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ORIGINAL ARTICLE

Feasibility and Safety of Early Oral Feeding in Patients with Gastric Cancer After Radical Gastrectomy

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Abstract

An enhanced recovery after surgery (ERAS) protocol is useful in patients undergoing colorectal surgery. However, its feasibility for gastric surgery remains unclear. This study aimed to evaluate the feasibility and safety of early oral feeding (EOF) for patients with gastric cancer after radical gastrectomy. The EOF protocol was implemented in 397 patients who underwent radical gastrectomy between 2005 and 2014 at our hospital. The protocol was common in 277 patients after distal gastrectomy (DG) and 120 patients after total gastrectomy (TG). The patients were scheduled to start drinking water in the morning of the first postoperative day and to start thin rice gruel with a liquid nutrition supplement on the second postoperative day. We analyzed the incidence of postoperative complications and surgical outcomes in these patients. Furthermore, we analyzed risk factors for dropout from the EOF protocol. All patients started drinking water, while 26 patients were unable to start eating. The EOF protocol was implemented in 371 patients (93%), and 48 patients stopped eating. Specifically, 227 patients (87%) after DG and 96 patients (88%) after TG followed the EOF protocol perfectly. The incidence of postoperative complications, including anastomotic leakage ($n = 0$), ileus ($n = 22$), and pneumonia ($n = 11$), was 15% and that of clinically significant events (≥ grade 3) was 4.3%. Multivariate analysis showed that the male gender, comorbidities, and intra-operative bleeding are independent risk factors for dropout from the EOF protocol. EOF can be safely implemented in patients after radical gastrectomy.

Keywords Gastric cancer · Gastrectomy · Early oral feeding · Complications · Risk factors for dropout

Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death globally [1]. In Japan, gastric cancer is the third most common cause of cancer-related death, following lung cancer and colorectal cancer. Early tumor detection; curative surgical resection, including extended lymph node dissection (D2 or D3); and appropriate adjuvant therapy have improved the survival rate of patients with primary gastric cancer. However, surgery for gastric cancer is still a high-risk procedure involving clinically significant postoperative stress, complications, and sequelae. In addition, radical gastrectomy–related morbidity and mortality range from 10 to 46% and from 0 to 13%, respectively [2–8].

A postoperative nutritional status in the patient undergoing a major abdominal surgery is a major factor determining the patient's surgical outcome and might be improved by early postoperative enteral feeding [9, 10]. In addition, appropriate perioperative management can help decrease the morbidity rate. In the 1990s, to enhance postoperative recovery and reduce morbidity in the field of elective colorectal surgery, Henrik Kehlet proposed the concept of multimodal perioperative care, such as enhanced recovery after surgery (ERAS) and fast-track surgery (FTS) [11, 12]. ERAS and FTS rapidly gained popularity among surgeons globally.

ERAS programs comprise many elements, such as (i) preoperative education, (ii) preoperative carbohydrate loading, (iii) omission of bowel preparation, (iv) epidural analgesia without opioids, (v) early postoperative enteral feeding, (vi) early mobilization of patients, and (vii) thromboprophylaxis. All these elements are independent but directed toward the same two goals: reducing surgical stress and optimizing recovery [13].

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Early oral feeding (EOF) is the most important part of ERAS. Several clinical randomized controlled trials (RCTs) have demonstrated the advantages of EOF after elective colorectal cancer surgery, such as reduced length of postoperative hospital stay and reduced postoperative morbidity and mortality compared with traditional postoperative oral feeding [9, 14–16]. However, the feasibility of EOF for gastric cancer surgery patients remains unclear because traditionally EOF is avoided to minimize strain to the anastomoses and reduce the inherent risks of postoperatively impaired gastrointestinal motility. As a result, many institutions in Japan still implement a period of 3–4 days of postoperative fasting, followed by subsequent stepwise slow dietary rehabilitation.

Recently, the Japanese conventional fixed dietary schedule after radical gastrectomy was reexamined, and many institutions in Japan are now adopting early postoperative oral intake. However, little data support the feasibility and safety of EOF after gastrectomy. Therefore, this study aimed to evaluate the feasibility and safety of EOF for patients with gastric cancer after radical gastrectomy. In addition, we retrospectively analyzed the risk factors for dropout from the EOF protocol.

Materials and Methods

Patients

We retrospectively reviewed the medical records of 463 consecutive patients with gastric cancer who had undergone curative gastrectomy between 2005 and 2014 at the Department of Digestive Surgery, National Hospital Organization Hokkaido Cancer Center, Japan. Patients who underwent emergency surgery for complications such as perforation or/and bleeding were excluded from the study. Patients who had poor performance status, gastric carcinoma in the remnant stomach, esophagus invasion gastric cancer, or other synchronous malignant diseases and multiple organ resections were also excluded. Finally, of these 463 patients, the EOF protocol was implemented in 397 patients undergoing Roux-en Y reconstruction after radical gastrectomy (86%). The protocol was common in 277 (277/283, 98%) patients after distal gastrectomy (DG) and 120 (120/180, 67%) patients after total gastrectomy (TG). All 397 patients were retrospectively analyzed for the incidence of postoperative complications and surgical outcomes. This study was reviewed and approved by the research ethics committee of National Hospital Organization Hokkaido Cancer Center (approval no. 30-102). Informed consent has been obtained from all patients included in this study.

Schedule of the EOF Protocol

All 397 patients were scheduled for immediate nasogastric tube removal postsurgery in the operation room. They were also scheduled to start drinking water in the morning of the first postoperative day (1POD), eat thin rice gruel with a liquid nutrition supplement on the second postoperative day (2POD), and gradually progress to regular rice porridge and solid food over a period of 4 days, as tolerated. The discharge criteria were as follows: adequate pain relief, no high fever, no inflammatory signs, ability to mobilize with self-care, and tolerance for more than half of the solid food intake, including liquid nutrition supplement.

Data Collection: End Points

All data were retrospectively retrieved from the patients' medical records. The primary end point was defined as the incidence of postoperative complications. Complications were defined as ≥ grade 2 complications according to the Clavien–Dindo classification within 30-day postsurgery. Secondary end points were defined as the incidence of anastomotic leakage, pneumonia, the percentage of patients starting oral feeding from 2POD, completion rate of the EOF protocol, length of postoperative hospital stay, 30-day postdischarge readmission rate, and 30-day postoperative mortality rate.

Meal step-up was delayed for patients who ate < 30% of meals for 2 days. Dropout from the EOF protocol was defined as stopping of meals for > 2 days because of postoperative observation of the patients' condition and postoperative complications.

Pathological findings were categorized on the basis of the *TNM Classification of Malignant Tumours* (7th edition) of the Union for International Cancer Control. Continuous data were expressed as medians (range).

Statistical Analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria). This modified version of R commander version 1.6-3 was designed to add statistical functions frequently used in biostatistics. Risk factors for dropout from the EOF protocol were identified using univariate and multivariate analyses with cross-linked tables and logistic regression models. $P < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

Table 1 summarizes the preoperative clinical characteristics of all 397 patients (251 men and 146 women). The mean age of the patients was 67 years, 240 patients (60.7%) had some

Table 1 Baseline clinical characteristics of the patients

Characteristics		Patients (n = 397)
Age (years)*		67 (24–95)
Gender	Male	251 (63.2)
	Female	146 (36.8)
Total body weight (kg)*		58.0 (27.0–91.9)
Body mass index (kg/m^2)*		22.5 (11.8–35.3)
Comorbidity		241 (60.7)
Diabetes mellitus		57 (14.4)
Hypertension		138 (34.8)
Ischemic heart disease		50 (12.6)
Respiratory disease		51 (12.8)
Brain or mental disease		36 (9.1)
Preoperative chemotherapy	Yes	47 (11.8)
	None	350
Preoperative fast	Yes	26 (6.5)
	None	371
History of the abdominal surgery	Yes	31 (7.8)
	None	366
Other malignant diseases (synchronous or metachronous)	Yes	64 (16.1)
	None	333
ASA-PS	1	77 (19.4)
	2	310 (78.1)
	3	10 (2.5)

ASA-PS, American Society of Anesthesiologists physical status; numbers in parentheses are percentages; *median (range)

comorbidity, and 47 patients (11.8%) received preoperative chemotherapy. Table 2 shows our surgical and oncological findings. Laparoscopic surgery was performed on 73 patients (18.4%), 52 patients (13.1%) underwent combined organ resection excluding cholecystectomy, and 245 patients (61.7%) received extended lymph node dissection (D2 or D3). The mean operating time was 255 min. The final pathologic examination showed that 198 patients (78.6%) were TNM stage I, 63 (15.9%) were TNM stage II, 70 (17.6%) were TNM stage III, and 66 (16.6%) were TNM stage IV. In addition, 52 patients (13.1%) had a noncurative resection.

Postoperative Outcomes

Tables 3 and 4 show postoperative outcomes and details of postoperative complications, respectively. The nasogastric tube could be removed for all patients, and all patients started drinking water from 1POD, while 26 patients (15 DG patients [5.4%] and 11 TG patients [9.2%]) were unable to start oral intake because of abdominal distention (DG11, TG3), hemorrhage (DG3, TG2), poor activities of daily living (ADLs) (TG2), or fever (TG1). The EOF protocol was implemented in 371 patients (93%), of which 48 patients (DG35, TG13) stopped eating because of remnant stomach dilatation (DG13), abdominal distention (DG6, TG2), intra-abdominal abscess (DG8, TG2), hemorrhage (DG3, TG3), aspiration pneumonia (DG2, TG2), or fever (DG1, TG1). Overall, 227 patients (87%) after DG and 96 patients (88%) after TG were able to follow the EOF protocol perfectly, and the EOF protocol completion rate was 81.4%. The incidence of postoperative complications (≥ Clavien–Dindo grade 2 complications), including anastomotic leakage (n = 0), ileus (n = 22), reoperation (n = 3), relaparotomy hemostasis (n = 5), endoscopic hemostasis (n = 3), intra-abdominal abscess (n = 19), and pneumonia (n = 11), was 12.3%. In addition, the incidence of clinically significant events (≥ grade 3 complications) was only 4.3% despite a high adaptation percentage of the EOF protocol. We performed reoperation in 10 patients (2.5%). The median length of postoperative hospital stay was 20 days, and 6 patients were readmitted to the hospital within 30 days postdischarge. The 30-day postoperative mortality rate was 0%.

Risk Factors for Dropout from the EOF Protocol

In total, 74 patients (18.6%) dropped out from the EOF protocol. Table 5 shows the results of univariate analyses performed to determine which variables were associated with dropout from the EOF protocol. We found that the rate of dropout from the EOF protocol significantly increased in male patients, the elderly, and patients with any comorbidity. No significant differences were observed between the two patient

Table 2 Surgical and oncological factors of the patients

Characteristics		Patients (n = 397)
Operative procedures	Distal gastrectomy (DG)	277 (69.8)
	Total gastrectomy(TG)	120 (30.2)
Operative approaches	Open surgery	324 (81.6)
	Laparoscopic surgery	73 (18.4)
Extent of lymph node dissection	D0	8 (2.0)
	D1	144 (36.4)
	D2	231 (58.2)
	D3	14 (3.5)
Total number of harvested lymph nodes, numbers, *		34 (1–106)
Combined organ resection (excluding cholecystectomy)	Yes	52 (13.1)
		242
Spleen		23
Pancreas		2
Colon, small intestine		12
Liver		7
Adrenal		3
Other		7
Curability	Curative (R0)	345 (87.0)
	Palliative (R1, R2)	52 (13.1)
Operating time (min)*		255 (95–490)
Intra-operative bleeding (ml)*		181 (3–2389)
Intra-operative transfusion	Yes	15 (3.8)
	None	382 (96.2)
Total volume of intra-operative infusion (ml/kg/h)*		8.72 (2.89–21.60)
Depth of invasion	T1	185 (46.6)
	T2	47 (11.8)
	T3	92 (23.2)
	T4a	55 (13.9)
	T4b	18 (4.5)
Lymph node metastasis	N0	226 (56.9)
	N1	52 (13.1)
	N2	54 (13.6)
	N3a	39 (9.8)
	N3b	26 (6.5)
Distant metastasis	M0	326 (82.1)
	M1	71 (17.9)
Tumor stage (UICC TNM 7th)	Stage I	198 (78.6)
	Stage II	63 (15.9)
	Stage III	70 (17.6)
	Stage IV	66 (16.6)

TNM, tumor node metastasis: the 7th edition of UICC/AJCC TNM stage; extent of lymph node dissection: the 13th Japanese edition and the 2nd English edition in 1998 of JGCA Japanese Gastric Cancer Association Classification; numbers in parentheses are percentages; *median (range)

groups in terms of preoperative chemotherapy and the body mass index. In addition, with regard to surgical factors, we found no significant differences in terms of surgery time, curability, type of approach (laparoscopy or open gastrectomy), extent of gastric resection (DG or TG), and extent of lymph node dissection (D2 or D3). However, pathologic stages and the amount of intra-operative bleeding significantly differed between the two groups.

Multivariate analysis showed that the male gender (P = 0.025; odds ratio [OR] = 0.501), comorbidities (P = 0.033;

Table 3 Postoperative complications

		Patients (n = 397)
Clavien–Dindo classification	Grade 0	254 (64.0)
	Grade 1	94 (23.7)
	Grade 2	32 (8.1)
	Grade 3a	6 (1.5)
	Grade 3b	10 (2.5)
	Grade 4a	1 (0.3)
Anastomotic leakage		0
Duodenal stump leakage		4
Reoperation		2
Abdominal infection		22
≥ grade 2		19
Percutaneous puncture drainage		3
Bleeding		11
≥ grade 2		8
Re-laparotomy hemostasis		5
Endoscopic hemostasis		3
Ileus, obstruction		22
≥ grade 2		18
Reoperation		3
Pneumonia		12
≥ grade 2		11
Enterocolitis		14
≥ grade 2		4
Gastric stasis (≥ grade 1)		8
SSI (≥ grade 1)		16
Mortality		0

Numbers in parentheses are percentages

OR = 0.523), and intra-operative bleeding (P = 0.041; OR = 0.565) were independent risk factors for dropout from the EOF protocol.

Discussion

The aim of the present study was to evaluate the safety, efficacy, and outcome of the EOF protocol employed in the perioperative treatment of radical gastrectomy for gastric cancer. This study was a retrospective, one-arm, nonrandomized analysis. However, the subjects included the elderly and also those who underwent preoperative chemotherapy. On the other hand, most previous RCTs were performed on selected patients who had good performance status and patients were excluded if they had advanced gastric cancer, malnutrition, or any important vital organ comorbidity.

Table 4 Postoperative outcomes

	Patients (n = 397)
Onset of liquid intake (POD*)	1
Onset of meal intake (POD*)	2 (1–14)
Allowed number of early oral intake (n (%))	371 (93.5)
DG	262 (94.6)
TG	109 (90.8)
Drop number of meal setup (n (%))	48 (12.9)
DG	35 (13.4)
TG	13 (11.9)
Accomplished clinical pathway (n (%))	323 (81.4)
DG	227 (81.9)
TG	96 (80.0)
Complication CD ≥ grade2 (n (%))	49 (12.3)
Complication CD ≥ grade3 (n (%))	17 (4.3)
Reinsert of NG tube (n (%))	18 (4.5)
Reoperation (n (%))	10 (2.5)
Readmission (n (%))	6 (1.5)
Allowed day of discharge (POD*)	16 ± 16.0 (7–165)
In the achievement of EOF protocol cases	15 ± 7.8 (7–64)
Postoperative hospital stay (POD*)	20 ± 18.4 (8–165)
In the achievement of EOF protocol cases	18 ± 10.9 (8–85)

POD, postoperative day; *CD*, Clavien–Dindo classification; *EOF*, early oral feeding; numbers in parentheses are percentages, *median ± SD (range)

In this study, the EOF protocol implemented in patients with gastric cancer after radical gastrectomy was common regardless of the extent of stomach resection, and the rate of use of the EOF protocol was high in 87% of all patients; especially, the rate was 98% in DG patients. Therefore, a common EOF protocol can be implemented in patients undergoing DG and TG routinely.

As mentioned before, previous studies have reported that morbidity and mortality from radical gastrectomy with conventional perioperative care range from 10 to 46% and from 0 to 13%, respectively [2–8]. Our data was good compared with these reported complication rates of conventional perioperative care study without the ERAS program. Some studies have advocated the benefits and feasibility of the EOF protocol after radical gastrectomy. In 2004, Suehiro et al. [17] first reported that implementing the EOF protocol within 48 h of radical gastrectomy is safe, with no evidence of increased postoperative morbidity and mortality, including nausea, vomiting, and anastomotic leakage, compared with conventional postoperative fasting. Recently, Hur et al. [18] reported in a small randomized trial that the EOF protocol on 2POD significantly enhances bowel recovery, reduces the length of postoperative hospital stay, and improves some elements of the patients' quality of life. Wang et al. [19] introduced the EOF protocol as part of the FTS program in patients with gastric cancer and found that the length of postoperative

Table 5 Univariate and multivariate analyses to determine clinicopathologic factors which effected on the drop from early oral feeding clinical pathway

Variable	Total	Complete	Drop	Univariate		Multivariate	
				Chi-square	*P* value	Odds ratio (95% CI)	*P* value
Age (years old)							
> 80	60	43	17	4.380	0.0036	0.535 (0.276–1.038)	0.0647
≤ 80	337	280	57				
Gender							
Male	251	194	57	7.453	0.0063	0.501 (0.274–0.916)	0.0248
Female	146	129	17				
BMI (kg/m^2)							
> 25	96	76	20	0.485	0.4862		
≤ 25	300	247	53				
Comorbidities							
Yes	241	185	56	8.545	0.0040	0.523 (0.288–0.949)	0.0329
None	156	138	18				
Preoperative chemotherapy							
Yes	47	39	8	2.595	0.0756		
None	350	284	66				
Preoperative fast							
Yes	26	20	6	0.116	0.7335		
None	371	303	68				
History of the abdominal surgery							
Yes	46	36	10	0.33	0.5659		
None	351	287	64				
Operative procedures							
DG	277	227	50	0.21	0.6469		
TG	120	96	24				
Operative approaches							
Open	324	263	61	0.041	0.8399		
Laparoscopic	73	60	13				
Extent of lymph node dissection							
D0/D1	152	125	27	0.125	0.7239		
D2/D3	245	198	47				
Combined resection (excluding cholecystectomy)							
Yes	52	46	6	1.487	0.2226		
None	345	277	68				
Curability							
Curative	345	280	65	0.005	0.7913		
Palliative	52	43	9				
Operating time (min)							
> 300	110	87	23	0.517	0.4723		
≤ 300	287	236	51				
Intra-operative bleeding (ml)							
> 300	119	87	32	7.629	0.0057	0.565 (0.326–0.98)	0.0413
≤ 300	278	236	42				
Intra-operative transfusion							
Yes	15	9	6	3.341	0.068		
None	382	314	68				

Table 5 (continued)

Variable	Total	Complete	Drop	Univariate		Multivariate	
				Chi-square	*P* value	Odds ratio (95% CI)	*P* value
Total volume of intra-operative infusion (ml/kg/h)							
> 10	137	114	23	0.473	0.4917		
≤ 10	260	209	51				
Stage (UICC TNM 7th)							
Stage I	198	173	25	9.419	0.0021	1 (0.995–1.01)	0.0647
Stage II/III/IV	199	150	49				

BMI, body mass index; *DG*, distal gastrectomy; *TG*, total gastrectomy

hospital stay and medical costs reduced and the patients' quality of life improved. Other studies have also reported the usefulness of ERAS programs for radical gastrectomy [20–23]. The incidences of postoperative complications in these reports (morbidity, 8–20% and mortality, 0%) were similar to our results and were acceptable. Feng et al. [24] and Sierzega et al. [25] analyzed the potential applicability of the EOF protocol in TG patients. Both studies concluded that the EOF protocol reduces the incidence of complications compared with the conventional late oral feeding (morbidity, 10% vs. 28%; mortality, 20% vs. 36%). Our results and the findings of these studies showed that implementing the EOF protocol after radical gastrectomy for gastric cancer is feasible in terms of safety.

Historically, surgeons believed that decompression with a nasogastric tube and a fasting period of 2–5 days after gastrointestinal surgery was required to prevent anastomotic leakage and aspiration pneumonia. This fasting period was deemed necessary at the time of transient ileus postsurgery and to ensure protection of the anastomotic site [26]. Therefore, in this study, we set the incidence of anastomotic leakage and pneumonia as secondary end points. As reported, the incidence of anastomotic leakage was none-to-low, similar to previous studies (0.8–1.9%) based on conventional perioperative management [5, 7, 8]. Some studies evaluated the value of ERAS programs in a Japanese high-volume center and reported low incidence of anastomotic leakage (0.8–1.5%) [21, 27], same as in this study.

Another potential disadvantage of the EOF protocol is aspiration pneumonia. Sunil et al. [28] reported a 4.6% incidence of respiratory events following D2 gastrectomy without the ERAS program, but in this study, we observed respiratory events in only 3% of the patients (12/397, including 4 patients with aspiration pneumonia). Previous studies on ERAS protocols for colorectal cancer have shown a 7.8% incidence of respiratory complications [29]. Similarly, Feng et al. [24] reported pneumonia in 8.5% of TG patients who received the EOF protocol. However, other studies have reported no pneumonia after initiation of the EOF protocol after radical gastrectomy [18, 19, 21, 27]. Therefore, we concluded that the incidence of aspiration pneumonia does not increase because of the EOF protocol after radical gastrectomy.

Traditionally, many surgeons often left nasogastric tubes in for several days until the first flatus after gastric resection. Recent studies comparing nasogastric decompression versus no decompression demonstrated that the nasogastric tube might induce pulmonary complications after gastric cancer surgery and prolong the time to first flatus with no difference in the anastomotic leakage rate [30–31]. In this study, we could immediately remove the nasogastric tube postsurgery, and only 18 patients (4.5%) required insertion of a nasogastric tube. We recommend the practice of not routinely using nasogastric tubes.

In this study, we determined several risk factors for dropout from the EOF protocol. Suni et al. [28] reported that the male gender is a risk factor due to associated smoking, which can predispose the patient to respiratory events. In this study, there were more male patients with some comorbidities than female patients (89/251 male patients, or 64.5%). Several studies have reported that age is a risk factor for dropout of the EOF protocol [22, 32]. In addition, Choi et al. [32] suggested that the extent of gastric resection, operative approach, and combined resection could be significant risk factors for dropout of the EOF protocol. These results were not different from our analysis. Therefore, we could use the EOF protocol regardless of the extent of gastric resection and surgical approach.

Conclusions

EOF can be safely implemented in patients with gastric cancer after radical gastrectomy regardless of the extent of stomach resection. The male gender, comorbidities, and intra-operative bleeding are independent risk factors for dropout from the EOF protocol.

Author Contributions Toshiki Shinohara designed the study, collected the data including patient care, analyzed the data, and drafted the manuscript. All the other authors (Maeda, Koyama, Minagawa, Hamaguchi, and Hamada) contributed to the data collection and interpretation including patient care, and critical review of the manuscript. All the authors have read and approved the final version of the manuscript.

Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration of 1975. This article does not contain any studies with animal subjects performed by any of the authors.

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

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