Original article

Initial results of laparoscopic proximal gastrectomy with double-tract reconstruction using oblique jejunogastrostomy method on the long-term outcome of postoperative nutritional status: a propensity score-matched study

Kotaro Kimura[1)](ORCID 0000-0002-3379-3890), Yuma Ebihara[1)2)], Kimitaka Tanaka[1)], Yoshitsugu Nakanishi[1)], Toshimichi Asano[1)], Takehiro Noji[1)], Yo Kurashima[1)], Soichi Murakami[1)], Toru Nakamura[1)], Takahiro Tsuchikawa[1)], Keisuke Okamura[1)], Toshiaki Shichinohe[1)], Satoshi Hirano[1)]

[1)]Department of Gastroenterological Surgery II, Hokkaido University Faculty of Medicine, North 15 West 7, Kita-ku, Sapporo, Hokkaido, 0608638, Japan.

[2)]Division of Minimally Invasive Surgery, Hokkaido University Hospital. North 15 West 7, Kita-ku, Sapporo, Hokkaido, 0608638, Japan.

Corresponding author: Yuma Ebihara, Department of Gastroenterological Surgery II, Hokkaido University Faculty of Medicine, North 15 West 7, Kita-ku, Sapporo, Hokkaido, , 0608638, Japan

Tel: +81 11 706 7714 Fax: +81 11 706 7158

Email: yuma-ebi@wc4.so-net.ne.jp

Running head: Comparison between LPG with DTR using OJG method and LTG with RY reconstruction for gastric cancer

Word count: 1757 words

AUTHOR CONTRIBUTIONS

Study conception and design: Kotaro Kimura and Yuma Ebihara.

Acquisition of data: Kotaro Kimura and Yuma Ebihara.

Analysis and interpretation of data: Kotaro Kimura.

Drafting of manuscript: Yuma Ebihara.

Critical revision of manuscript: Yuma Ebihara, Kimitaka Tanaka, Yoshitsugu Nakanishi, Toshimichi Asano, Takehiro Noji, Yo Kurashima, Soichi Murakami, Toru Nakamura, Takahiro Tsuchikawa, Keisuke Okamura, Toshiaki Shichinohe, and Satoshi Hirano.

Declarations

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hokkaido University Hospital (Approval No. 015-0104)

CONSENT TO PARTICIPATE

The requirement for informed consent from patients was waived because of its retrospective design.

CONSENT FOR PUBLICATION

The requirement for informed consent for publication was waived because of its retrospective design.

AVAILABILITY OF DATA AND MATERIALS

All data in the study are available on request from the corresponding author.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

Abstract

Backgrounds: To evaluate the long-term nutritional state of patients with gastric cancer who underwent laparoscopic proximal gastrectomy with double-tract reconstruction (LPG-DTR) using oblique jejunogastrostomy method (OJG).

Methods: Medical records of 38 patients who underwent LPG-DTR using OJG (21 patients) or laparoscopic total gastrectomy with Roux-en-Y reconstruction (LTG-RY) (17 patients) between October 2011 and March 2018 were retrospectively reviewed. In these patients, clinicopathological variables were analyzed using propensity score matching for age, sex, body mass index, American Society of Anesthesiologists physical state, clinical stage, and lymph node dissection. Operative outcomes and postoperative nutritional status were compared between the two groups.

Results: A total of 16 patients were matched to analyze the LPG-DTR and LTG-RY groups. The serum hemoglobin, total protein, and albumin levels at 12 months postoperatively (p = 0.008, 0.034, 0.049) and serum hemoglobin level at 24 months (p = 0.025) in the LPG-DTR group was significantly superior to those in the LTG-RY group.

Conclusions: The postoperative nutritional status as long-term outcomes of patients who underwent LPG-DTR using OJG was significantly superior to those who underwent LTG-RY. The results hereby presented suggest that LPG-DTR using OJG for gastric cancer produces better postoperative nutritional status.

Keywords: laparoscopic proximal gastrectomy, gastric cancer, postoperative nutritional status, propensity score matching

Introduction

The number of early-stage gastric cancers at the upper third of the stomach has been recently increasing in both Western and Asian countries [1-4]. In some reports, some groups have found evidence of better survival in laparoscopic proximal gastrectomy (LPG) for upper early gastric cancer. Some studies have demonstrated that limited LPG with regional lymph node dissection could achieve oncological outcomes equivalent to those of total gastrectomy, at least in patients with upper-third gastric cancer [5-8]. Conversely, the effect of LPG on postoperative nutritional status has not been sufficiently elucidated.

In 1988, Aikou et al. reported that double-tract reconstruction (DTR) was one of the reconstruction methods for proximal gastrectomy (PG) [9]. In 1995, Uyama et al. reported a DTR method using a laparoscopic approach [10], and laparoscopic proximal gastrectomy with double-tract reconstruction (LPG-DTR) became a common reconstruction method for early-stage upper gastric cancer [11-13]. In DTR, foods can flow through the physiological route, the duodenum, but also directly to the jejunum [14], which can worsen the postoperative nutritional status.

Our previous study demonstrated that LPG-DTR using oblique jejunogastrostomy method (OJG), a modified DTR, prevents food from flowing directly into the jejunum [15]. This technique is unique because the posterior walls of the remnant stomach and jejunum are anastomosed by twisting them forward, making the anastomosis wider and allowing the jejunum to ride on the remnant stomach, resulting in a vertical food flow. As a result, food is less likely to flow into the jejunum. In this study, we first showed the long-term effect on the nutritional status of patients after LPG-DTR using OJG for gastric cancer by comparing laparoscopic total gastrectomy with Roux-en-Y reconstruction (LTG-RY).

Materials and methods

Patients

A total of 73 patients underwent LPG or LTG for gastric cancer at Hokkaido University between October 2011 and March 2018. All patients were diagnosed with gastric cancer by endoscopy, computed tomography, or endoscopic ultrasound. The Japanese Classification of Gastric Carcinoma was used for tumor staging [16].

Among these patients, 38 who underwent LPG-DTR using OJG (21 patients) or LTG-RY (17 patients) with standard lymph node dissection for gastric cancer (Stage I or II) without chemotherapy were reviewed (Figure 1). Their clinicopathological variables were analyzed using propensity score matching for age, sex, body mass index, American Society of Anesthesiologists physical state, clinical stage and range of lymph node dissection. Surgical results and postoperative outcomes were compared between the two groups. Postoperative nutritional status, including body weight and serum hemoglobin, total protein, and albumin levels, was evaluated every 3 months postoperatively. Complications were classified based on the Clavien–Dindo (CD) postoperative complication classification grade [17, 18].

Surgical procedures

The eligibility criteria for patients undergoing LPG-DTR were (1) preoperative diagnosis of clinical Stage I or II, (2) in a group of patients without lymph node metastasis (cN0), and (3) tumor located more than 5 cm distance from the angular region.

In the LPG-DTR using OJG, details of our reconstruction method have been previously described [15]. In brief, esophagojejunostomy (EJ) was performed using a functional end-to-end technique [19]. When performing our jejunogastrostomy method, OJG, a linear stapler is inserted into the greater curvature side of the remnant stomach and the antimesenteric wall of the jejunum. Then, the posterior walls of both the stomach and jejunum are then twisted anteriorly and anastomosed as shown in Figure 2a. Thus, the once the jejunum is untwisted, the jejunum rides on the remnant stomach and the anastomosis is wide and vertical (Figure 2b).

LTG-RY was broadly performed as previously described [20]. In RY reconstruction, EJ was performed using a linear stapler for an end-to-end antecolic anastomosis.

In both groups, the extent of lymph node dissection was determined according to the Japanese Gastric Cancer Association guidelines [21].

Statistical analysis

Chi-square tests for categorical variables and Student’s t-test for unpaired data for continuous variables

were performed to compare clinicopathological characteristics between the two groups. A p-value of <0.05 was considered significant. All analyses were performed using the JMP Pro version 14.0.0 software (SAS Institute Inc., Cary, NC, USA).

Results

A total of 21 patients underwent LPG-DTR and 17 underwent LTG-RY during the entire study period. Results on differences between the two groups are shown in Table 1. The mean age, male dominant, and preoperative body mass index were similar between the LPG-DTR and LTG-RY groups (70.9 ± 1.9 vs. 67.4 ± 2.7 years; p = 0.288, 85.7 vs. 82.3 %; p =0.778, 24.3 ± 0.5 vs. 22.6 ± 0.8 kg/m^2; p = 0.081, respectively). Additional surgery after an endoscopic submucosal dissection was significantly higher in the LPG-DTR than in the LTG-RY group (42.7 vs. 5.9 %; p = 0.010). In the LPG-DTR group, intraoperative blood loss was significantly less than in the LTG-RY group (8.2 ± 4.3 vs. 32.9 ± 10.4 mL; p = 0.039).

In the propensity score matching, a total of 16 patients were matched through the analysis of the LPG-DTR and LTG-RY groups. Results on differences between the two groups are shown in Table 2. In the LPG-DTR group, the operative time was significantly shorter and intraoperative blood loss was significantly less than in the LTG-RY group (294.1 ± 33.9 vs. 383.4 ± 20.7 min; p = 0.045, 6.3 ± 6.3 vs. 48.8 ± 16.8 mL; p = 0.043). No differences were found in postoperative complications (CD≥ III) and postoperative hospital stays between the LPG-DTR and LTG-RY groups (25.0 vs. 12.5 %; p = 0.522, 15.4 ± 3.3 vs. 14.6 ± 2.2 days; p = 0.852).

Figure 3 shows comparisons of postoperative nutritional states between the LPG-DTR and LTG-RY groups: body weight and serum hemoglobin, total protein, and albumin levels at 24 months postoperatively. Body weights tended to be consistently higher in the LPG-DTR group than in the LTG-RY group at 24 months postoperatively, but without significant differences (Figure 3a). The serum hemoglobin level was significantly higher in the LPG-DTR group than in the LTG-RY group at 6, 9, 12, 18, and 24 months postoperatively (99.0 ± 7.7 vs 87.4 ± 6.8 %; p = 0.013, 100.8 ± 8.3 vs 85.3 ± 4.1 %; p = 0.016, 96.7 ± 3.2 vs 88.3 ± 7.0 %; p = 0.018, 96.4 ± 3.6 vs 89.4 ± 4.0 %; p = 0.008, 99.7 ± 6.0 vs 89.6 ± 5.2 %; p = 0.025, respectively) (Figure 3b). The serum total protein level was significantly higher in the LPG-DTR group than

in the LTG-RY group at 12 months postoperatively (97.3 ± 1.8 vs. 92.4 ± 4.9 %; $p = 0.034$). However, no significant difference was observed at other time points between the LPG-DTR and LTG-RY groups, with the former group having consistently higher (Figure 3c). Serum albumin levels were significantly higher in the LPG-DTR group than in the LTG-RY group at 12 months postoperatively (97.6 ± 6.5 vs. 88.1 ± 9.2 %; $p = 0.049$). However, no significant difference was observed at other time points between the LPG-DTR and LTG-RY groups, with the former group having consistently higher (Figure 3d).

Discussion

DTR, a method developed for PG reconstruction, is known to have the advantage of allowing food to flow through the duodenum, a physiological pathway [9, 14, 22]. In fact, some previous studies demonstrated less nutritional deterioration following LPG-DTR compared to LTG. Jung et al.'s retrospective study comparing 92 patients who underwent LPG-DTR and 156 patients who underwent LTG 156 for stage 1 gastric cancer showed that LPG-DTR had shorter operative time, lower bleeding volume, and lower hemoglobin decrease at 1 or 2 years postoperatively than LTG had [23].

On the other hand, Parks. et al. reported no significant difference in serum hemoglobin, iron, albumin, total protein, and total cholesterol levels and postoperative weight changes between LPG-DTR and LTG, except for the vitamin B12 level [24]. As this study examining the nutritional impact of DTR did not adequately consider the actual food passage into the rest of the stomach and duodenum, they may have underestimated the nutritional value of DTR.

DTR is considered advantageous in terms of digestion and absorption as food passes through the remnant stomach and duodenum [25]. In fact, when stable isotope ^{13}C-labeled lipid compounds were allowed to pass through the duodenum in patients who had undergone gastrectomy, better absorption capacity and physiological status were observed [26]. Furthermore, even with DTR after PG, a large influx of food into the remnant stomach can prevent malnutrition after gastrectomy [25]. If majority of the ingested food passes directly through the jejunum, it may be similar to what is experienced after total gastrectomy. Significant weight loss and nutritional deficiencies are frequently observed in patients with LTG [27].

Our previous study reported that LPG-DTR using OJG is a safe reconstruction method and that food can flow into the duodenum [15]. Therefore, this is the first retrospective study to show long-term effects on the nutritional status of patients who underwent LPG-DTR using OJG for the treatment of gastric cancer. Results of this study showed that LPG-DTR is superior to LTG-RY in terms of operation time and intraoperative blood loss. We also demonstrated that LPG-DTR using OJG was significantly superior to LTG-RY in serum hemoglobin, total protein, and albumin levels at 12 months postoperatively and in the serum hemoglobin level at 24 months postoperatively by propensity score matching. This anastomosis method facilitates easier food passage in the remnant stomach because the posterior walls of the remnant stomach and jejunum are widened and the jejunum rides on the remnant stomach, making the food flow more vertical [15].

This study has several limitations. First, this was a retrospective, observational, non-experimental study with a comparatively small sample size. Therefore, a selection bias in study results was inevitable. Second, we should have compared conventional LPG-DTR and LPG-DTR using OJG to show the usefulness of LPG-DTR using OJG. However, since OJG has been used for all patients who underwent LPG-DTR since 2011, we were not able to compare it with the conventional LPG-DTR. Therefore, in this study, we compared LPG-DTR using OJG and LTG-RY. Third, we could not examine results of postoperative endoscopy and the proton-pump inhibitor oral intake rate in this study. Therefore, the incidence of postoperative complications was not determined. Fourth, LPG-DTR was performed by expert surgeons, whereas LTG-RY was performed by multiple surgeons. Therefore, their technique and experience levels may differ. And since LPG-DTR using OJG is done by expert surgeons, LPG-DTR using OJG may require higher technical skills than LTG-RY. Thus, a well-designed randomized controlled trial is required to validate our findings.

Conclusion

This study showed that LPG-DTR using OJG was significantly superior to LTG-RY in terms of serum hemoglobin, total protein, and albumin levels at 12 months postoperatively and serum hemoglobin level at 24 months postoperatively. We think that LPG-DTR using OJG for gastric cancer is useful in postoperative

nutritional status.

References

1. Ahn HS, Lee HJ, Yoo MW *et al.* Changes in clinicopathological features and survival after gastrectomy for gastric cancer over a 20-year period. *Br J Surg* 2011; 98: 255-260.
2. Wu H, Rusiecki JA, Zhu K, Potter J, Devesa SS. Stomach Carcinoma Incidence Patterns in the United States by Histologic Type and Anatomic Site. *Cancer Epidemiology Biomarkers & Prevention* 2009; 18: 1945-1952.
3. Steevens J, Botterweck AAM, Dirx MJM, Van Den Brandt PA, Schouten LJ. Trends in incidence of oesophageal and stomach cancer subtypes in Europe. *European Journal of Gastroenterology & Hepatology* 2009: 1.
4. Dassen AE, Lemmens VEPP, Van De Poll-Franse LV *et al.* Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: A population-based study in the Netherlands. *European Journal of Cancer* 2010; 46: 1101-1110.
5. Japanese Gastric Cancer Association. Janapease gastric cancer treatment guidelines 2014(ver.4). *Gastric Cancer* 2017; 20: 1-19.
6. Giacopuzzi S, Bencivenga M, Weindelmayer J, Verlato G, De Manzoni G. Western strategy for EGJ carcinoma. *Gastric Cancer* 2017; 20: 60-68.
7. Ahn SH, Lee JH, Park DJ, Kim HH. Comparative study of clinical outcomes between laparoscopy-assisted proximal gastrectomy (LAPG) and laparoscopy-assisted total gastrectomy (LATG) for proximal gastric cancer. *Gastric Cancer* 2013; 16: 282-289.
8. Rosa F, Quero G, Fiorillo C *et al.* Total vs proximal gastrectomy for adenocarcinoma of the upper third of the stomach: a propensity-score-matched analysis of a multicenter western experience (On behalf of the Italian Research Group for Gastric Cancer–GIRCG). *Gastric Cancer* 2018; 21: 845-852.
9. Aikou T, Natsugoe S, Shimazu H, Nishi M. Antrum preserving double tract method for reconstruction following proximal gastrectomy. *The Japanese Journal of Surgery* 1988; 18:

114-115.

10. Uyama I, Ogiwara H, Tetsuya T, Kaichiro K, Shuhei I. Laparoscopic and Minilaparotomy Proximal Gastrectomy and Esophagogastrostomy: Technique and Case Report. *Surgical Laparoscopy Endoscopy* 1995; 5: 5.
11. Ahn S-H, Jung DH, Son S-Y, Lee C-M, Park DJ, Kim H-H. Laparoscopic double-tract proximal gastrectomy for proximal early gastric cancer. *Gastric Cancer* 2014; 17: 562-570.
12. Kim DJ, Kim W. Laparoscopy-assisted Proximal Gastrectomy with Double Tract Anastomosis Is Beneficial for Vitamin B12 and Iron Absorption. *Anticancer Research* 2016; 36: 4753-4758.
13. Hong J, Qian L, Wang Y-P, Wang J, Hua L-C, Hao H-K. A novel method of delta-shaped intracorporeal double-tract reconstruction in totally laparoscopic proximal gastrectomy. *Surgical Endoscopy* 2016; 30: 2396-2403.
14. Aburatani T, Kojima K, Otsuki S *et al.* Double-tract reconstruction after laparoscopic proximal gastrectomy using detachable ENDO-PSD. *Surgical Endoscopy* 2017.
15. Tanaka K, Ebihara Y, Kurashima Y *et al.* Laparoscopic proximal gastrectomy with oblique jejunogastrostomy. *Langenbecks Arch Surg* 2017; 402: 995-1002.
16. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd, English edition. *Gastric Cancer*. 2011; 14: 101-112.
17. Clavien PA, Barkun J, de Oliveira ML *et al.* The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; 250: 187-196.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205-213.
19. Ebihara Y, Okushiba S, Kawarada Y, Kitashiro S, Katoh H. Outcome of functional end-to-end esophagojejunostomy in totally laparoscopic total gastrectomy. *Langenbeck's Archives of Surgery* 2013; 398: 475-479.

20. Kyogoku N, Ebihara Y, Shichinohe T *et al.* Circular versus linear stapling in esophagojejunostomy after laparoscopic total gastrectomy for gastric cancer: a propensity score-matched study. *Langenbecks Arch Surg* 2018; 403: 463-471.
21. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018, 5th edition. *Gastric Cancer*. 2020.
22. Fujimoto D, Taniguchi K, Kobayashi H. Double-Tract Reconstruction Designed to Allow More Food Flow to the Remnant Stomach After Laparoscopic Proximal Gastrectomy. *World Journal of Surgery* 2020.
23. Jung DH, Lee Y, Kim DW *et al.* Laparoscopic proximal gastrectomy with double tract reconstruction is superior to laparoscopic total gastrectomy for proximal early gastric cancer. *Surgical Endoscopy* 2017; 31: 3961-3969.
24. Park JY, Park KB, Kwon OK, Yu W. Comparison of laparoscopic proximal gastrectomy with double-tract reconstruction and laparoscopic total gastrectomy in terms of nutritional status or quality of life in early gastric cancer patients. *Eur J Surg Oncol* 2018; 44: 1963-1970.
25. Yamashita K, Iwatsuki M, Koga Y *et al.* Preservation of physiological passage through the remnant stomach prevents postoperative malnutrition after proximal gastrectomy with double tract reconstruction. *Surgery Today* 2019; 49: 748-754.
26. Takase M, Sumiyama Y, Nagao J. Quantitative evaluation of reconstruction methods after gastrectomy using a new type of examination: digestion and absorption test with stable isotope 13 C-labeled lipid compound. *Gastric Cancer* 2003; 6: 134-141.
27. Kosuga T, Hiki N, Nunobe S *et al.* Feasibility and Nutritional Impact of Laparoscopy-assisted Subtotal Gastrectomy for Early Gastric Cancer in the Upper Stomach. *Annals of Surgical Oncology* 2014; 21: 2028-2035.

Figure Legends

Figure 1：Flow diagram of the study: Between October 2011 and March 2018 at Hokkaido University, 73 patients underwent LPG or LTG for gastric cancer. Among these patients, 38 patients who underwent LPG with DTR (21 patients) or LTG with RY (17 patients) with standard lymph node dissection for gastric cancer (Stage I or II) without chemotherapy were reviewed. *LPG* laparoscopic proximal gastrectomy, *LTG* laparoscopic total gastrectomy, *DTR* double-tract reconstruction, *RY* Roux-en-Y reconstruction

Figure 2 : Feature of our reconstruction method: (a) The posterior walls of both the stomach and jejunum (arrow) are then twisted anteriorly and anastomosed. (b) The once the jejunum is untwisted, the jejunum rides on the remnant stomach and the anastomosis is wide and vertical.

Figure 3 : Comparisons of postoperative nutritional states between LPG-DTR and LTG-RY groups: (a) body weight, (b) serum hemoglobin, (c) total protein, and (d) albumin levels. All postoperative data were presented as values (mean ± SE) relative to preoperative data. * p <0.05, significant. M: month postoperatively

Figure.1: Patients selection

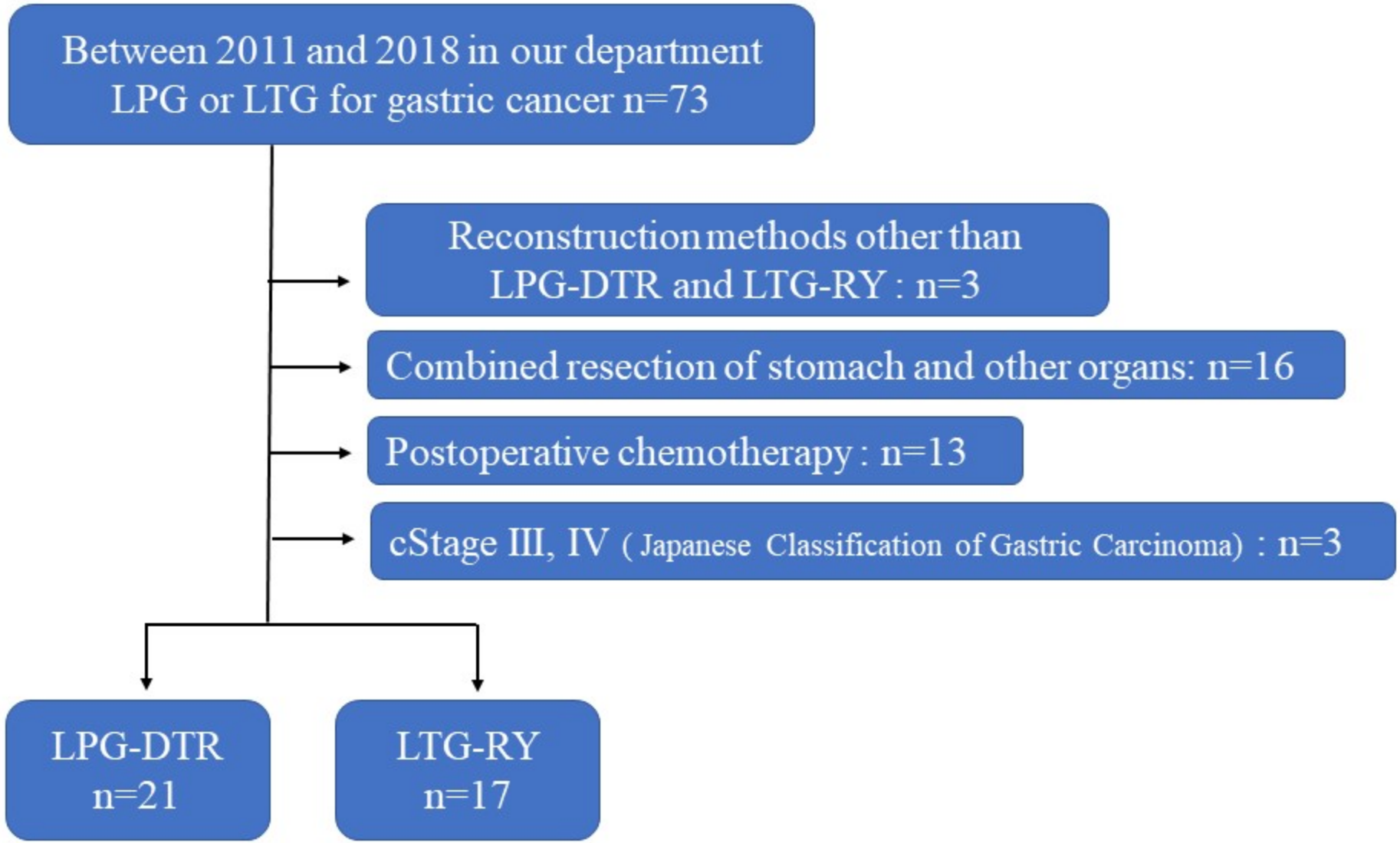


Figure.2: Feature of our reconstruction method

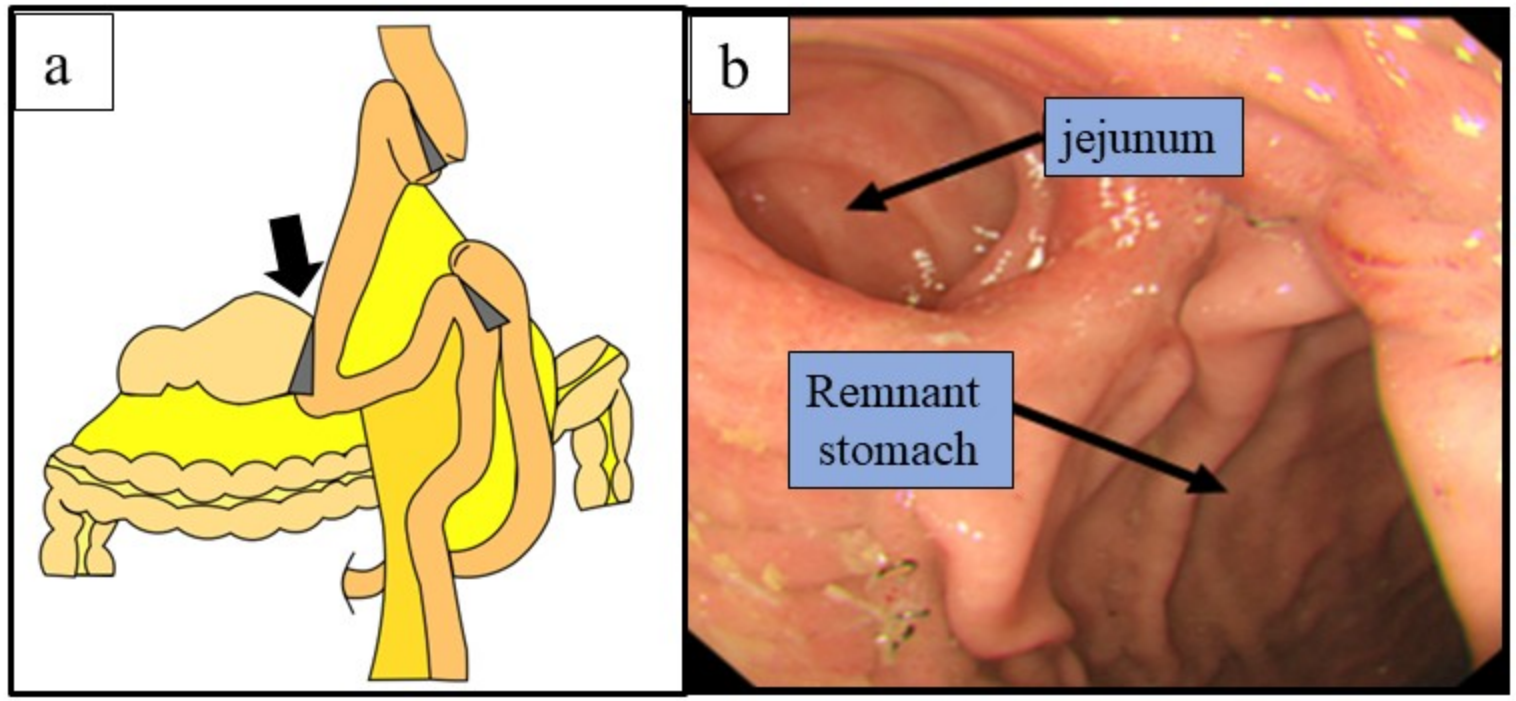
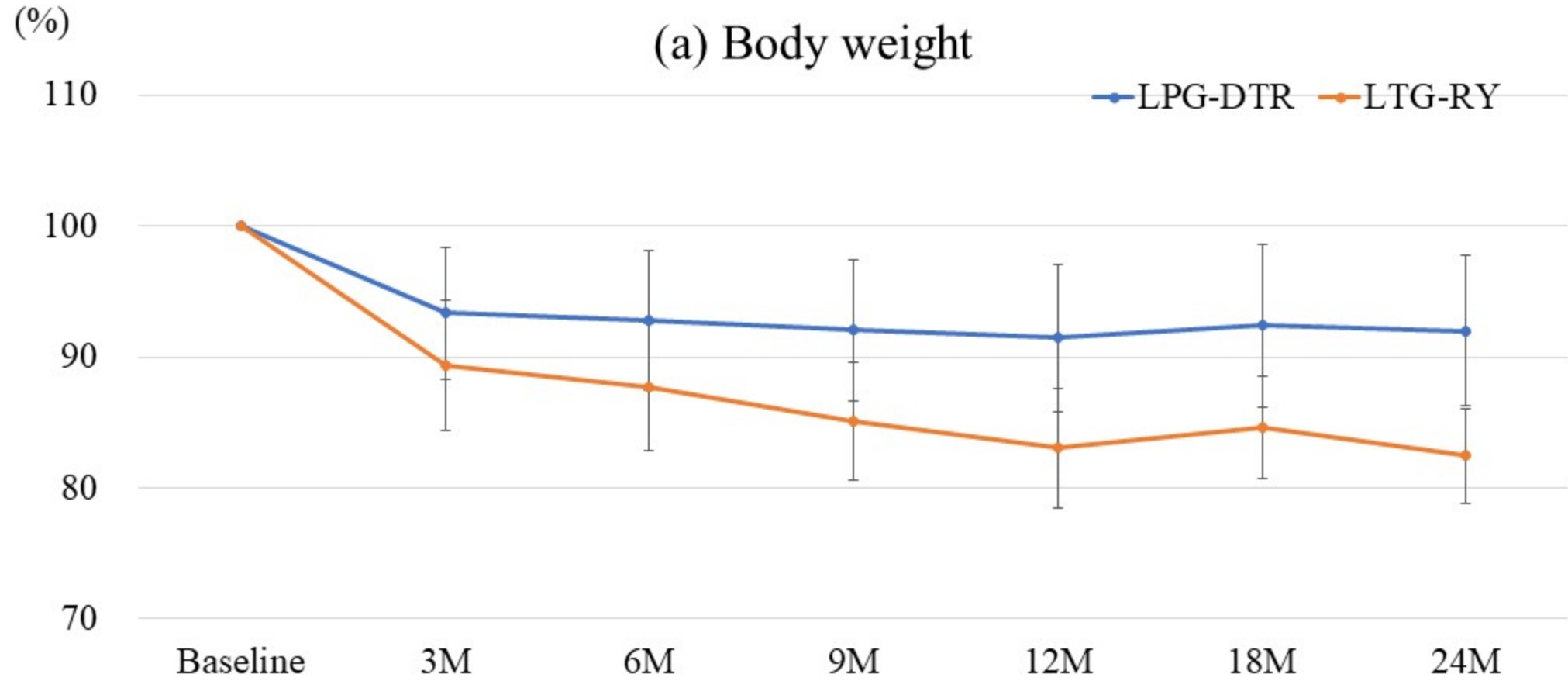
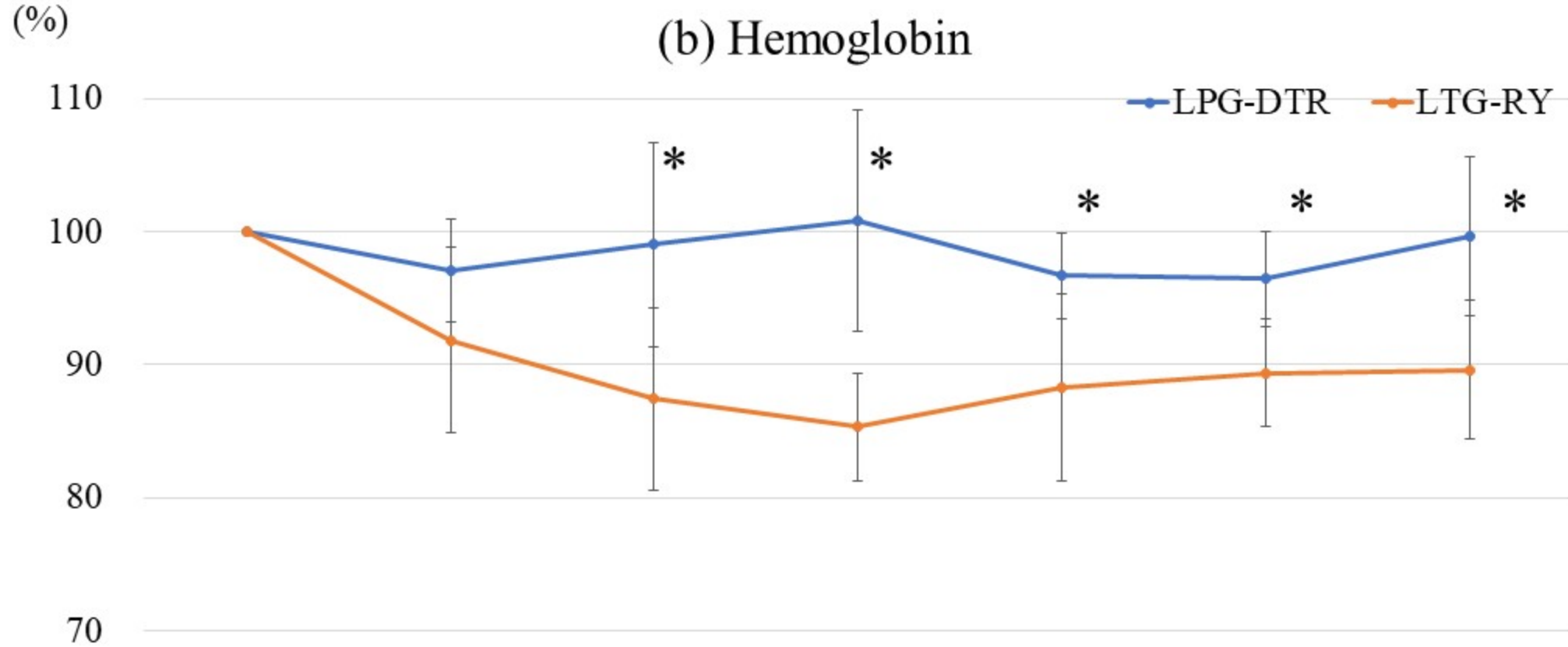


Figure.3: Comparisons of postoperative nutritional states between LPG-DTR and LTG-RY



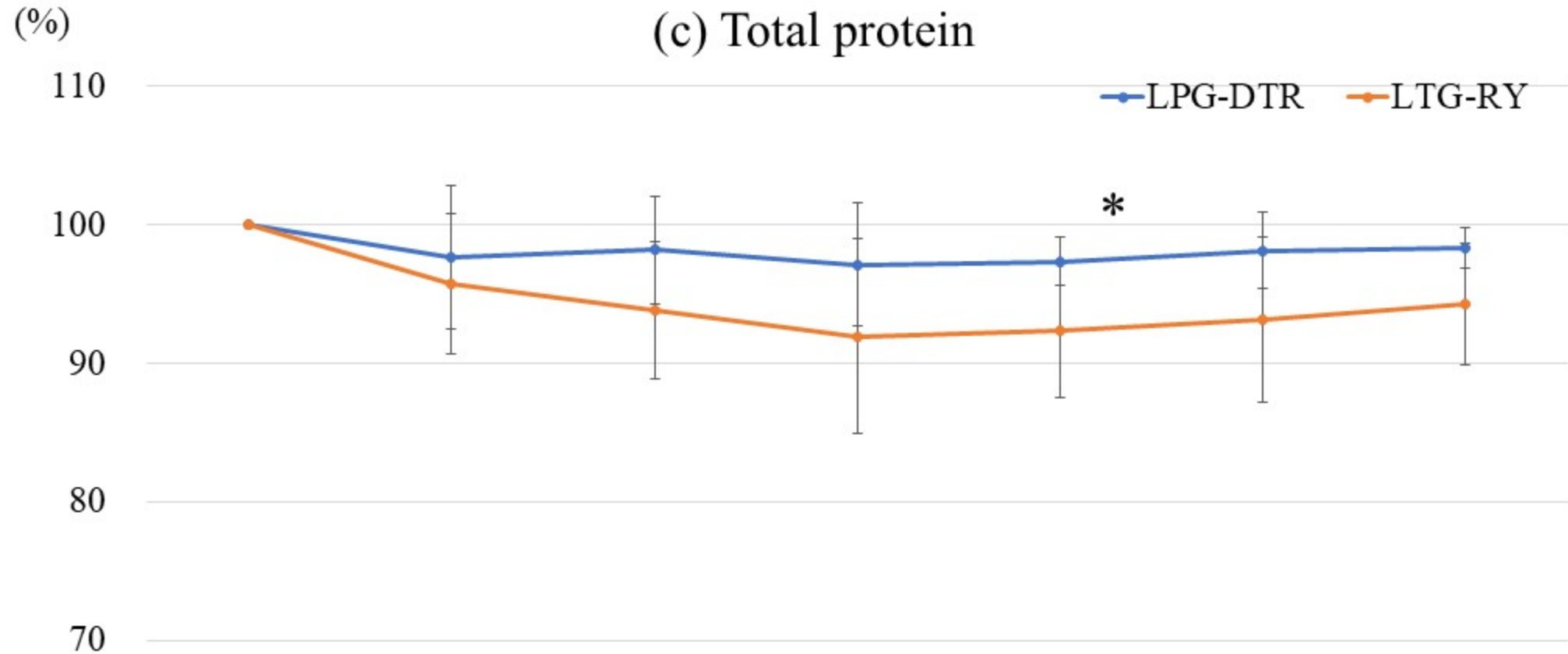
	Baseline	3M	6M	9M	12M	18M	24M
LPG-DTR	100 (n=8)	93.3 ± 5.0 (n=8)	92.8 ± 5.4 (n=7)	92.0 ± 5.4 (n=6)	91.5 ± 5.6 (n=7)	92.4 ± 6.2 (n=7)	92.0 ± 5.7 (n=6)
LTG-RY	100 (n=8)	89.4 ± 5.0 (n=7)	87.7 ± 4.9 (n=7)	85.1 ± 4.5 (n=6)	83.0 ± 3.9 (n=7)	84.6 ± 3.9 (n=6)	82.4 ± 3.7 (n=4)
P-value	-	0.125	0.459	0.275	0.239	0.365	0.412

Figure.3: Comparisons of postoperative nutritional states between LPG-DTR and LTG-RY



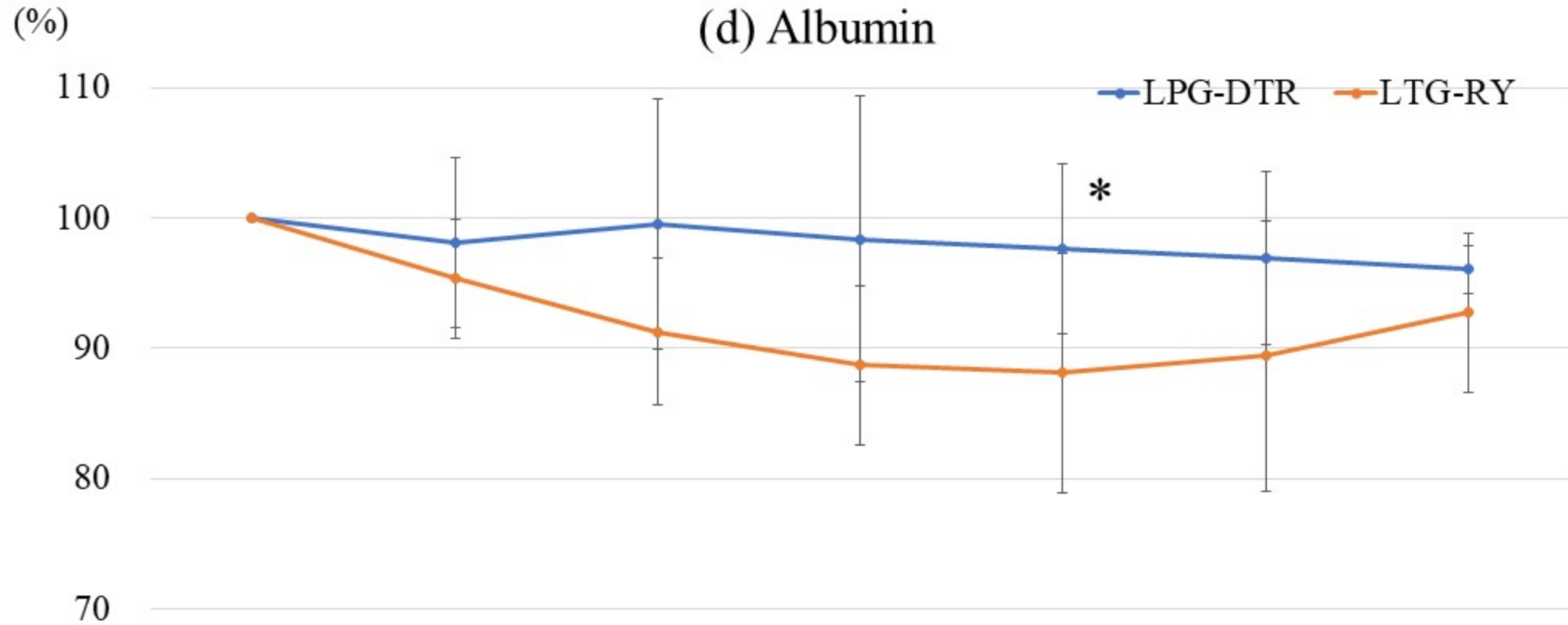
	Baseline	3M	6M	9M	12M	18M	24M
LPG-DTR	100 (n=8)	97.1 ± 3.9 (n=8)	99.0 ± 7.7 (n=8)	100.8 ± 8.3 (n=5)	96.7 ± 3.2 (n=7)	96.4 ± 3.6 (n=7)	99.7 ± 6.0 (n=6)
LTG-RY	100 (n=8)	91.9 ± 7.0 (n=8)	87.4 ± 6.8 (n=7)	85.3 ± 4.1 (n=6)	88.3 ± 7.0 (n=8)	89.4 ± 4.0 (n=7)	89.6 ± 5.2 (n=5)
P-value	-	0.113	0.013	0.016	0.018	0.008	0.025

Figure.3: Comparisons of postoperative nutritional states between LPG-DTR and LTG-RY



	Baseline	3M	6M	9M	12M	18M	24M
LPG-DTR	100 (n=8)	97.7 ± 5.2 (n=8)	98.2 ± 3.9 (n=8)	97.2 ± 4.4 (n=5)	97.3 ± 1.8 (n=7)	98.1 ± 2.7 (n=7)	98.4 ± 1.5 (n=6)
LTG-RY	100 (n=8)	95.7 ± 5.1 (n=8)	93.9 ± 5.0 (n=7)	92.0 ± 7.0 (n=6)	92.4 ± 4.9 (n=8)	93.2 ± 6.0 (n=7)	94.3 ± 4.4 (n=5)
P-value	-	0.486	0.112	0.211	0.034	0.101	0.140

Figure.3: Comparisons of postoperative nutritional states between LPG-DTR and LTG-RY



	Baseline	3M	6M	9M	12M	18M	24M
LPG-DTR	100 (n=8)	98.1 ± 6.5 (n=7)	99.5 ± 9.6 (n=8)	98.4 ± 11.0 (n=5)	97.6 ± 6.5 (n=7)	96.9 ± 6.7 (n=7)	96.0 ± 1.9 (n=6)
LTG-RY	100 (n=8)	95.4 ± 4.6 (n=8)	91.3 ± 5.6 (n=7)	88.7 ± 6.1 (n=5)	88.1 ± 9.2 (n=8)	89.4 ± 10.4 (n=7)	92.7 ± 6.1 (n=5)
P-value	-	0.413	0.080	0.170	0.049	0.166	0.347