant limits: (1) it is a single-center experience over a long period of time; (2) it is not double-blind, with the intrinsic risk of intentional or unconscious bias; (3) exclusion criteria because of "non-compliance" may be considered arbitrary and interfere with the effectiveness estimation, even if symptoms actually or potentially related to complications make patients not amendable for any early discharge (neither on POD 2, nor on POD 4), and thus beyond the aim of the study (in fact we do not recommend any kind of precocious discharge if the risk of potential complications is feared).

In conclusion, our prospective randomized trial showed that "Ultra" E.R.A.S. is safe, actual and economically effective: discharge on POD 2 after the first flatus passage and in the absence of complication-related symptoms should be actively considered in a modern, multidisciplinary, multimodal laparoscopic management of colonic cancer, aimed to maximize both short- and long-term clinical and economical outcomes.

Authors contribution Dr. Gianluca Garulli and Dr. Luca Maria Siani contributed to concept and study design; acquisition of data; analysis and interpretation; drafting the article and critical revision; final approval of the version to be published. Dr. Andrea Lucchi contributed to acquisition of data; analysis and interpretation; drafting the article and critical revision; final approval of the version to be published. Dr. Pierluigi Berti and Carlo Gabbianelli helped with acquisition of data; analysis and interpretation; drafting the article and critical revision; final approval of the version to be published.

Compliance with ethical standard

Disclosures The authors Gianluca Garulli, Andrea Lucchi, Pierluigi Berti, Carlo Gabbianelli and Luca Maria Siani declare no conflict of interest or any financial support to disclose.

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