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Implementation of an enhanced recovery after surgery protocol for colorectal cancer in a regional hospital network supported by audit and feedback: a stepped wedge, cluster randomised trial

Eva Pagano ,[1] Luca Pellegrino,[2] Manuela Robella,[2] Anna Castiglione,[1] Francesco Brunetti,[1] Lisa Giacometti ,[1] Monica Rolfo,[3] Alessio Rizzo,[4] Sarah Palmisano,[5] Maurizio Meineri,[5] Ilaria Bachini,[6] Mario Morino,[7] Marco Ettore Allaix,[7] Alfredo Mellano,[2] Paolo Massucco,[4] Paola Bellomo,[8] Roberto Polastri,[9] Giovannino Ciccone,[1] Felice Borghi,[2] ERAS-colorectal Piemonte group

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For numbered affiliations see end of article.

Correspondence to
Dr Eva Pagano, Unit of Clinical Epidemiology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino 10126, Italy; eva.pagano@cpo.it

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ABSTRACT

Background Enhanced recovery after surgery (ERAS) protocols are known to potentially improve the management and outcomes of patients undergoing colorectal surgery, with limited evidence of their implementation in hospital networks and in a large population. We aimed to assess the impact of the implementation of an ERAS protocol in colorectal cancer surgery in the entire region of Piemonte, Italy, supported by an audit and feedback (A&F) intervention.

Methods A large, stepped wedge, cluster randomised trial enrolled patients scheduled for elective surgery at 29 general surgery units (clusters). At baseline (first 3 months), standard care was continued in all units. Thereafter, four groups of clusters began to adopt the ERAS protocol successively. By the end of the study, each cluster had a period in which standard care was maintained (control) and a period in which the protocol was applied (experimental). ERAS implementation was supported by initial training and A&F initiatives. The primary endpoint was length of stay (LOS) without outliers (>94th percentile), and the secondary endpoints were outliers for LOS, postoperative medical and surgical complications, quality of recovery and compliance with ERAS items.

Results Of 2626 randomised patients, 2397 were included in the LOS analysis (1060 in the control period and 1337 in the experimental period). The mean LOS without outliers was 8.5 days during the control period (SD 3.9) and 7.5 (SD 3.5) during the experimental one. The adjusted difference between the two periods was a reduction of −0.58 days (95% CI −1.07, −0.09; p=0.021). The compliance with ERAS items increased from 52.4% to 67.3% (estimated absolute difference +13%; 95% CI 11.4%, 14.7%). No difference in the occurrence of complications was evidenced (OR 1.22; 95% CI 0.89, 1.68).

Conclusion Implementation of the ERAS protocol for colorectal cancer, supported by A&F approach, led to a substantial improvement in compliance and a reduction in LOS, without meaningful effects on complications.

Trial registration number NCT04037787.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Enhanced recovery after surgery (ERAS) protocols are expected to improve the management and outcomes of colorectal surgery patients, but the effectiveness of their implementation, supported by an audit and feedback (A&F) strategy, in a large regional hospital network remains unproven.

⇒ A&F strategies were proven to be effective in improving quality of care and are considered a key component of the ERAS protocols.

INTRODUCTION

Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care pathways developed for several surgical procedures to achieve early recovery after surgery by preserving preoperative organ function and reducing physical stress responses. The key elements of the ERAS protocols include preoperative counselling and nutritional

WHAT THIS STUDY ADDS

⇒ A regional implementation of the ERAS protocol in elective colorectal cancer surgery with the support of an A&F strategy markedly increased the compliance with most items and slightly reduced the length of stay, without meaningful effects on complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The A&F approach can be employed as an effective strategy to engage clinicians and centres and may overcome resistance to the cultural and organisational changes required by the ERAS implementation.

assessment, avoidance of preoperative fasting and bowel preparation, standardised opioid-sparing analgesic and anaesthetic regimens, and early refeeding and mobilisation. Such multimodal stress-minimising approach has been shown to reduce the rates of morbidity, improve recovery and shorten length of stay (LOS) after major colorectal surgery.[1] Despite the strong background theory and the available evidence supporting the potential improvements in colorectal cancer surgery,[1–4] the ERAS protocols still pose a challenge to traditional surgical doctrine.

After the fourth updated version of the ERAS protocol in colorectal cancer,[1] only three selected hospitals, particularly open to change, have adopted this approach in routine care in Piemonte, an Italian region of around 4.2 million inhabitants.[5] The Piemonte region has a large network of medium-small public-funded hospitals treating colorectal cancer, referring to the Piemonte e Valle d'Aosta Cancer Network (http://www.reteoncologica.it/). Initiatives to improve the quality of cancer care within the network were mainly based on the adaptation and implementation of regional clinical guidelines (https://next.cpo.it/it/publications) and their monitoring with administrative data.[6] The slow, spontaneous diffusion of the ERAS protocol within the hospital network has had a limited impact on the overall quality of perioperative care at the regional level and may have increased heterogeneity between centres and inequalities between patients. In addition to the usual barriers to implementing new organisational models, the limited evidence from properly designed randomised trials[2 7 8] and the lack of structured local audit and feedback (A&F) strategies may have limited the dissemination of the ERAS protocol.[9]

The ERAS Protocol Implementation in Piemonte Region for Colorectal Cancer Surgery (ERAS Colon-Rectum Piemonte study)[10] was conducted to promote a systematic adoption of the protocol throughout the entire regional hospital network, with the goal of enhancing quality of care through an equitable and pragmatic approach. The study, registered with ClinicalTrials.gov (NCT04037787), is part of a larger project that evaluates the effectiveness of A&F interventions in different settings and health services (EASY-NET), a network project funded by the Italian Ministry of Health and the participating regions.

The aim of this study was to assess the impact of introducing an ERAS protocol, supported by an A&F intervention,[11] on LOS and other clinical outcomes in a large population undergoing elective surgery for colorectal cancer, using a stepped wedge, cluster randomised trial (SW-RCT) design[12] and involving the entire hospital regional network.

METHODS

The article was written according to the Consolidated Standards of Reporting Trials (CONSORT) statement for SW-CRT[13–15] and the Reporting on ERAS Compliance, Outcomes and Elements Research (RECOvER) checklist[16] (online supplemental annex). The study protocol has been previously published.[10]

Design and participants

The ERAS Colon-Rectum Piemonte study is a pragmatic SW-RCT conducted among patients with colorectal cancer at 29 general surgery departments located in public hospitals in the Piemonte region.

Given all the available evidence on the ERAS protocol, with a favourable balance of benefits and risks (for both patients and staff), the SW-CRT was considered an appropriate design to allow sufficient time for training all the regional hospital teams, to send them periodic feedback while the study was ongoing and to achieve roll-out of ERAS across the entire hospital network at the end of the trial.[12]

All regional general surgery units that performed at least 30 elective surgical procedures for colorectal cancer in 2018 were invited to participate. The surgical units formed the study clusters, which sequentially adopted the ERAS protocol, by group of units.

All consecutive patients with colorectal cancer scheduled for elective surgery between 1 September 2019 and 31 May 2021 were included, with very few exclusions (eg, emergency admissions and patients with an American Society of Anesthesiologists (ASA) score of 5). All participants provided written informed consent and data were collected by the hospital staff on paper case report forms.

The recruitment period, originally set at 15 months, was later extended to 21 months to compensate for the negative impact of the COVID-19 pandemic on hospital activity. The third step was completed in August 2021 instead of May 2021 to allow for more time to organise the web-based training (previously scheduled in person) and to ask centres to start implementing ERAS during a remission of the COVID-19 pandemic in September 2021. The last step was extended due to concerns that the COVID-19 pandemic would be a

barrier to the centres' ability to change clinical practice and improve quality of care.

During the first 3 months of the study (baseline), standard treatment was continued in all groups. Thereafter, the four groups started adopting the ERAS protocol every 3 months, until all groups had a 'control' period of standard treatment and an 'experimental' period of application of the ERAS protocol, as described in online supplemental figure S1.

Randomisation

Surgical units were stratified by volume of colorectal procedures performed in 2018 and then randomly divided into four groups with a similar number of procedures. The randomisation procedure was carried out by the clinical epidemiology unit after the surgical units had been anonymised. The allocation was concealed to centres until 2 months before the start of the experimental period to allow sufficient lead time to train the local ERAS team and organise the trial activities.

Due to the nature of the intervention, it was not possible to blind participants, carers and researchers to group allocation.

Procedure

Each centre identified an 'ERAS team', including at least a surgeon, an anaesthetist, a nurse and a dietitian, to support local implementation of the protocol and to serve as a reference for data collection. These local teams received a 1-day interactive course on the principles of ERAS as well as organisational aspects and practical experience. All four editions of the training were delivered by a team of experts with consolidated experience in teaching and working with the ERAS protocol, with the last two editions delivered online due to COVID-19 restrictions.

The ERAS protocol to be implemented at the regional level was adapted from the ERAS Society guidelines for colorectal surgery.[1 17] The ERAS items are described in online supplemental table S1, together with related indicators and discharge criteria.

A newsletter was sent to all local ERAS teams every 2 months to maintain commitment and motivation for the overall project and to share information on the progress of the study. To monitor the completeness of study enrolment at each centre, a graph was constantly updated on the study website comparing the number of patients actually enrolled with the expected number in the same calendar period of the previous year. According to the A&F intervention, once the experimental period had started, the hospital teams were given access to a feedback section of the study website to assess their progress in implementing the protocol, so that critical issues could be immediately identified and corrective actions addressed. The feedback indicators were also discussed with each group of centres in meetings, mostly online, a few months after the introduction of ERAS, together with the experts previously involved in the training and the study coordination/data management team.

Details on the intervention are reported in the Template for Intervention Description and Replication checklist[18] in the online supplemental materials.

Outcomes

The primary endpoint was LOS, which was calculated after excluding outliers (LOS >94th percentile).

The secondary endpoints were the percentages of LOS outliers; of postoperative complications, defined according to the Clavien-Dindo classification[19]; and of admissions to the intensive care unit, transfusions and reinterventions during the postoperative hospital stay. Other clinical outcomes assessed within 30 days of discharge were any readmission to the emergency department (ED), readmission to hospital and reintervention.

Postoperative complications were analysed as the presence of at least one complication, total and major complications (Clavien-Dindo III–IV) or death. All the outcomes before discharge were collected with the case report form. Outcomes at 30 days after discharge were collected from regional administrative data.

The quality of postoperative recovery was measured with the validated Italian version of the Quality of Recovery-15 (QoR-15) questionnaire,[20 21] filled in by patients approximately 48 hours after surgery. The QoR-15 is an instrument based on 15 items with a scale of 0–10 and a Visual Analogue Scale (VAS) for well-being, where 0 indicates the worst health status and 10 the best. Other secondary outcomes, including patients' and professionals' interviews, and an analysis of healthcare costs will be presented in another article.

Difference in compliance with ERAS items between the two study periods was measured overall, by phase of care and by single items.

Statistical analysis

Considering available literature and local data, the study was planned with a statistical power of 0.98 and with an alpha error of 0.05 (two-sided) to detect a reduction of 1 day of mean LOS without outliers (from 9.0 to 8.0, SD=3.7). Details on the sample size calculation were extensively reported in the study protocol publication[10] and are summarised in the online supplemental materials.

Compliance with ERAS

Compliance with ERAS items during the two study periods was measured as the mean percentage of adherence with a list of indicators (online supplemental table S1), overall and for groups of items classified by phase of care (preoperative, intraoperative and postoperative). Multilevel linear models were used to estimate the difference in average compliance levels between the two study periods, overall and by

phase of care, adjusting for patient characteristics and time period, and considering surgical units as random effects. Patient covariates included in the models were sex, age, Charlson Comorbidity Index (0 or 1), body mass index (BMI) class (<18.5, 18.5–24.9, 25–29.9, ≥30) and ASA score (1–2 or 3–4). The same set of covariates was used for adjusting Poisson models used to estimate the difference in compliance between the two study periods for each individual ERAS indicator (dichotomous).

Primary endpoint

LOS without outliers was described as median, mean and SD. The difference between the two study periods was estimated using a multilevel linear model adjusted for patient characteristics and time period and accounting for surgical units as random effects. In addition to the covariates included in the analysis of compliance, the cancer site (colon, rectum), the creation of a stoma and the type of surgical access, classified as open or minimally invasive (laparoscopic or robot-assisted), were also included.

Secondary endpoints

The percentages of outliers for LOS, postoperative complications (total, surgical and medical), incidence of transfusions, access to ICU after surgery, 30-day mortality after surgery, and ED admissions, readmissions and reinterventions were all analysed as dichotomous variables using random-effects logistic regression models, with the same set of covariates included in the model for the LOS analysis, except for BMI, cancer site and ASA score.

For the QoR assessment, only questionnaires with all 15 items completed within 1–4 days after surgery were included. The mean total scores and the mean scores for the physical and psychological subscales were reported. The effect of ERAS on the QoR scales and well-being VAS was estimated using multilevel linear models, with centres serving as random effects and adjusting for the same set of covariates used for the other secondary outcomes.

Subgroup and sensitivity analyses

For the primary endpoint, planned subgroup analyses were conducted by patient characteristics (sex, age, education, tumour location, Charlson Comorbidity Index, ASA score, surgical approach) and by centre characteristics (level of compliance with the ERAS protocol during the control period, increase in compliance with the ERAS protocol after its adoption, completeness of enrolment, volume of interventions). Enrolment completeness was assessed using the regional hospital discharge record database. To assess the achievement curve, we also analysed the change in LOS according to the time (in quarters) elapsed since the introduction of ERAS.

To account for the learning phase in each centre, the impact of the intervention on LOS was also analysed excluding the first month of each implementation period of the ERAS protocol.

Subgroup analyses were also conducted for compliance, using the same analytical approach as for LOS, to identify facilitators and barriers to the intervention. Finally, the association between the level of compliance with the ERAS protocol (10% increase) and the clinical outcomes was analysed, overall and by study period. To control for a possible reverse-causation effect between compliance with the protocol (especially for postoperative items) and patient-level outcomes, LOS was analysed with centre mean compliance with the protocol as a fixed effect.

Statistical analyses were performed using SAS V.9.4.

RESULTS

Of the 36 public general surgery facilities treating patients with colorectal cancer in the Piemonte region in 2018, 3 were excluded because they had already implemented the ERAS protocol, 3 because they had a low case load and 1 declined to participate. Six centres had a case load slightly below 30 cases in 2018, but they asked to be included in light of an expected increase in activity during the study period. The final number of participating centres was therefore 29.

As described in the flow chart of the study (figure 1), 2626 patients were included (a more detailed flow chart can be found in online supplemental figure S2).

The personal and clinical characteristics of the participants are shown in table 1. Overall, the mean age was 72 years (SD 10.9), 43% were women, about 70% of cases had colon cancer and 50% had a Charlson Comorbidity Index ≥1. No evident unbalances were observed between the two study periods.

Table 2 shows the impact of the implementation of ERAS on the outcomes of the study.

Primary endpoint

The mean LOS without outliers (defined as LOS >20 days, corresponding to the 94th percentile of the LOS distribution) was 8.5 days during the control period (SD 3.9) and 7.5 (3.5) during the experimental period, with a raw reduction of 1 day (table 2). After excluding six patients with missing data on the covariates, the estimated adjusted difference between the two periods was a reduction of −0.58 days (95% CI −1.07, −0.09; p=0.021).

The planned subgroup analyses, depicted in figure 2, revealed only moderate differences in LOS reduction by patients' and centres' characteristics. A tendency towards larger effects on LOS reduction was observed in centres that had a lower compliance with ERAS at baseline (−0.78 days; 95% CI −1.31, −0.26; p value for interaction=0.056) and in centres with ≥80% completeness of enrolment (−0.68 days; 95% CI −1.18, −0.18; p value for interaction=0.058).

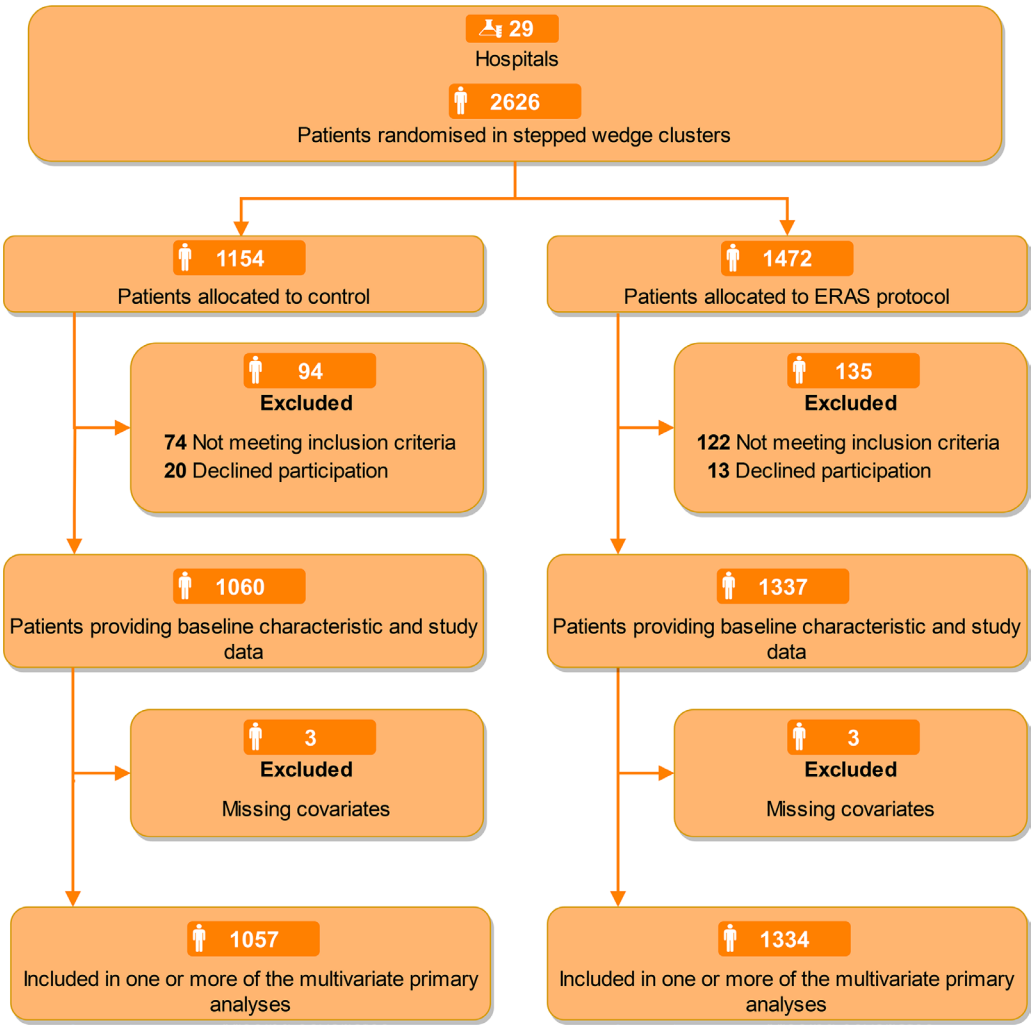

Figure 1 ERAS Colon-Rectum Piemonte study flow. ERAS, enhanced recovery after surgery.

For minimally invasive surgery, where the initial LOS was already at the target level of 8 days, the adoption of ERAS had a smaller impact on LOS (−0.49 days; 95% CI −1.00, 0.02), while for open surgery, with an initial LOS of 10 days, the reduction was more pronounced (−1.03 days; 95% CI −1.83, −0.22; p value for interaction=0.162).

Online supplemental figure S3 describes the change in LOS according to time elapsed since the introduction of ERAS (in quarters), showing a stable effect over time.

After excluding data collected in the first month of the roll-out period of the ERAS protocol, the results did not change (LOS reduction −0.61; 95% CI −1.15, −0.07).

Secondary endpoints

No differences were observed in the frequency of outliers in LOS, complications, need for transfusion, access to intensive care in the postoperative period and in-hospital mortality (table 2).

The incidence of postoperative complications is described in online supplemental table S2 by study period. The occurrence of complications did not differ either overall (OR 1.22; 95% CI 0.89, 1.68; p=0.211) or by type (surgical, medical) or severity (Clavien-Dindo I–II, III–IV).

Outcomes at 30 days after discharge did not differ between the two study periods.

Patients included in the QoR (1762, 73.5%) and VAS (1850, 77.2%) analyses are described in online supplemental figure S4. The mean QoR score was 7.12 and 7.46 in the control and ERAS periods, with a small improvement of 0.24 points (95% CI 0.01, 0.47; p=0.039). This improvement was mainly due to a difference in the physical scale. There was also a small improvement between the two study periods in the VAS score for general well-being (0.31; 95% CI 0.05, 0.57; p=0.021).

Compliance with ERAS protocol

Overall, the level of compliance with the ERAS protocol changed from 52.4% during the control period to 67.3% during the experimental period, with an adjusted absolute difference of +13% (95% CI 11.4%, 14.7%; p=0.0001) (table 3A). Compliance

Table 1 Personal and clinical characteristics of the participants

	Control period (n=1060)		ERAS period (n=1337)		Total (N=2397)	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**
Sex						
Male	603	56.9	762	57.0	1365	56.9
Female	457	43.1	575	43.0	1032	43.1
Age classes						
<70	414	39.1	504	37.7	918	38.3
70–79	317	29.9	431	32.2	748	31.2
≥80	329	31.0	402	30.1	731	30.5
Education						
Low	303	28.6	386	28.9	689	28.7
Medium	369	34.8	440	32.9	809	33.8
High	282	26.6	407	30.4	689	28.7
Missing	106	10.0	104	7.8	210	8.8
Marital status						
Not married	301	28.4	387	28.9	688	28.7
Married	712	67.2	884	66.1	1596	66.6
Missing	47	4.4	66	4.9	113	4.7
Charlson Comorbidity Index						
0	526	49.6	671	50.2	1197	49.9
≥1	533	50.3	665	49.7	1198	50.0
Missing	1	0.1	1	0.1	2	0.1
ASA class						
1–2	607	57.3	740	55.3	1347	56.2
3–4	452	42.6	595	44.5	1047	43.7
Missing	1	0.1	2	0.1	3	0.1
BMI class						
<18.5	40	3.8	36	2.7	76	3.2
18.5–24.9	509	48.0	542	40.5	1051	43.8
25–29.9	365	34.4	534	39.9	899	37.5
≥30	144	13.6	224	16.8	368	15.4
Missing	2	0.2	1	0.1	3	0.1
Cancer location						
Colon	743	70.1	949	71.0	1692	70.6
Rectum	317	29.9	388	29.0	705	29.4
Neoadjuvant therapy						
Not executed	906	85.5	1103	82.5	2009	83.8
Executed	153	14.4	233	17.4	386	16.1
Missing	1	0.1	1	0.1	2	0.1
Type of procedure						
Right colectomy	420	39.6	510	38.1	930	38.8
Left colectomy	182	17.2	254	19.0	436	18.2
Transverse colectomy	38	3.6	73	5.5	111	4.6
Partial mesorectal excision	104	9.8	91	6.8	195	8.1
Total mesorectal excision	175	16.5	242	18.1	417	17.4
Miles' resection	52	4.9	65	4.9	117	4.9
Others	89	8.4	99	7.4	188	7.8
Missing	–	–	3	0.2	3	0.1
Stoma						
Absent	806	76.0	1010	75.5	1816	75.8
Present	251	23.7	326	24.4	577	24.1
Missing	3	0.3	1	0.1	4	0.2
Type of surgery						
Laparotomy	741	69.9	906	67.8	1647	68.7

Continued

Table 1 Continued

Characteristics	Control period (n=1060)		ERAS period (n=1337)		Total (N=2397)	
	n	%	n	%	n	%
Laparoscopy	222	20.9	237	17.7	459	19.1
Robotic	96	9.1	193	14.4	289	12.1
Missing	1	0.1	1	0.1	2	0.1

ASA, American Society of Anesthesiologists; BMI, body mass index; ERAS, enhanced recovery after surgery.

was lowest for postoperative items (35.4% and 52.5% in the control and experimental periods). The largest absolute difference between the two periods was recorded for preoperative items (+18.2%; 95% CI 16.5%, 20.0%; p=0.0001). Intraoperative items also appeared to be frequently used during the control period (67.8%) and showed a small increase in compliance (+5.4%; 95% CI 2.4%, 8.3%; p<0.001). Table 3B shows the adjusted implementation effect (risk ratio) on compliance for each individual ERAS indicator, grouped by phase of care. Online supplemental figure S5 describes the change in compliance according to the time elapsed since the introduction of ERAS (in quarters). Compared with the baseline period, the increase in compliance was larger in the first two quarters after starting the experimental period (around 11%) but remained stable afterwards (around 8.5% in all the following quarters). The results of the subgroup analyses are shown in online supplemental figure S6. Patients' characteristics did not impact the change in ERAS compliance, but low compliance with the ERAS items prior to initiation of the study, high completeness of patient inclusion in the study and high volume of surgical activity were relevant facilitating factors.

Online supplemental table S3 shows the impact of compliance with ERAS items overall and stratified by study period on study outcomes. A 10% increase in overall compliance was associated with a reduction in LOS (−0.65 days; 95% CI −0.76, −0.54) and in most clinical outcomes, with a stronger effect during the ERAS period, when an integrated implementation of all items was supported by the A&F approach. After adjustment for mean centre-level compliance,

Table 2 Effect of ERAS implementation on study outcomes

Study outcomes	Control period (n=1060)		ERAS period (n=1337)		Effect measure		
Primary endpoint	**n**	**Mean (median; SD)**	**n**	**Mean (median; SD)**	**Mean difference**	**95% CI**	**P value**
LOS	979	8.55 (7; 3.87)	1264	7.5 (7; 3.49)	−0.58	−1.07, −0.09	0.021
Secondary endpoints	**n/total**	**%**	**n/total**	**%**	**OR**	**95% CI**	**P value**
LOS outliers	81/1060	7.64	73/1337	5.46	1.02	0.58, 1.80	0.944
Complications							
Total	285/1058	26.9	364/1336	27.2	1.22	0.88, 1.68	0.218
Medical	148/1058	14.0	182/1336	13.6	1.20	0.79, 1.84	0.380
Only minor medical	125/1058	11.8	133/1336	10.0	0.94	0.59, 1.49	0.770
Major medical	22/1058	2.1	44/1336	3.3	2.13	0.98, 4.62	0.055
Surgical	194/1058	18.3	257/1336	19.2	1.32	0.94, 1.85	0.109
Only minor surgical	112/1058	10.6	151/1336	11.3	1.43	0.94, 2.19	0.093
Major surgical	84/1058	7.9	108/1336	8.1	1.12	0.68, 1.85	0.636
Transfusions	107/1058	10.1	120/1336	9.0	0.71	0.45, 1.12	0.136
ICU access	144/1058	13.6	191/1336	14.3	0.97	0.61, 1.54	0.906
Inpatient mortality	16/1060	1.51	21/1337	1.57	1.63	0.61, 4.38	0.316
30-day ED admissions	61/1044	5.84	76/1316	5.78	1.51	0.88, 2.60	0.131
30-day hospital readmissions	98/1044	9.39	105/1316	7.98	1.16	0.74, 1.81	0.511
30-day reinterventions	78/1044	7.47	95/1316	7.22	1.47	0.89, 2.44	0.131
	n	**Mean (median; SD)**	**n**	**Mean (median; SD)**	**Mean difference**	**95% CI**	**P value**
Mean QoR score	760	7.12 (7.2; 1.52)	1002	7.46 (7.6; 1.37)	0.24	0.01, 0.47	0.039
Mean QoR score - physical scale	760	7.14 (7.3; 1.64)	1002	7.56 (7.80; 1.50)	0.33	0.08, 0.57	0.011
Mean QoR score - mental scale	760	7.08 (7.60; 2.00)	1002	7.26 (7.80; 1.97)	0.08	−0.24, 0.40	0.622
Well-being Visual Analogue Scale score	813	6.72 (7; 1.72)	1037	7.14 (7; 1.6)	0.31	0.05, 0.57	0.021

ED, emergency department; ERAS, enhanced recovery after surgery; ICU, intensive care unit; LOS, length of stay; QoR, Quality of Recovery.

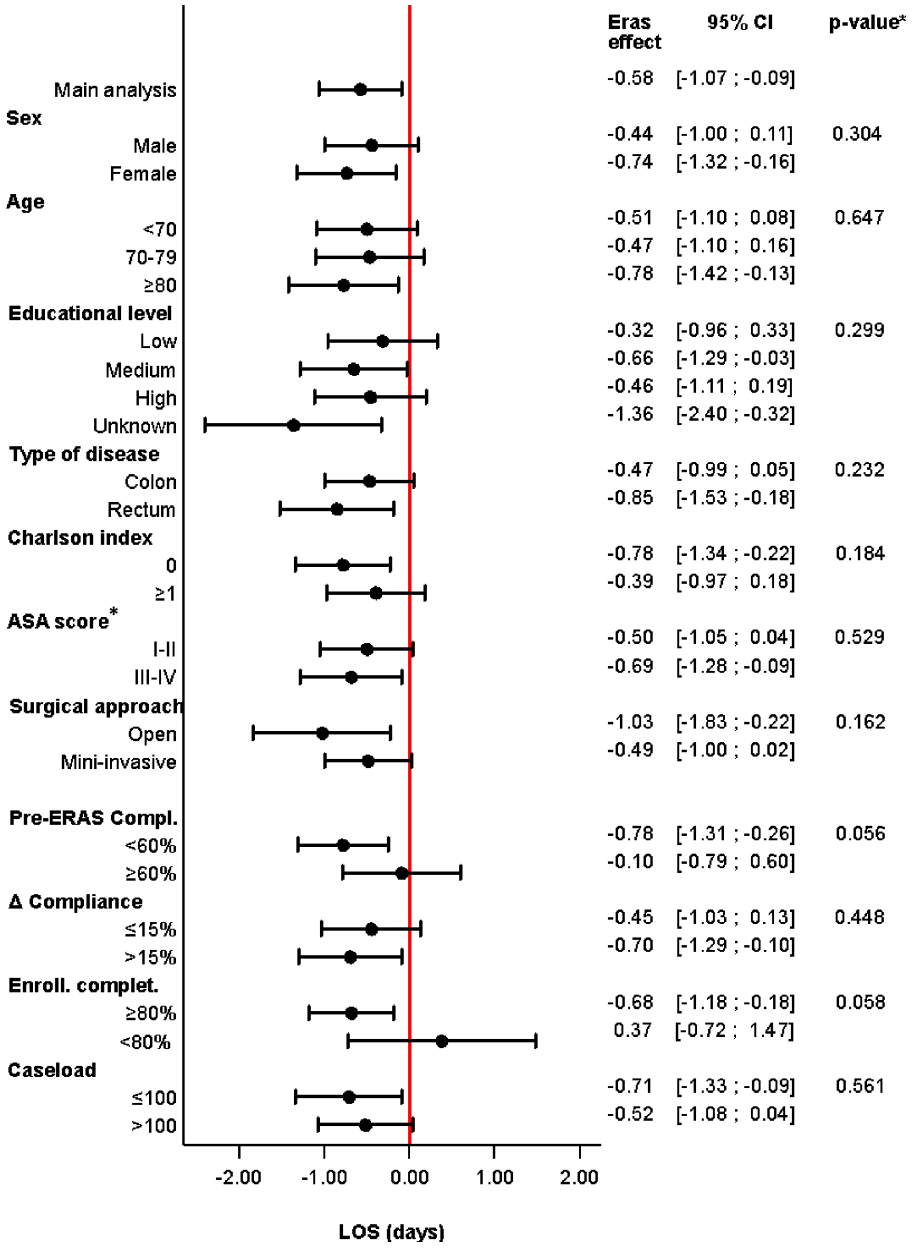

Figure 2 Estimated difference in LOS (primary outcome) between the two study periods and related subgroups analyses: patients' and structure characteristics. ASA, American Society of Anesthesiologists; ERAS, enhanced recovery after surgery; LOS, length of stay.

*** Interaction p value.**

the estimated LOS reduction was −0.30 days (95% CI −0.50, −0.10) (data not shown).

DISCUSSION

Key findings

In this large, pragmatic SW-RCT of patients surgically treated for colorectal cancer, implementation of the ERAS protocol supported by an A&F intervention across the network of regional hospitals in Piemonte reduced the mean LOS by 0.6 days during the experimental period compared with the control period. The subgroup analyses showed greater improvements in hospitals where the opportunity to improve compliance with the ERAS protocol was greater. The application of the ERAS programme did not lead to any meaningful impact on postoperative complications, either during hospitalisation or 30 days after discharge.

The A&F initiative supporting ERAS implementation determined a relevant change in clinical practice, with an absolute increase in compliance with the ERAS protocol of around 13%, an impact much larger than the average effect (median 4.3% improvement) estimated by a previous systematic review.[22]

Comparison with existing literature

The decrease in LOS observed in our study is consistent with, but smaller than, that estimated by a

Table 3 Compliance with ERAS items in the two study periods and the adjusted effect: (A) difference in compliance (%) overall and by phase of care and (B) risk ratio on compliance for each single ERAS indicator

(A) Overall and by phase of care	Control period (%)	ERAS period (%)	Delta % compliance	95% CI	P value
All items	52.4	67.3	13.04	11.42, 14.66	<0.0001
Preoperative items	61.2	80.5	18.21	16.46, 19.96	<0.0001
Intraoperative items	67.8	70.7	5.35	2.38, 8.31	0.001
Postoperative items and follow-up	35.4	52.5	12.18	9.49, 14.87	<0.0001
(B) Single indicators	**Control period (%)**	**ERAS period (%)**	**Risk ratio**	**95% CI**	**P value**
Preoperative items					
Anaesthesiological visit time	32.4	29.4	0.84	0.60, 1.19	0.332
Preadmission counselling	32.7	85.6	2.89	1.43, 5.83	0.003
Nutritional risk assessment	41.0	91.0	2.30	1.32, 4.01	0.003
Anaemia correction	41.0	43.6	0.94	0.62, 1.41	0.757
No bowel preparation - colon	88.8	90.2	1.03	0.90, 1.17	0.707
No premedication	96.9	97.1	0.98	0.93, 1.04	0.532
Thromboembolism prophylaxis	90.9	95.4	1.11	0.94, 1.30	0.219
Antibiotics prophylaxis	80.6	76.5	0.98	0.85, 1.12	0.763
No prolonged fasting	74.6	89.2	1.23	0.89, 1.71	0.209
Carbohydrate loading	30.2	87.1	2.89	1.45, 5.75	0.003
Intraoperative items					
Mini-invasive surgery	69.3	72.9	1.04	0.89, 1.22	0.629
No surgical drainage - colon	42.8	49.4	1.25	0.91, 1.72	0.176
Epidural anaesthesia in laparotomy	42.8	44.3	1.08	0.71, 1.65	0.702
Prevention of hypothermia	72.8	72.3	0.94	0.72, 1.23	0.677
Fluid normovolaemia intraoperatively	55.1	60.2	1.02	0.74, 1.42	0.882
Postoperative nausea and vomiting prevention	90.2	91.8	0.97	0.89, 1.06	0.544
Postoperative items					
Fluid normovolaemia postoperatively	58.0	77.3	1.38	0.92, 2.07	0.121
Early removal of intravenous therapy	21.2	39.5	1.91	0.85, 4.30	0.116
Early rehydration	22.5	41.9	1.90	0.84, 4.28	0.122
Early refeeding	21.5	42.8	2.11	0.99, 4.50	0.054
No nasogastric tubes	59.6	75.5	1.44	1.00, 2.08	0.053
Early removal of urinary catheter	43.1	55.3	1.34	1.05, 1.71	0.020
Early mobilisation - day 1 media	14.1	22.5	2.43	1.44, 4.12	0.001
Minimised opioid use	55.1	75.9	1.42	1.00, 2.02	0.051
Early follow-up	26.8	47.3	2.12	1.38, 3.25	0.001

ERAS, enhanced recovery after surgery.

meta-analysis of randomised controlled trials for elective colorectal surgery, reporting a mean LOS of 5.8 and 8 days in the ERAS and control groups, respectively.[2] Similar effects on LOS were reported by meta-analyses of randomised trials including colorectal surgery and other types of interventions.[3 4] A reduction in median LOS associated with the adoption of the ERAS programme in colorectal cancer surgery was also reported by cohort studies conducted within hospital networks,[23 24] despite a reduced impact when the results were adjusted for the background time trend reduction of LOS.[25] Analyses of data from the international multicentre ERAS registry for elective colorectal cancer resection reported a median overall LOS of 6 days (IQR 4–8).[26]

The absence of a meaningful impact of our study on postoperative complications is in contrast to previous experiences,[2–4] but in line with some recent systematic reviews of randomised controlled trials assessing specific ERAS items, as prehabilitation[27] and early mobilisation interventions.[28]

According to a Cochrane systematic review of the efficacy of A&F[22] in modifying healthcare behaviours, the global change in compliance observed in the present study can be considered a relevant result. Specific comparisons with previous experiences of ERAS implementation are not easy because it is not clear whether and how explicit A&F interventions were adopted.[9] Consistent with the findings of Nelson *et al*,[29] the greatest increase in compliance was for preoperative items (+18.2%), which included practices not commonly found outside ERAS, such as counselling, nutritional risk assessment and introduction of a carbohydrate load.

Interpretation

Although the adjusted effect on LOS in our study (−0.6 days) was smaller than planned in the study protocol (−1 day, from 9 to 8), it should be noted that the mean LOS in the baseline period of the study was already reduced to 8.5 days, which left little room for further improvement. The reduction in LOS from 2018 to the end of 2019 may be partly the result of a long-term trend and partly an indirect effect of the centres' involvement in writing the study protocol.

The decrease in LOS was achieved in the first period of implementation of the ERAS protocol, that is, up to 6 months, and thereafter LOS remained stable. This result seems to contradict the notion of a learning curve.[30 31] However, a major influence on this result is probably the COVID-19 pandemic, which affected the organisation of the hospital and the implementation of the study. In the fourth quarter of the implementation of ERAS, corresponding to the peak of the pandemic in the Piemonte region (March–May and October–December 2020), no decrease in LOS was observed compared with baseline, likely due to organisational stress for COVID-19 management.

In general, the COVID-19 pandemic had a strong impact on the study's ability to change clinical practice and improve the quality of care. As reported by the healthcare staff in the feedback meetings, it affected the full implementation of the ERAS protocol and weakened the adoption of the A&F approach in several ways. ERAS implementation requires close collaboration between different health professionals,[1] with nurses and anaesthetists playing a key role, both of whom were heavily involved in pandemic management. In addition, ERAS benefits from strong patient[32 33] and caregiver[34] involvement, which was drastically reduced by social distancing measures. Similarly, A&F requires discussion of results in meetings with all stakeholders, but due to the pandemic, only one meeting was held per group of centres, and for two groups only via web conference. To limit the negative impact of COVID-19, the study duration was extended by three additional months in both the third and fifth steps. As this extension affected the middle and last period of the study, the variation in the final study sample size and the imbalance between the two groups were negligible.

Strengths and weaknesses

The most original features of our study, which to our knowledge is the largest ERAS randomised trial to date, are the cluster randomisation design and its pragmatic approach, the implementation of the programme within the entire regional hospital network, and the high level of engagement and involvement of most eligible patients. Participating centres also included those usually excluded from research projects and unlikely to adopt the ERAS and A&F approach on their own. The research framework allowed a full adoption of ERAS across the entire regional network, reducing heterogeneity in patient care and consequently inequalities.

The subgroup analyses on compliance with ERAS items found that some centre characteristics resulted as facilitating factors. Other factors perceived as facilitators of such positive results were the substantial methodological and organisational support, the leading role of referral centres experienced in delivering ERAS and the presence of the PeriOperative Italian Society offering specific expertise. In addition, the intervention has benefited from the presence of a regional oncology network and the strong commitment of the regional healthcare authority.

Our study differs from most previous studies, mainly monocentric and with small sample sizes, in which individual patients were randomised within the same ward, with a high risk of bias. This is because implementing the ERAS protocol requires cultural and organisational changes that cannot be achieved with an 'on/off' intervention at the patient level. In addition, the stepped wedge design allowed us to account for time trend effects, a bias that typically occurs in studies comparing outcomes between pre-implementation and postimplementation periods.[25 29]

As the ERAS protocol circulated within the regional hospital network as part of the ERAS Colon-Rectum Piemonte study protocol, group contamination cannot be excluded. The groups waiting to implement ERAS may have anticipated some changes during the standard period, reducing the potential difference between the two periods in terms of adherence to ERAS items and impact on clinical outcomes. The suboptimal level of compliance achieved during the ERAS period (67%), at least in part attributable to the COVID-19 pandemic, may have compromised the ability to achieve relevant effects on secondary outcomes.

In our opinion, the A&F approach was useful in engaging clinicians and centres and in overcoming resistance to the cultural and organisational changes required by the ERAS implementation, but a formal analysis of the data collected by surveying local ERAS teams was not included in the present paper.

Because the study was conducted in a region with a public health system, the results may have limited generalisability to other countries with different health systems. A final issue is the recognition that it is difficult to monitor detailed quality of care measures after the study is completed using only currently available data.

CONCLUSIONS

A regional implementation programme supported by an A&F approach led to a successful adoption of the ERAS protocol for colorectal cancer surgery across an entire hospital network, with significant improvement in compliance and reduction in LOS. However, the overall suboptimal compliance achieved after the

introduction of the ERAS protocol may have precluded a significant impact on clinical outcomes and represents an area for further quality improvement. The A&F approach has been a useful and effective strategy for engaging clinicians and centres and overcoming resistance to cultural and organisational change required to implement the ERAS protocol for colorectal cancer surgery in the entire regional hospital network.

Author affiliations
[1]Unit of Clinical Epidemiology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[2]Surgical Oncology Department, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Torino, Italy
[3]Presidio Sanitario Gradenigo, Torino, Italy
[4]General Surgery and Oncology Unit, Azienda Ospedaliera Ordine Mauriziano di Torino, Torino, Italy
[5]Anaesthesia and Intensive Care Unit, S Croce and Carle Cuneo Hospital Districts, Cuneo, Italy
[6]Clinical Nutrition and Dietetics Department, Azienda Ospedaliera Ordine Mauriziano di Torino, Torino, Italy
[7]Digestive and Oncological Surgery, Center for Minimal Invasive Surgery, Department of Surgery, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[8]General Surgery, Presidio Sanitario Gradenigo, Torino, Italy
[9]Department of Surgery, General Surgery Unit, Hospital of Biella, Ponderano, Biella, Italy

Collaborators ERAS-colorectal Piemonte group: Site investigators: AO Alessandria: Tatiana Maan, Fabio Priora; AO Maggiore della Carità, Novara: Sergio Gentilli, Luca Portigliotti; AO Mauriziano, Torino: Marco Palisi, Paolo Massucco; AO S Croce e Carle, Cuneo: Luca Pellegrino, Felice Borghi; AO San Luigi Gonzaga, Orbassano (TO): Mario Solej, Maurizio De Giuli; Gradenigo - Humanitas, Torino: Paola Bellomo; IRCCS Candiolo (TO): Alfredo Mellano, Dario Ribero; Nuovo Ospedale degli Infermi, Biella: Roberto Polastri; Ospedale Civile Agnelli, Pinerolo (TO): Nicoletta Sveva Pipitone Federico, Andrea Muratore; Ospedale degli Infermi, Rivoli (TO): Mauro Garino; Ospedale Cardinal Massaia, Asti: Elisabetta Castagna; Ospedale Castelli, Verbania: Andrea Caneparo; Ospedale Civico, Chivasso (TO): Adriana Ginardi, Reggina Lagana; Ospedale Civile, Ciriè (TO): Monica Carrera; Ospedale Civile, Ivrea: Luca Panier Suffat; Ospedale Maggiore, Chieri (TO): Alberto Kiss, Marcello Cucinelli; Ospedale Martini, Torino: Donatella Scaglione, Roberto Saracco; Ospedale Regina Montis Regalis, Mondovì (CN): Andrea Gattolin, Roberto Rimonda; Ospedale S Biagio, Domodossola (VCO): Francesco Battafarano; Ospedale S Croce, Moncalieri (TO): Carlo Palenzona, Luca Lorenzin; Ospedale S Giacomo, Novi Ligure (AL): Carmine Gianfranco Di Somma, Eliana Giaminardi; Ospedale Ferrero, Verduno (CN): Marco Naddeo, Marco Calgaro; Ospedale S Lorenzo, Carmagnola (TO): Emma Marchigiano, Piero Cumbo; Ospedale S Spirito, Casale Mto (AL): Francesca Cravero, Francesco Lemut; Ospedale San Giovanni Bosco, Torino: Luciano Bonaccorsi, Tiziana Viora; Ospedale Sant'Andrea, Vercelli: Clemente De Rosa, Silvio Testa; Ospedale SS Annunziata, Savigliano (CN): Marco Brunetti; Ospedale SS Trinità, Borgomanero (NO): Matteo Gatti; Presidio Cottolengo, Torino: Enrico Gibin, Carlo Bima; Ospedale Maria Vittoria, Torino: Francesco Quaglino; AOU Città della Salute e della Scienza, Torino: Marco Ettore Allaix, Paolo De Paolis, Mario Morino, Ida Marina Raciti, Gitana Scozzari. Study coordination: AO S Croce e Carle, Cuneo: Felice Borghi, Danilo Donati, Maurizio Meineri, Sarah Palmisano, Luca Pellegrino; AOU Città della Salute e della Scienza, Torino: Giovannino Ciccone, Rosalba Galletti, Eva Pagano, Sergio Sandrucci; AO Mauriziano, Torino: Ilaria Bachini; Paola Coata, Barbara Mitola, Paolo Massucco, Alessio Rizzo; AO San Luigi Gonzaga, Orbassano (TO): Pietro Caironi; Humanitas, Torino: Monica Rolfo; Regione Piemonte: Anna Orlando; Rete Oncologica Piemonte e Valle d'Aosta: Oscar Bertetto. Technical staff: AOU Città della Salute e della Scienza, Torino: Francesco Brunetti, Corinna Defilè, Vitor Hugo Dias Martins, Lisa Giacometti, Matteo Papurello, Fabio Saccona, Danila Turco.

Contributors EP, LP, MR, AR, SP, MMe, IB, GC and FBo conceptualised the study. EP, LP, AC, GC and FBo designed the study. LP, MRo, SP, MMe, MMo, MEA, AM, PM, PB, RP and FBo acquired the data. EP, AC, FBr, LG and GC analysed and verified the data. EP, LP, MRo, AC, LG, GC and FBo drafted the manuscript. MR, FBr, AR, SP, MMe, IB, MMo, MEA, AM, PM, PB and RP critically reviewed the work. All authors had final responsibility for the decision to submit for publication. EP, GC and FBo had overall final approval of the published version. LG submitted the manuscript for publication. The corresponding author (EP) attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. EP is responsible for the overall content as guarantor.

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ORCID iDs
Eva Pagano http://orcid.org/0000-0001-7552-2901
Lisa Giacometti http://orcid.org/0009-0004-4930-6622

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