

Functional Evaluation for Various Methods of Gastrectomy and Reconstruction for Gastric Cancer

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Objective: This study of 45 patients aimed to retrospectively examine whether the relationships among the postoperative to preoperative body weight ratio (BWR), meal intake as a good indicator of quality of life (QOL), and absorptive kinetics from the small intestine could be expressed by the acetaminophen (AAP) concentration.

Methods: The postoperative/preoperative BWR and meal intake ratio (MIR) were evaluated in 30 patients who underwent open distal gastrectomy for advanced gastric cancer (ODG group) and 15 patients who underwent laparoscopic proximal gastrectomy for early gastric cancer (LPG group). In addition, all patients underwent functional evaluation using the AAP method. Correlation coefficients of the BWR and MIR with the plasma AAP concentration after meal intake were evaluated.

Results: There was a negative correlation between the AAP concentration at 15 min and the BWR in all patients ($r = -0.438$, $P = 0.00259$, $n = 45$) and a weak negative correlation between the AAP concentration at 15 min and the MIR ($r = -0.309$, $P = 0.0368$, $n = 45$).

Conclusions: There were some relationships between slow intestinal absorption in the early postprandial phase and the maintenance of postoperative body weight and meal intake. Namely, operative methods that maintained preoperative slow intestinal absorption were thought to be better for maintaining postoperative QOL.

Key words: functional evaluation, acetaminophen method, gastrectomy and reconstruction, quality of life, gastric cancer

INTRODUCTION

The primary functions of the stomach are to act as a reservoir, initiate the digestive process, and release its contents gradually into the duodenum to optimize digestion in the small bowel. Gastric cancer patients require various forms of gastrectomy, which is the surgical removal of a portion or all of the stomach. The anatomical changes that result after gastrectomy decrease meal intake, followed by a decrease in the amount of muscle and fat, which leads to weight loss [1]. The mechanisms of malabsorption include: 1) reduction of gastric volume; 2) rapid emptying time of the stomach [2]; 3) abnormal secretion of gastric, pancreatic, and bile juices [3]; and 4) pancreatico-cibal asynchrony [4]. However, the effects of these factors cannot be evaluated with a simple unified method because of differences in the various methods of gastric resection and reconstruction.

We have used the acetaminophen (AAP) method for postoperative functional evaluation after gastrectomy. The AAP method is a rather invasive examination

because of the need to take frequent blood samples, but it has been commonly used to indirectly investigate gastric emptying function [5, 6]. AAP is not absorbed in the stomach, but is absorbed in the duodenum, jejunum, and ileum, and this property can be used to measure gastric emptying [7, 8]. Furthermore, we have used the AAP method in patients who have undergone proximal gastrectomy to investigate the absorptive dynamics of the whole reconstructive procedure following proximal gastrectomy [9, 10].

This study aimed to examine whether the relationships among the postoperative to preoperative body weight ratio, meal intake as a good indicator of quality of life (QOL), and absorptive kinetics from the small intestine could be expressed by the AAP concentration. Namely, attempts were made to identify factors that should be considered to maintain better postoperative QOL.

PATIENTS AND METHODS

Study population

This study evaluated 30 patients who underwent

Table 1 Characteristics of patients according to type of reconstruction

	1/3B1	1/3RY	1/5RY	OTG	L-1/2DT	L-1/2JIP	L-TG
Age (years)	64.9 ± 3.1	68.9 ± 6.5	65.8 ± 7.4	66.8 ± 8.6	68.6 ± 7.9	68.4 ± 8.4	67.2 ± 7.6
Sex (male:female)	8:2	7:3	4:1	3:2	4:1	3:2	3:2
Stage							
I	8	6	3	3	4	5	4
II	2	3	2	1	1	0	1
III	0	1	0	1	0	0	0
IV	0	0	0	0	0	0	0
Administration of anti-cancer drug (cases)	2	3	2	2	1	0	1

Table 2 Questionnaire survey of postoperative body ang meal intake

1. Please state your body weight at present. _____ Kg
2. Please put a circle around the number below that fits your present postoperative whole amount of meal intake per day compared to your preoperative whole meal intake.
1) 20%
2) 40%
3) 60%
4) 80%
5) 100%
6) Other _____%

open distal gastrectomy (ODG), including 5 patients who underwent total gastrectomy for advanced gastric cancer between August 2006 and March 2012 (ODG group) and 15 patients who underwent laparoscopic proximal gastrectomy (LPG), including 5 patients who underwent laparoscopic total gastrectomy for early gastric cancer between April 2011 and June 2016 (LPG group). The ODG group included selected cases that underwent D2 lymph node dissection based on a preoperative diagnosis of advanced gastric cancer and stage II, 10 patients who underwent distal 2/3 gastrectomy with Billroth 1 reconstruction (1/3B1), 5 patients who underwent total gastrectomy with Roux-en-Y reconstruction (OTG) between August 2006 and March 2009, 10 patients who underwent 2/3 distal gastrectomy with Roux-en-Y reconstruction (1/3RY), and 5 patients who underwent 4/5 distal gastrectomy with Roux-en-Y reconstruction (1/5RY) between April 2008 and March 2012. The LPG group included 5 patients who underwent laparoscopic proximal 1/2 gastrectomy with double-tract reconstruction (1/2L-DT), 5 patients who underwent laparoscopic proximal 1/2 gastrectomy with jejunal interposition reconstruction (1/2L-JIP), and 5 patients who underwent laparoscopic total gastrectomy with Roux-en-Y reconstruction (L-TG) (Table 1). Patients in the LPG group underwent D1 + lymph node dissection (dissection of lymph node

stations 7, 8a, 9, and 11p, in addition to the perigastric nodes). The hepatic and pyloric branches of the vagal nerve were routinely preserved, but preservation of the celiac branch was not considered.

Questionnaire survey

The postoperative/preoperative body weight ratio (BWR) and the postoperative/preoperative meal intake ratio (MIR) were evaluated at 12 months postoperatively using an in-house questionnaire. The MIR was approximated as the mean of the whole meal intake per day compared to the preoperative intake (Table 2).

Functional evaluation

In addition, functional evaluation using the AAP method was performed for patients who were being regularly followed-up at our hospital and agreed to be involved in the study at 12 months after surgery. Furthermore, patients with diabetes mellitus preoperatively were excluded, and no patients were administered any drugs that significantly affected peristaltic gastrointestinal activity.

The course of intestinal absorption and gastric non-absorbable stasis was investigated with AAP in 30 patients in the ODG group and 15 patients in the LPG group. Patients swallowed an alimentary liquid (200 ml of Ensure liquid mixed[®]; Meiji, Tokyo, Japan) con-

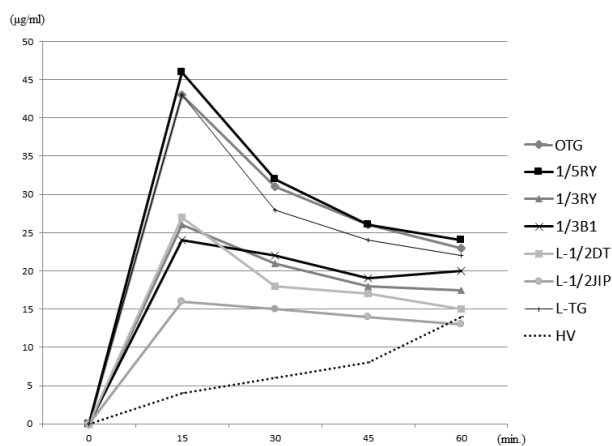


Fig. 1 Changes in plasma acetaminophen concentrations in the seven groups

The emptying test using the AAP method shows that plasma AAP concentrations in the TG, 1/5RY, and L-TG groups are markedly increased 15 and 30 min after oral administration, while increases in the 1/3B1, 1/3RY, and L1/2DT groups are gradual, with the increase in the L-1/2JIP group being the most gradual.

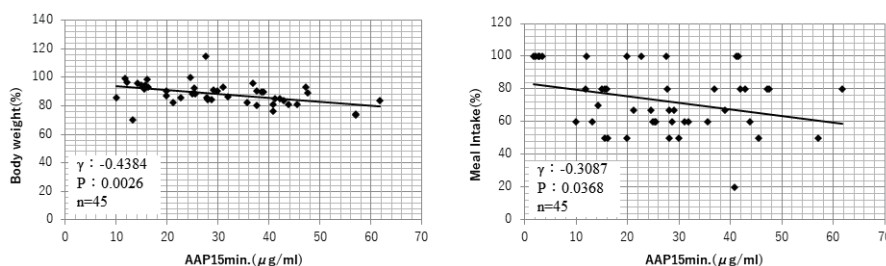


Fig. 2 Correlations between the acetaminophen concentration at 15 min and the postoperative/preoperative body weight and meal intake ratio.

There is a negative correlation between the AAP concentration at 15 min and the postoperative/preoperative body weight ratio in all patients ($r = -0.438$, $P = 0.00259$, $n = 45$) and a weak negative correlation between the AAP concentration at 15 min and the postoperative/preoperative meal intake ratio in all patients ($r = -0.309$, $P = 0.0368$, $n = 45$).

taining 1.5 g of AAP, and the concentration of AAP in the blood taken from a cubital vein was measured every 15 min for 60 min with the patient in the supine position. According to Headings' original method, the amount of AAP given was 1.5 g.

Although background characteristics differed between ODG for preoperative stage II cases and LPG for early gastric cancer cases (Table 1), the relationships among postoperative body weight, meal intake, and the AAP concentration were examined. Correlation coefficients between BWR/MIR and plasma AAP concentrations at 15 min, 30 min, 45 min, and 60 min after meal intake were evaluated and in all patients who underwent AAP concentration measurements.

Ethics approval

This study protocol was approved by the Human Ethics Review Committee of Osaka Medical College (No. 371) and Tokai University, School of Medicine (No. 14R043). Informed consent was obtained from each enrolled patient before study entry in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using Statcel 3 software (OMS Publishing Inc., Tokorozawa, Japan). Student's *t*-test and the χ^2 test were used for comparisons. Values of $P < 0.05$ were considered significant. Pearson's correlation coefficient tests were used to evaluate correlations between the AAP value and BWR/MIR.

RESULTS

Patients' characteristics

All patients completed the questionnaires on digestive function. Patient demographics stratified according to surgical procedure are presented in Table 1. On follow-up 18 months after surgery, no evidence of recurrence was seen in any of the patients. Severe postoperative emptying disturbances occurred in 1 case before discharge from the hospital and were addressed by appropriate treatment, such as endoscopic balloon dilatation. Thus, no complications were seen in any of the patients by 1 year postoperatively.

Emptying and absorption test

The emptying test using the AAP method demonstrated that plasma AAP concentration in the TG, 1/5RY, and L-TG groups was markedly increased 15 and 30 min after oral administration, whereas increases in the 1/3B1, 1/3RY, and L1/2DT groups were gradual, with the increase in the L-1/2JIP group identified as the most gradual (Fig. 1). Significant differences were apparent between the TG, 1/5RY, and L-TG groups and the other groups at 15 min after oral administration. Although significant differences were seen between the L-1/2DT and L-1/2JIP groups, the difference was not significant between the 1/3B1 and 1/3RY groups and the L-1/2JIP group ($P < 0.10$). For reference, the emptying patterns of five healthy volunteers (HVs) (five male authors, mean age, 47.5 years) were compared to those of other groups. Significant

differences between the HV group and the other seven groups were seen from 0 to 30 min after AAP administration.

Pearson's correlation coefficient tests

Pearson's correlation coefficient tests were used to evaluate correlations between the AAP concentrations at 15 min, 30 min, 45 min, and 60 min and the BWR in all patients (Fig. 2) ($n = 45$): $r = -0.4384$, $P = 0.00259$, (15 min); $r = -0.3475$, $P = 0.0193$ (30 min); $r = -0.3207$, $P = 0.0317$ (45 min); and $r = -0.3387$, $P = 0.0229$ (60 min). Similarly, results for the MIR were ($n = 45$): $r = -0.3087$, $P = 0.0368$ (15 min); $r = -0.09632$, $P = 0.5291$ (30 min); $r = -0.0451$, $P = 0.7688$ (45 min); and $r = -0.0155$, $P = 0.9193$ (60 min). A negative correlation was identified between the AAP concentration at 15 min and the BWR, and a weak negative correlation was seen between the AAP concentration at 15 min and the MIR. As mentioned above, the dose of AAP was 1.5 g, according to Headings' original method, but it has recently been suggested that the dose of AAP should be 20 mg/kg. Had there been a negative correlation between postoperative body weight and AAP concentration, the present results would be meaningless; however, there was no relationship between them ($n = 45$; $r = -0.1341$, $P = 0.3796$).

DISCUSSION

Currently, resection procedures for gastric cancer differ according to the tumor location and stage, and reconstructive procedures differ between institutions [11]. Various investigations have sought to identify the best procedures [12-14].

In our previous analysis of open surgery for early gastric cancer, reduction of the extent of gastrectomy and preservation of the vagal branches and of the pyloric ring were associated with better QOL [9]. In particular, we think that minimizing the extent of gastrectomy is the most important factor [8, 15, 16]. Furthermore, we reported that, following open and laparoscopic distal gastrectomies [8, 15] and proximal gastrectomy [16], the BWR and MIR showed better preservation in patients with a larger stomach remnant regardless of the reconstruction. Following LPG, the BWR was affected by the reconstruction when the remnant stomach was the same size [10].

Furthermore, S-1 has been standard postoperative adjuvant chemotherapy for advanced gastric cancer in Japan [17]. Aoyama *et al.* [18] demonstrated that weight loss was the most important risk factor for compliance with S-1 adjuvant chemotherapy in patients with stage II or III gastric cancer who underwent D2 gastrectomy. To improve drug compliance and survival, maintaining weight before starting adjuvant S-1 chemotherapy is key. Thus, 21 patients with early enteral feeding and 22 patients without early enteral feeding who underwent open TG and were R0-resectable cases were compared [19]. No significant differences were seen between the two groups in blood laboratory data and the rate of complications. However, in patients with complications, lymphocyte counts 7 days after operation and the BWR at discharge were significantly higher in the early enteral feeding group than in the group without early enteral feeding. It was concluded that early enteral feeding should be given especially

for patients in whom severe disease is possible and avoidance of TPN is desirable, and efforts to reduce weight loss should be made for immunostimulation. In these ways, the significance of and the means to reduce weight loss have become obvious.

Various disturbances that decrease QOL can be seen after gastrectomy [1-4]. Weight loss and loss of appetite are particularly apparent and marked, and they are thought to be among the most objective and easily detectable disturbances. In the present study, the parameters of better operative procedures, irrespective of the stage or reconstructive method, were studied using body weight and meal intake. AAP concentrations at 15 min were found to correlate negatively with better QOL. Since fluid meals are promptly emptied from or flow in the remnant stomach in the postgastrectomy state, there were significant differences in the AAP concentration at the earlier postprandial time among the operative methods. There was only a weak negative correlation between the AAP concentration at 15 min and meal intake in all patients. The reason for this might be the effects of other emotional factors, such as sense of satisfaction with the operation or adjuvant chemotherapy with S-1. If body weight was one of the best parameters, a relationship might exist between absorption speed from the small intestine and body weight. Brener *et al.* [20] reported that the normal stomach slowed its emptying rate as the nutrient content increased in caloric concentration, with the result that calories were delivered to the duodenum at a constant rate through the feedback mechanism from the intestine. Conversely, if the postoperative emptying speed was close to the preoperative one, the nutritional condition could be maintained at the preoperative physiological condition. Despite the kinetics of hormonal secretion, postoperative complications such as reflux esophagitis, anastomotic stricture, and postprandial symptoms have to be investigated. Studying the operative methods that show relatively slow intestinal absorption after immediate meal intake might represent the first step to identifying better reconstructive methods. Furthermore, if appropriately slowly absorbed meals were developed for each operation, the postoperative nutritional condition of patients could be improved.

Some weaknesses of this study must be considered. The sample size was relatively small, and the AAP method is primarily an indirect investigation of gastric emptying function. Furthermore, the dose of AAP was 1.5 g, according to Headings' original method, but it has recently been suggested that the dose of AAP should be 20 mg/kg. Heading *et al.* [5] reported that there were significant correlations between the half time of gastric emptying and both the maximum plasma paracetamol (AAP) concentrations and the time taken to reach the peak. As shown in Fig.1, AAP concentrations in all groups promptly reached the peak at 15 minutes, so that the gastric emptying rate was associated with the AAP concentrations at 15 minutes. Namely, for gastrectomized patients, the effects of body weight on plasma AAP concentrations may be small. Thus, it was thought that the ease of intestinal absorption could be evaluated, and the intestinal absorptive condition of each operative method could be identified.

In conclusion, there were some relationships be-

tween slow intestinal absorption in the early postprandial phase and the maintenance of postoperative body weight and meal intake. Namely, operative methods that maintained preoperative slow intestinal absorption were thought to be better for maintaining postoperative QOL. However, this does not apply to cases showing severe emptying disturbances, such as anastomotic stenosis, at the time of examination.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

ABBREVIATIONS

AAP: acetaminophen

1/3B1: distal 2/3 gastrectomy with Billroth 1 reconstruction

BWR: postoperative/preoperative body weight ratio

1/2L-DT: laparoscopic proximal 1/2 gastrectomy with double tract reconstruction

1/2L-JIP: laparoscopic proximal 1/2 gastrectomy with jejunal interposition reconstruction

LPG: laparoscopic proximal gastrectomy

L-TG: laparoscopic total gastrectomy with Roux-en-Y reconstruction

MIR: postoperative/preoperative meal intake ratio

ODG: open distal gastrectomy

OTG: open total gastrectomy with Roux-en-Y reconstruction

QOL: quality of life

1/3RY: 2/3 distal gastrectomy with Roux-en-Y reconstruction

1/5RY: 4/5 distal gastrectomy with Roux-en-Y reconstruction

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