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ORIGINAL ARTICLE

Enhanced recovery after surgery in gastric cancer: which are the main achievements from the Italian experience?

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Abstract

In the last years, the concept of 'enhanced recovery after surgery' (ERAS) has become a routine in the perioperative care of patients undergoing colorectal resection. The application of ERAS programs in gastric surgery had a more difficult penetration into clinical practice, mainly for the introduction of radical changes in the traditional postoperative management. The aim of the study was to analyze the rate of compliance to a standardized ERAS protocol in different Italian centers and evaluate the results in terms of postoperative outcomes. From April 2015 to July 2017, a prospective observational study was conducted among seven centers participating in the Italian Group for Research for Gastric Cancer (GIRCG), in patient candidates to elective gastrectomy for cancer. A standardized ERAS perioperative protocol was approved by all centers. Compliance to the protocol was then evaluated and postoperative outcomes (morbidity and mortality rate, duration of hospital stay and readmission rate) were analyzed. Two-hundred and seventy unselected patients operated on for gastric cancer were enrolled. The median age was 73 years; 40.4% of patients were female; 24.1% had a nutritional risk score ≥ 3. Perioperative chemotherapy was used in 23.7% of cases. Total gastrectomy was performed in 57.4% of patients; minimally invasive approach was adopted in 28.1% of patients. Adherence to the protocol varied between 23 and 88% for single items. It was quite low for pre- and intraoperative items, mainly for items related to nutritional care. Postoperative complications occurred in 35.5% of patients, mortality was 0.7%. Median length of hospital stay was 8 days (range 4–72) and the readmission rate was 6.3%. There is a growing attention on the implementation of ERAS protocol for gastric cancer surgery, but several elements of this protocol are still not routinely adopted, among them items regarding nutritional care.

Keywords Enhanced recovery after surgery · Gastrectomy · Gastric cancer

Introduction

The "enhanced recovery after surgery" (ERAS) program has been recently defined as the gold standard of perioperative care for patients undergoing colorectal resection. Yet, no unanimous consensus has been reached on which (if any)

The list of the authors of the Italian Group for Enhanced Recovery in Gastric Surgery is given in "Acknowledgements" section.

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are the key items of the perioperative protocol for improving outcomes.

Recent data suggest that ERAS program can be safely applied also to major upper gastrointestinal (GI) tract surgery with promising results on primary endpoints. Nevertheless, the experience is still limited and restricted to Far-East countries such as China, Korea and Japan [1, 2]. European studies are few and conducted in small series [3].

The ERAS program has been developed by combining several evidence-based techniques for perioperative care intended to reduce the stress response and organ dysfunction. As a consequence, it is expected that ERAS implementation may shorten the time required for full recovery and reduce postoperative complications associated with an excessive response to surgical stress without increasing postoperative morbidity.

The surgical approach and the type of perioperative care may have a major influence on morbidity after gastrectomy and probably comprehensive pathways such as an ERAS standardized protocol may be effective in improving the clinical course with subsequent economic benefits on the health care systems.

Currently, even if feasibility and safety of fast-track rehabilitation programs in patients undergoing gastric surgery have been demonstrated at least in the East for low-risk patients with early-stage neoplasms, there are no convincing data on how the rate of adherence to single ERAS domain may affect outcomes.

Therefore, in April 2015 we started a multicenter prospective observational study (the ERGS study—Enhanced Recovery in Gastric Surgery), among seven centers, members of the Italian Research Group for Cancer of the Stomach (GIRCG).

The primary aim of the study was to analyze the rate of compliance to a standardized ERAS protocol in different centers, evaluating the results in terms of postoperative morbidity and mortality rate, duration of hospital stay and readmission rate. Differences among centers might lead to evaluate the most important items for achieving better results. We hypothesized that the highest adherence to the protocol would imply the greatest benefit for patient recovery.

This paper describes the characteristic of the patients included in the study and the clinical results with respect to compliance and adherence to the various protocol elements.

Methods

From April 2015 to July 2017, unselected patient candidates to elective gastrectomy (total or subtotal) for cancer in seven Italian centers were enrolled in this prospective study. The standardized ERAS perioperative pathway is reported in Table 1. Surgeons were invited to comply as much as possible with the protocol. The protocol was composed of several items, divided into pre-, intra- and postoperative ones, based on the common elements of the ERAS program, with preoperative optimization of risk factors (including nutritional care), counseling, intra- and postoperative fluid restriction policy, use of nutritional devices, avoidance of tubes, optimal pain management, early enteral feeding and early mobilization.

Data on compliance to the single items and data on postoperative course were registered and shared in a specific database. Any postoperative complication occurring within 30 days from surgery were defined as by the GIRCG [4]. Morbidity was defined as the occurrence of any complication, directly or indirectly related to surgery. The severity of complications was graded according to the Clavien–Dindo (CD) classification [5].

Discharge criteria were defined as: (1) the patient has achieved full mobilization, (2) pain is fully controlled by oral therapy, and (3) home nutritional requirements are achievable: the patient should tolerate oral nutrition and/or enteral feeding reaching a nutritional intake of at least 60% of daily energy requirement. Discharge criteria were evaluated from the fifth postoperative day and then checked every day. In-hospital and 30-day mortality rates were registered, as well as length of hospital stay (LOHS).

Results are shown as median, range or numbers and percentage where appropriate. No statistical analysis was performed since the aim of the study was a description of the population and protocol adherence.

Results

Two-hundred and seventy cancer patient candidates to potentially curative resection were included in the study.

Table 2 reports the clinical characteristics of patients included in the study, type of treatment used, surgical approach and tumor stage.

The median age was 73 years (range 27–90); median BMI was 24 kg/m^2 (range 17–44), with 24% of patients being at risk for malnutrition (nutritional risk score ≥ 3). In 155 patients (57.4%) a total gastrectomy was performed, mainly (69.6%) with a D2 lymph node dissection. Minimally invasive resections (either laparoscopic or robotic) were performed in 76 patients (28.1%). Early pathological stages were diagnosed in 86 cases (31.8%) and 9.4% of these cases experienced cancer downstaging after neoadjuvant treatments.

Postoperative results are reported in Table 3. Two patients died in the postoperative period (30-day mortality rate 0.7%). Postoperative morbidity rate was 35.6% with 39 patients (14.4%) experiencing a severe complication (CD ≥ 3). The median duration of hospital stay was 8 days

Table 1 Perioperative protocol

		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5–7[a]
Preoperative							
Preadmission counseling	x						
Evaluation and optimization of risk factors	x						
Identification of nutritional problems	x						
Immunonutrition	x						
Preoperative carbohydrate load	x						
Intraoperative							
Antibiotic prophylaxis		x					
Mechanical and pharmacological deep venous thrombosis prophylaxis	x	x	x	x	x	x	x
Avoid pre-medication		x					
Peridural catheter (PC)		x	x	x	x		
Avoid central venous catheter (CVC)		x					
Active patient warming		x					
Avoid NGT		x					
Avoid abdominal drains in subtotal gastrectomy (STG)		x					
In case of NRS > 3 place nutritional device		x					
Postoperative							
Avoid morphine		x	x	x	x	x	x
Early urinary catheter removal			x	x	x		
Early mobilization		x	x				
Early oral feeding for liquids within POD 3			x	x	x		
Early oral feeding for solids within POD 4					x	x	
Immunonutrition if NRS > 3			x	x	x	x	x

[a]Consider discharge criteria

(range 4–72), with a readmission rate within 30 days of 6.3%. This frequency was higher in centers with a lower duration of hospitalization. The median time to fulfill discharge criteria was 7 days.

The compliance to the protocol is reported separately for pre- and intraoperative items (Table 4) and for postoperative items (Table 5). Adherence to the protocol varied between 23 and 88% for single items. It was quite low for pre- and intraoperative items, mainly for nutritional care. Tubes (nasogastric tube and abdominal drains) were used in nearly 50% of cases, with a low adherence to the protocol. A higher adherence to the postoperative protocol was registered, with the most important items being fulfilled in more than 70% of patients.

Discussion

In 2001, Wilmore and Kehlet proposed a standardized management for patients undergoing major surgery with the aim to reduce postoperative stress and organ dysfunction, allowing a shortened time to full recovery, with a low rate of postoperative complications and improved postoperative outcomes without increasing specific surgical morbidity. At present, ERAS programs have been implemented in many different fields of surgery (i.e. colorectal, urology, gynecology) showing good results with an improvement of postoperative outcomes [6].

Gastric surgery is still burdened by postoperative complications with a rate up to 45% [7, 8]. The high rate of postoperative morbidity in gastric cancer surgery is related to patient characteristics that surgeons cannot modify before surgery. For total gastrectomy, age over 65 years, gender, and comorbidities represent negative prognostic factors for postoperative complications [9, 10]. Moderate or severe malnutrition, which is more frequent in patients with these characteristic and generally in patients with gastric cancer, is also a predictor of poor outcomes. However, it is one of the few elements that can be corrected by the surgeon and is an important aspect of the ERAS programs.

Efforts to reduce postoperative morbidity and mortality rates may include the adoption of ERAS programs in gastric surgery. These programs have been mainly adopted in Eastern countries, due to the higher prevalence of early tumor stages, occurring in younger and healthier populations, that are exposed to lower complication risks. In fact, most of

Table 2 Preoperative, operative and pathological data

Groups (no. of patients)		A (46)	B (42)	C (45)	D (13)	E (29)	F (65)	G (30)	Total 7 (270)
Age	Median	71	76	75	76	76	69	76	73
	Range	44–88	27–87	42–88	52–89	49–85	31–89	51–90	27–90
Gender	Male (%)	26 (56.5)	24 (57.1)	27 (60)	10 (76.9)	14 (48.2)	41 (63)	19 (63.3)	161 (59.6)
BMI (kg/m^2)	Median	24	24	25	27	24	26	24	24
	Range	18–32	17–38	18–44	18–35	17–37	18–34	19–35	17–44
Nutritional risk score (NRS)	NRS < 3 (%)	27 (58.7)	23 (54.8)	37 (82.2)	11 (84.6)	22 (75.9)	63 (96.9)	22 (73.3)	205 (75.9)
Neoadjuvant therapy	No (%)	26 (56.5)	30 (71.4)	37 (82.2)	13 (100)	26 (89.6)	47 (72.3)	27 (90)	206 (76.3)
ASA score	I–II (%)	37 (80.4)	20 (47.6)	27 (60)	6 (46.1)	27 (93.1)	48 (73.8)	14 (46.7)	179 (66.3)
Pathological stage	≥ II (%)	30 (65.2)	29 (69.1)	30 (66.7)	9 (69.2)	17 (58.7)	48 (73.9)	19 (63.3)	184 (68.2)
Operation time median	Min	261	207	270	245	240	298	263	255
	Range	180–351	118–384	150–455	150–310	170–318	100–420	110–386	100–455
Type of gastrectomy	STG (%)	30 (65.2)	11 (26.2)	36 (80)	7 (53.9)	23 (79.3)	28 (43.1)	20 (66.7)	115 (42.6)
	TG (%)	16 (34.8)	31 (73.8)	9 (20)	6 (46.1)	6 (20.7)	37 (56.9)	10 (33.3)	115 (57.4)
Type of reconstruction	Billroth II (%)	0	0	10 (22.2)	0	1 (3.5)	0	3 (10)	14 (5.2)
	Roux (%)	46 (100)	42 (100)	35 (77.8)	13 (100)	28 (96.5)	65 (100)	27 (90)	256 (94.8)
Surgical approach	Open (%)	28 (60.9)	11 (26.1)	25 (55.6)	12 (92.3)	23 (79.3)	65 (100)	30 (100)	194 (71.9)
	Mini-invasive (%)	18 (39.1)	31 (73.9)	20 (44.4)	1 (7.7)	6 (20.7)	0	0	76 (28.1)
Lymph node dissection	D1 (%)	16 (34.8)	3 (7.1)	0	7 (53.8)	10 (34.5)	8 (12.3)	12 (40)	55 (20.3)
	D2 (%)	30 (65.2)	37 (88.1)	43 (95.6)	5 (38.5)	17 (58.6)	38 (58.5)	18 (60)	188 (69.7)
	D2 plus (%)	0	1 (2.4)	0	1 (7.7)	2 (6.9)	11 (16.9)	0	16 (5.9)
	D3 (%)	0	1 (2.4)	2 (4.4)	0	0	8 (12.3)	0	11 (4.1)

STG subtotal gastrectomy, *TG* total gastrectomy

Table 3 Postoperative outcomes

Groups (no. patients)		A (46)	B (42)	C (45)	D (13)	E (29)	F (65)	G (30)	Total (270)
Postoperative complication number (%)	CD I–II	18 (39.1)	5 (11.9)	9 (20.0)	6 (46.2)	1 (3.5)	13 (20.0)	4 (13.3)	57 (21.2)
	CD III–IV	7 (15.2)	10 (23.8)	2 (4.4)	0	5 (17.2)	10 (15.4)	5 (16.7)	39 (14.4)
Mortality	No. (%)	0	1 (2.4)	0	0	0	0	1 (3.3)	2 (0.7)
Length of hospital stay, days	Median (range)	10 (6–53)	9 (5–72)	7 (4–34)	8 (7–12)	6 (4–31)	7 (5–32)	10 (6–54)	8 (4–72)
Readmission rate	No. (%)	2 (4.3)	2 (4.9)	2 (4.4)	2 (15.4)	4 (13.8)	4 (6.2)	1 (3.4)	17 (6.3)

Table 4 Compliance to preoperative and intraoperative ITEMS

Groups (no. patients)	A (46)	B (42)	C (45)	D (13)	E (29)	F (65)	G (30)	Total (270)
Nutritional support, *n* (%)	4 (8.7)	2 (4.8)	6 (13.3)	2 (15.4)	0	1 (1.5)	0	15 (5.6)
Immunonutrition, *n* (%)	33 (71.7)	41 (97.6)	34 (75.6)	6 (46.2)	0	0	0	114 (42.2)
Nutricia preop, *n* (%)	46 (100)	41 (97.6)	36 (80)	0	0	40 (61.5)	11 (36.7)	174 (64.4)
Avoid pre-medication, *n* (%)	46 (100)	42 (100)	44 (97.8)	1 (7.7)	26 (89.7)	0	10 (33.3)	169 (62.6)
Peridural catheter (PC), *n* (%)	27 (58.7)	36 (85.7)	13 (28.9)	4 (30.8)	22 (75.9)	41 (63.1)	21 (70)	164 (60.7)
Avoid central venous catheter (CVC), *n* (%)	44 (95.7)	40 (95.2)	32 (71.1)	3 (23.1)	10 (34.5)	45 (69.2)	23 (76.7)	198 (73.3)
Avoid abdominal drains in subtotal gastrectomy (STG), *n* (%)	27 (90.0)	5 (45.5)	6 (16.7)	0	19 (82.6)	17 (58.6)	2 (10.0)	75 (48.4)
Avoid NGT, *n* (%)	42 (91.3)	26 (61.9)	13 (28.9)	5 (38.5)	24 (82.8)	36 (55.4)	2 (6.7)	148 (54.8)
In case of NRS > 3, place nutritional device, *n* (%)	23 (74.2)	1 (5.9)	2 (22.2)	0	0	0	0	26 (38.2)
PONV, *n* (%)	0 (0)	42 (100)	44 (97.8)	12 (92.3)	29 (100)	65 (100)	30 (100)	222 (82.2)

Table 5 Compliance to postoperative items

Postoperative item	A (46)	B (42)	C (45)	D (13)	E (29)	F (65)	G (30)	Total (270)
Early urinary catheter removal, *n* (%)	31 (67.4)	37 (88.1)	36 (80.0)	10 (76.9)	25 (86.2)	58 (89.2)	25 (83.3)	222 (82.2)
Early mobilization, *n* (%)	40 (87)	39 (92.9)	31 (68.9)	12 (92.3)	29 (100)	60 (92.3)	26 (86.7)	237 (87.7)
Early oral feeding for liquids within POD 3, *n* (%)	30 (65.2)	28 (66.7)	30 (66.7)	11 (84.6)	27 (93.1)	56 (86.2)	26 (86.7)	208 (77.0)
Early oral feeding for solids within POD 4, *n* (%)	27 (58.7)	21 (50)	33 (73.3)	8 (61.5)	27 (93.1)	52 (80.0)	23 (76.7)	191 (70.7)
Avoid morphine, *n* (%)	33 (71.7)	41 (97.6)	30 (66.7)	13 (100)	27 (93.1)	63 (96.9)	30 (100)	237 (87.8)

the experiences with the ERAS programs in gastric surgery included patients with these characteristics (Table 6). Western experiences are limited and all the available randomized trials are from Eastern countries. Western patients present more often with diseases that are more advanced, higher BMI, and more severe malnutrition.

The endpoints considered for the evaluation of safety and feasibility of ERAS protocols focus on morbidity and mortality rate, length of hospital stay and readmission rate. Several meta-analyses demonstrated that these parameters are frequently improved when an ERAS program is adopted even though the studies included in analyses are extremely heterogeneous [24]. Several items have been considered important to improve the results of ERAS protocols such as the use of minimally invasive techniques given the effects on reduction of stress response and inflammation and improvement of postoperative respiratory function [25, 26].

In 2014, consensus guidelines for ERAS after gastrectomy have been published to provide a comprehensive advice for an evidence-based perioperative care program for patients undergoing gastrectomy although the included items had different grades of recommendation and evidence levels. These guidelines formed the basis for studies aiming at identifying the importance of single items in improving the results of gastric surgery [27].

In Italy, the application of ERAS program in gastric surgery was seldom reported starting in 2012, but not widely diffused until 2015, even in high-volume centers for gastric surgery. In a GIRCG survey, conducted in 2014 (unpublished results) among high-volume centers for gastric surgery on the possible implementation of the ERGS study, most of the surgeons declared that they routinely used drains and nasogastric tubes after gastric surgery and most of them did not have defined nutritional perioperative protocols, including immunonutrition and perioperative nutritional support in malnourished patients.

Starting in April 2015, these centers implemented an ERGS protocol in their daily practice, and most elements were considered for the care of patients undergoing major gastric surgery.

The ERGS study, as per our knowledge, is one of the first Western prospective analyses conducted on the application of ERAS protocol in gastric surgery for malignancy. This analysis represents an updated mirror of Italian situation in this field of surgery. The patients included in this study were unselected as demonstrated by the high rate of patients at risk for malnutrition (28%), with a high ASA score (33.7% ASA III–IV), and with an advanced age (median 73 years). Almost 24% of patients underwent neoadjuvant treatment and had an advanced stage. The great majority of included patients had a radical D2 gastrectomy, with minimally invasive approach being used in 28% of cases. Globally, the protocol was followed in more than two-third of patients, even if the applications of single items differed significantly by centers. The analysis of the results suggests that the consideration of surgeons for preoperative nutritional status should be implemented. This is of utmost importance since malnutrition is one of the few parameters affecting postoperative morbidity and that can be corrected by medical intervention. Preoperative optimizations of other risk factors (among them anemia and smoking habits) can be addressed in general surgical practice. Notwithstanding the general characteristic of this series, postoperative results in terms of mortality and morbidity rate are satisfactory and the length of postoperative stay was shorter than expected for a complex case mix such as ours.

The results of this study show that there is a growing attention to the implementation of an ERAS protocol in gastric cancer surgery, but several items of this protocol are still not routinely adopted and among them, particularly, nutritional screening and care.

Table 6 Randomized trial on ERAS programs in gastric surgery

References	Year	Country	Outcomes	Methods	No. of pts	No. of control pts	Open/laparosc.
Kiyama et al. [11]	2004	Japan	1, 2, 8, 9	Inclusion of cancers and gastrointestinal stromal tumors	47	38	n.a.
Jiang et al. [12]	2007	China	1, 7, 8, 9, 10	n.a.	40	40	n.a.
He et al. [13]	2010	China	1, 2, 7, 9	n.a.	41	41	n.a.
Wang et al. [14]	2010	China	1, 2, 3, 4, 5, 6, 7, 9	Adenocarcinoma, years < 80, no neoadjuvant treatment. 15 ≥ BMI ≤ 30, no primary diabetes, no primary hepatoenteric disease and no primary cardio-cerebral disease	45	47	n.a.
Liu et al. [15]	2010	China	1, 2, 3, 4, 5, 7, 10	n.a.	33	30	Open
Kim et al. [16]	2012	Korea	1, 5, 7, 9	Distal gastric tumor, cTNM ≤ T2N0M0, no pregnancy, no inflammatory bowel disease, no chronic renal or liver disease, no cardiopulmonary dysfunction, no complicated diabetes, no anticholinergic medications, ASA score ≤ 2 or ECOG ≤ 2	22	22	VLS
Hu et al. [17]	2012	China	1, 2, 7, 9	Adenocarcinoma, 25 ≥ age ≤ 75 age, cStage any T, N0, M0; no history of autoimmune or severe cardiopulmonary diseases; no preoperative radiotherapy or chemotherapy; no digestive obstruction, no perioperative blood or albumin infusion or combined intraoperative evisceration	19 21	22 20	VLS Open
Feng et al. [18]	2013	China	1, 2, 3, 4, 7, 9	18 ≥ age ≤ 75 years; no preoperative radiotherapy or chemotherapy; no distant metastasis; no history of primary diabetes mellitus, no bowel obstruction, no severe cardiopulmonary diseases and immune-related diseases; no pregnancy or breast feeding; ASA ≤ II	59	60	Open
Bu et al. [19][a] Bu et al.[b]	2015	China	1, 2, 3, 4, 7, 9	cStage ≤ III (TNM 10), ASA score grades I–III, age ≥ 45 and ≤ 90 years, no emergency surgery, no preoperative radiotherapy or chemotherapy, receipt of open gastric cancer radical surgery, and no preoperative complete digestive tract obstruction or digestive tract perforation	64 64	64 64	n.a.
Abdikarim et al. [20]	2015	China	1, 2, 3, 4, 7,	Advanced gastric cancer, elective laparoscopic surgery < 75 years. Patients with early gastric cancer received neoadjuvant chemotherapy, and those with pyloric obstruction or with distant metastasis were excluded	30	31	VLS
Liu et al. [21]	2016	China	1, 2, 3, 5, 7, 9	Age ≥ 60 years; no surgical contraindications according to "Japanese gastric cancer treatment statute". No history of cancer, no abdominal surgery or recent acute infection; cStage < IV according to intraoperative assessment; no obstruction or perforation; no receiving preoperative radiotherapy or chemotherapy; no contraindications of anesthesia or pneumoperitoneum; no autoimmune diseases, metabolic diseases, or major diseases of other systems	21 21	21 21	VLS Open

Table 6 (continued)

References	Year	Country	Outcomes	Methods	No. of pts	No. of control pts	Open/laparosc.
Tanaka et al. [22]	2017	Japan	1, 2, 3, 4, 5, 7, 9, 10	Adenocarcinoma, no multiple organ resection except for the gallbladder, no involvement of the duodenum or esophagus, age 20–85 years, sufficient oral intake, ASA score < 4, no prior chemotherapy or radiotherapy for any malignancy. No pregnancy, inflammatory bowel disease, chronic renal disease, severe cardiopulmonary dysfunction and complicated diabetes were excluded	73	69	VLS/open
Mingjie et al. [23]	2017	China	1, 2, 3, 5, 7	Adenocarcinoma cStage ≤ T4a, any N, M0, no digestive obstruction, possibility to be treated with LAG[c]; age 18–75; normal hematological, renal, hepatic, and cardiac parameters, ASA score ≤ III; no history of treatment with neoadjuvant chemotherapy and/or radiotherapy	73	76	VLS

Outcomes: 1, length of hospital stay; 2, operative morbidity; 3, operative mortality; 4, readmission rate; 5, inflammatory response; 6, maximum postoperative pain score; 7, time to passage of flatus/defecation; 8, duration of intravenous fluid therapy; 9, total cost; 10, postoperative body weight loss

n.a. not available

[a] < 75 years old

[b] 75 ≥ years ≤ 90

[c] Laparoscopic gastrectomy

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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