ORIGINAL ARTICLE

Prognostic nutritional index is a prognostic factor for patients with gastric cancer and esophagogastric junction cancer undergoing proximal gastrectomy with esophagogastrostomy by the double-flap technique: A secondary analysis of the rD-FLAP Study

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Competing Interests

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Abstract

Purpose: Although proximal gastrectomy (PG) is commonly used in patients with upper gastric cancer (GC) and esophagogastric junction (EGJ) cancer, long-term prognostic factors in these patients are poorly understood. The double-flap technique (DFT) is an esophagogastrostomy with anti-reflux mechanism after PG; we previously conducted a multicenter retrospective study (rD-FLAP) to evaluate the short-term outcomes of DFT reconstruction. Here, we evaluated the long-term prognostic factors in patients with upper GC and EGJ cancer.

Methods: The study was conducted as a secondary analysis of the rD-FLAP Study, which enrolled patients who underwent PG with DFT reconstruction, irrespective of disease type, between January 1996 and December 2015.

Results: A total of 509 GC and EGJ cancer patients were enrolled. Univariate and multivariate analyses of overall survival demonstrated that a preoperative prognostic nutritional index (PNI) <45 (p<0.001, hazard ratio [HR]: 3.59, 95% confidential interval [CI]: 1.93-6.67) was an independent poor prognostic factor alongside pathological T factor ([pT] ≥2) (p=0.010, HR: 2.29, 95% CI: 1.22-4.30) and pathological N factor ([pN] ≥1) (p=0.001, HR: 3.27, 95% CI: 1.66-6.46). In patients with preoperative PNI ≥45, PNI change (<90%) at 1-year follow-up (p=0.019, HR: 2.54, 95%CI: 1.16-5.54) was an independent poor prognostic factor, for which operation time (≥300 min) and blood loss (≥200 mL) were independent risk factors. No independent prognostic factors were identified in patients with preoperative PNI <45.

Conclusions: PNI is a prognostic factor in upper GC and EGJ cancer patients. Preoperative nutritional enhancement and postoperative nutritional maintenance are important for prognostic improvement in these patients.

Key words

Double-flap technique; Gastric cancer; Prognostic factor; Prognostic nutritional index; Proximal gastrectomy.

Introduction

The overall incidence of gastric cancer (GC) is declining in some countries, including Japan, because of *Helicobacter pylori* eradication, whereas the rates of GC located in the upper third of the stomach and esophagogastric junction (EGJ) cancer are increasing [1]. The Japanese Gastric Cancer Treatment Guidelines (5th edition) describe proximal gastrectomy (PG) as a procedure that can be considered for early upper GC (cT1N0) and EGJ cancer (any stage) along with total gastrectomy (TG) [2]. Many recent reports suggest that PG is superior to TG in terms of maintenance of nutrition and quality of life (QOL) after surgery if the incidence of postoperative complications such as anastomotic strictures and reflux esophagitis are properly suppressed. In contrast, the survival rates of early upper GC and EGJ cancer after PG are equivalent to that of TG, and based on this background, PG is now selected more often for treating upper GC and EGJ cancer [3-7].

The double-flap technique (DFT) [8-10], the side overlap with fundoplication by Yamashita (SOFY) [11], tube-like stomach [12], jejunal interposition [13], jejunal pouch interposition [14], and double-tract (DT) [15] are representative post-PG reconstruction procedures. However, no standard procedures have yet been determined, primarily due to issues associated with gastroesophageal reflux disease after surgery, which can lead to a substantial decline in postoperative QOL [16]. The DFT is characterized by covering of the distal esophagus and anastomosis with a seromuscular double-flap created at the anterior wall of the gastric remnant. This technique provides strong anti-reflux activity, although anastomotic stricture is a potential postoperative complication requiring careful observation. We previously conducted a large-scale multicenter retrospective study (rD-FLAP) in which the incidence of reflux esophagitis

at 1-year follow-up was 10.6% for any grade Los Angeles Classification (LA) and 6.0% for LA grade ≥B. The incidence of anastomotic leakage and strictures was 1.5% and 5.5%, respectively, which were considered acceptable as real-world data [17]. Although many studies examining reconstruction procedures after PG, including the rD-FLAP Study, have mentioned the usefulness based on short-term outcomes, long-term outcomes and prognostic factors for GC or EGJ patients who underwent PG are poorly understood.

As a secondary analysis of the rD-FLAP Study, in the present study, we identified prognostic factors for overall survival (OS) in GC and EGJ cancer patients who underwent PG with DFT reconstruction. The study population was limited to patients with GC and EGJ cancer, although other diseases such as gastric submucosal tumors and benign tumors were also included in the original rD-FLAP Study, in which the incidence of reflux esophagitis and anastomosis-related complications were the primary and secondary endpoints. We believe that the results of this study provide useful suggestions for further improving the long-term prognosis of patients with upper GC and EGJ cancer for whom PG is indicated.

Materials and Methods

Study design

This was a multicenter retrospective study conducted as a secondary analysis of the rD-FLAP Study, which involved 18 participating institutions and enrolled patients who underwent PG with DFT reconstruction irrespective of disease type and surgical approach (open or laparoscopic) between January 1996 and December 2015. In this study, the target population was limited to patients with GC or EGJ cancer because it

assessed prognostic factors for OS.

The study conformed to the provisions of the Declaration of Helsinki, and the protocol was approved by the Okayama University Hospital Institutional Review Board (approval no. 1705-023) and the institutional review boards of each participating institution.

Medical records

Preoperative patient background data collected included age, sex, body mass index (BMI), and prognostic nutritional index (PNI) which was calculated by 10 × serum albumin value (g/dL) + 0.005 × lymphocyte count (/mm^3) [18], and tumor-related factors included disease type (GC/EGJ cancer), pathological T factor (pT), pathological N factor (pN), and histology (differentiated [Dif]/undifferentiated [Undif]), which were described according to the third English version of the Japanese Classification of Gastric Carcinoma [19]. Surgical factors included institutional experience with PG with DFT reconstruction, extent of lymph node dissection (D0, D1/D1+), operation time, blood loss, preservation of celiac branch and hepatic branch nerves, surgical approach (open/laparoscopic), location of anastomosis (intra-abdomen/mediastinum, intra-thorax), postoperative complications assessed according to the Clavien-Dindo classification [20], anastomosis-related complications such as leakage, strictures, and bleeding, and postoperative length of hospital stay. Patient status at 1-year follow-up was evaluated based on BMI and PNI changes relative to preoperative values, use of proton-pump inhibitors (PPIs) or H2 blockers, and the incidence of reflux esophagitis, which was evaluated according to the LA classification system [21].

Statistical analysis

Statistical analyses were conducted using JMP software, ver. 14.2 (SAS Institute, Cary, NC, USA). The Pearson chi-square test or Fisher exact test was used for categorical variables, and the Mann-Whitney *U* test or Student's *t* test was used for continuous variables. The Kaplan-Meier method was used to estimate OS, and the log-rank test was used for comparisons of OS. Cox proportional hazards regression models and logistic regression models were used for multivariate analysis of survival data and binary variables, respectively. A probability (*p*) less than 0.05 was considered statistically significant.

Results

Clinicopathological features

A total of 509 patients were finally enrolled in this study after exclusion of 37 of 546 patients registered in the original rD-FLAP Study due to non-cancer (Fig. 1). Detailed information regarding the patients' background, tumor factors, surgical outcomes, and status at 1-year follow-up are shown in Table 1.

The average age of the included patients was 68.8 years, and the proportion of males and females was 76.0% (387/509) and 24.0% (122/509), respectively. Average BMI and PNI were 23.0 kg/m^2 and 50.6, respectively. Regarding tumor factors, most of the patients had GC (92.9%; 473/509), with EGJ cancer accounting for the remaining 7.1% of patients (36/509). pT1, pN0, and Dif accounted for 76.2% (388/509), 87.0% (443/509), and 73.7% (375/509) of cases, respectively. In terms of surgical factors, D1+ lymph node dissection was performed in 83.5% (425/509) of patients. Open and laparoscopic surgery were performed in 61.9% (315/509) and 38.1% (194/509) of

patients, respectively. Postoperative complications (any CD grade) were observed in 12.0% (61/509) of patients, in which 2.8% (14/509) were CD grade ≥III. Anastomosis-related complications such as leakage, strictures, and bleeding were observed in 7.3% (37/509) of patients. At 1-year follow-up, average changes in BMI and PNI were 88.6% and 98.1%, respectively, and 24.4% (99/406) of patients used a PPI or H2 blocker. The incidence of reflux esophagitis was 10.8% (47/435) for any LA grade and 6.0% (26/435) for LA grade ≥B.

Prognostic factors

Median follow-up period after surgery was 4.41 years (interquartile range: 2.31-6.63 years). Univariate analysis of prognostic factors shown in Table 1 for GC and EGJ cancer patients who underwent PG with DFT reconstruction showed that age (≥80 years), PNI (<45), pT (≥2), pN (≥1), and lymph node dissection (D0, D1) were significantly associated with OS. Multivariate analysis of these 5 factors revealed that PNI (<45) (p<0.001, hazard ratio [HR]: 3.59, 95% confidence interval [CI]: 1.93-6.67), pT (≥2) (p=0.010, HR: 2.29, 95% CI: 1.22-4.30), and pN (≥1) (p=0.001, HR: 3.27, 95% CI: 1.66-6.46) were independent poor prognostic factors in these patients (Table 2).

Focusing on the PNI, Kaplan-Meier survival analysis showed that 5-year and 10-year OS of patients with preoperative PNI <45 was 62.2% and 44.4%, respectively, which was considered very low when compared with 89.3% and 84.6% for patients with preoperative PNI ≥45 (Fig. 2). The association of low PNI and poor OS was also indicated by a scatter plot of PNI and OS showing that the area of the 95% CI of deceased patients included lower PNI and shorter OS than living patients (Supplementary Fig. S1). The univariate and multivariate analyses showed that

independent risk factors of preoperative PNI <45 were age (≥80 years) (p<0.001, odds ratio [OR]: 3.55, 95% CI: 1.76-7.00) and pT (≥2) (p=0.007, OR: 2.35, 95% CI: 1.23-4.39) (Supplementary Table S1).

Prognostic factors in patients with preoperative PNI <45 or ≥45

Univariate analysis of prognostic factors in patients with preoperative PNI <45 showed that BMI (<22 kg/m^2), pT (≥2), pN (≥1), anastomosis location (mediastinum, intra-thorax), postoperative complications (CD grade ≥III), and PNI change (<100%) were significantly associated with OS; however, no independent prognostic factors were derived from the multivariate analysis of these 6 factors (Table 3).

By contrast, with regard to patients with preoperative PNI ≥45, the univariate analysis showed that pT (≥2), pN (≥1), and PNI change (<90%) were significantly associated with OS, and the multivariate analysis of these 3 factors identified PNI change (<90%) (p=0.019, HR: 2.54, 95% CI: 1.16-5.54) as the sole independent poor prognostic factor in this population (Table 4). The association of high PNI reduction with poor OS was also shown by a scatter plot of PNI change and OS indicating the area of the 95% CIs of living and deceased patients (Supplementary Fig. S2). Kaplan-Meier survival analysis showed that the 5-year and 10-year OS of patients with PNI change <90% was 81.0% and 72.0%, respectively, which was low compared with 93.8% and 89.6% in patients with PNI change ≥90% (Fig. 3). Univariate and multivariate analyses of risk factors of PNI change (<90%) (i.e., risk factors of ≥10% PNI reduction in patients with preoperative PNI ≥45) demonstrated that operation time (≥300 min) (p=0.044, OR: 1.77, 95% CI: 1.02-3.08) and blood loss (≥200 mL) (p=0.029, OR: 1.85, 95% CI: 1.06-3.27) were independent risk factors of ≥10% PNI reduction in this

population, along with pN (≥1) (p=0.038, OR: 2.50, 95% CI: 1.05-5.96) (Table 5).

Discussion

The PNI, which is calculated based on the serum albumin concentration and peripheral blood lymphocyte count, is an indicator of the nutritional and immunological condition of patients with various cancers [22]. Considerable attention has been focused on the PNI as related to GC as well, and many reports have indicated that preoperative PNI is a predictive indicator of long-term prognosis and short-term outcomes in GC patients, such as postoperative complications [23-25]. Poor nutritional status, causing sarcopenia, is considered as risk factors for OS including cancer-specific death and non-cancer-related death [26, 27]. Considering that PG is applied mainly to early gastric cancer, association with non-cancer-related death may be stronger and more important in this population. In the present study as well, the PNI was an independent prognostic factor along with pT and pN in GC and EGJ cancer patients who underwent PG with DFT reconstruction. Surprisingly, age was not an independent prognostic factor in the multivariate analysis, although there was a significant correlation with OS in the univariate analysis. Although age has often been identified as a prognostic factor in many cancer studies, PNI was a stronger prognostic factor than age in this study.

Further analyses of the patient population divided based on PNI <45 versus ≥45 revealed that among patients with preoperative PNI <45, no prognostic factor was identified in the multivariate analysis, indicating that some nutritional intervention before surgery would be needed to improve the prognosis in this population. Perioperative malnutrition is widely considered a risk factor for increased postoperative complications and poor survival outcomes in GC, and nutritional intervention for

patients with malnutrition has been performed in clinical practice, although there is little evidence that perioperative nutritional intervention effectively improves short- or long-term outcomes [28]. In contrast, among patients with preoperative PNI ≥45, a change in PNI of <90% was the sole independent prognostic factor. Furthermore, the surgical factors of operation time ≥300 min and blood loss ≥200 mL were identified as independent risk factors for ≥10% PNI reduction. This may be reasonable because postoperative complications strongly associated with long operation time and large amount of blood loss often hamper oral food intake for a while after gastrointestinal surgery, leading to malnutrition [29]. These findings indicate that nutritional maintenance after surgery is important even in patients with good nutrition before surgery, with good surgery resulting in short operation time and low blood loss also important factors leading to better prognosis.

The hypothesis that PG is superior to TG in terms of nutritional maintenance after surgery has gained broad consensus. However, no standard post-PG reconstruction procedures have yet been established, because they all have advantages and disadvantages. For example, esophagogastrostomy (EG) involving an anti-reflux procedure such as DFT or SOFY, and DT reconstruction have become popular in recent years as laparoscopic and robotic surgeries increase. Although a comparison of EG and DT would be interesting, only a few studies have compared these two reconstruction procedures in terms of nutritional status. Ojima et al. reported in their short study that nutritional indicators (body weight reduction and albumin level) at 3 months after surgery were better with DT (n=5) than EG (n=6) [30]. However, all six patients in the EG group required an oral PPI in this study, although it was unclear whether the PPIs were for therapeutic or prophylactic use, whereas one of five patients in the DT group

required a PPI, leading us to conclude that these patients may have had reflux symptoms that led to hampering of oral food intake. Eom et al. reported no significant differences between EG and DT in terms of nutritional status at 1 year after surgery, although reflux esophagitis was observed in as many as 17.8% of EG patients in this study as well [31]. Reflux esophagitis can hamper oral food intake, leading to a decline in QOL. From this standpoint, DFT has a strong anti-reflux potential, which have been demonstrated in several clinical studies, including the original rD-FLAP Study, in which the incidence of reflux esophagitis at 1-year follow-up was 10.6% for LA grade ≥A and 6.0% for LA grade ≥B, and thus, DFT is predicted to contribute to better nutritional status and QOL after surgery [10, 17, 32, 33]. We previously showed that postoperative QOL of patients who underwent PG with DFT reconstruction was well-maintained [6]. Although there was no case of robotic approach in the present study, robotic surgery is considered to have a big advantage in DFT reconstruction, all steps of which are performed by hand-sewn suturing technique, and contribute to safe and accurate performance of DFT reconstruction.

Although this study has provided some important evidence, it has several limitations. First, this was a retrospective study that spanned over 20 years, which is very long for a clinical study, and this could have affected the study quality due to changes in standard treatments for GC and EGJ cancer, including chemotherapy, as well as changes in technical details during this period. Although we didn't know the exact number of patients who received adjuvant chemotherapy in the present study, 26 patients (5.1%) were candidates for adjuvant chemotherapy based on pathological findings after 2007 when the evidence of adjuvant chemotherapy with S-1 was reported. Second, the median follow-up period after surgery was 4.41 years, which was

considered insufficient for analysis of OS, including other diseases as cause of death. Third, this study involved GC and EGJ cancer patients who underwent PG with only DFT reconstruction. Although this was a large cohort study in which almost 500 patients participated, they all had DFT reconstruction, and it is unclear whether this evidence would be universally applicable to other reconstruction procedures as well because postoperative nutritional status varies depending on reconstruction procedure.

Conclusion

In the present study, preoperative PNI <45 was an independent poor prognostic factor along with pT ≥2 and pN ≥1 in GC and EGJ cancer patients who underwent PG with DFT reconstruction. For patients with preoperative PNI <45, nutritional intervention before surgery is needed for prognostic improvement, and for patients with preoperative PNI ≥45, keeping the reduction in PNI to no more than 10% by performing good surgery was considered important for prognostic improvement. This study will be valuable in terms of providing evidence of long-term outcomes and prognostic factors in patients with primarily early GC located in the upper stomach and EGJ cancer for whom PG is indicated. The results described here have the potential to contribute to further prognostic improvement in these patients.

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Compliance with Ethical Standards

The authors declare that they have no competing interests.

The study conformed to the provisions of the Declaration of Helsinki, and the protocol was approved by the Okayama University Hospital Institutional Review Board (approval no. 1705-023) and the institutional review boards of each participating institution.

The IRB waived the requirement to obtain informed consent for this study because of the retrospective nature of the study.

Authors' contributions

Yoshihiko Kakiuchi: Conceptualization, Formal analysis, Writing - Original Draft. **Shinji Kuroda:** Conceptualization, Writing - Review & Editing. **Yasuhiro Choda:** Data Curation. **Shinya Otsuka:** Data Curation. **Satoshi Ueyama:** Data Curation.

Norimitsu Tanaka: Data Curation. **Atsushi Muraoka:** Data Curation. **Shinji Hato:** Data Curation. **Yasuaki Kamikawa:** Supervision. **Toshiyoshi Fujiwara:** Supervision.

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Figure legends

Fig. 1. CONSORT diagram.

Fig. 2. Kaplan-Meier survival curves of PNI ≥45 and <45 among the entire study population.

Fig. 3. Kaplan-Meier survival curves of PNI change ≥90% and <90% in patients with preoperative PNI ≥45.