Omental free-shaped flap reinforcement on anastomosis and dissected area (OFFROAD) following reconstruction after gastrectomy

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ABSTRACT

Omental free-shaped flap reinforcement on anastomosis and dissected area (OFFROAD) following reconstruction after gastrectomy

Background

As the detection and early surgical approach of gastric cancer increases, the extent of surgery is gradually decreasing and the paradigm continuously shifts toward individualized treatment. Technical advances in surgery are required to achieve more completeness and less complication rate than before in these current trends. We devised "Omental Free-shaped Flap Reinforcement On Anastomosis and Dissected area (OFFROAD)" following reconstruction after gastrectomy. The aim of this study was to evaluate its safety and early clinical outcomes.

Method

A total of 156 patients who underwent totally laparoscopic distal gastrectomy (TLDG) with delta anastomosis from July 2016 to April 2018 were divided into 80 of OFFROAD group and 76 of Non-OFFROAD group. All patients' data were retrospectively reviewed. The differences between two groups in 'Short-

term operative outcomes' and 'Surgical complications' were compared. All patients' inflammatory marker levels were measured In order to monitor flap necrotic change and inflammatory reactions which could promoted due to OFFROAD. Moreover, the clinical features of both groups in the situation of anastomotic leakage occur were transcribed.

Result

Short-term outcomes and surgical complications were no significantly different between both groups. Anastomotic leakage occurred in three patients in each group and there was no difference in incidence. However, unlike all patients of Non-OFFROAD group manifested every three features of peritonitis (high fever, abrupt abdominal pain that was not previously shown, and sudden increase in serum WBC concentration) each patient of OFFROAD group just manifested only one symptom (fever or abdominal pain) of peritonitis.

Conclusion

The safety and feasibility of OFFROAD has been observed. It might mitigate peritonitis aggravated from anastomotic leakage. Additional large-scale study is needed to assess the versatile usefulness of OFFROAD other than a role of simple physical barrier.

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1. Introduction

1.1 Study backgrounds

The surgical field of early gastric cancer treatment has made remarkable progress in terms of its survival rate and minimally invasive accessibility. At the same time, arise from the detection and early approach of gastric cancer increases, the extent of surgery is gradually decreasing and the paradigm continuously shifts toward individualized treatment. Technical advances in surgery are required to achieve more completeness and less complication rates than before in these current trends.

The most deteriorating complication after gastrectomy is anastomotic leakage (AL). The incidence of AL after gastrectomy has been reported to be 0.9% to 8%. Although the incidence has been reduced due to advances in surgical techniques, its mortality has been reported to be as high as 20% [1-3]

Based on the previous studies, we noted the possibility of utilizing omentum as an autologous graft, particularly in two ways; “adding a physical barrier” and “enhancing blood flow” to the anastomosis site. Omentum has been used as an anatomical supplementary material, especially in the field of reconstructive surgery[4, 5] and Goldsmith in 1977’ firstly reported a case that used omentum to reinforce anastomosis. Theoretically, there exists further versatility of utilizing omentum based on previous studies. Difficulties in future secondary intra-abdominal surgery could be avoided by preventing anastomosis from forming

adhesions with nearby organs[6, 7]. Furthermore, considering oncological viewpoint, to enhance anastomosis site blood perfusion not only promotes anastomotic healing but also magnify the effect of adjuvant chemotherapy and to reduce cancer recurrence[8, 9]. Also, gradually inclining trends of preserving omentum encourages attempts to utilize residual omentum.[10, 11]

We devised Omental Free-shaped Flap Reinforcement On Anastomosis and Dissected area (OFFROAD) to assess the versatile usefulness of omental reinforcement, and this study aims to evaluate its safety and early clinical outcomes.

1.2 Being reduced extent of oncological Omentectomy

The function of the greater omentum is to localize and encapsulate the sites of infection to limit intra-abdominal disease. Omentectomy is an additional surgical procedure to gastrectomy, which may lead to longer operation time and might add to morbidity [11, 12]. The European, American, and Japanese guidelines for the treatment of gastric adenocarcinoma have not reached uniform consensus with respect to omentectomy. The European guidelines do not give any advice regarding omentectomy [13], whereas the most recent American guidelines advise to resect both the greater and lesser omentum. Alternatively, the Japanese

Gastric Cancer Association recommends preservation of the greater omentum at >3cm from the gastroepiploic arcade for patients with T1-T2 tumors and total omentectomy for patients with T3-T4 tumors [14]. In terms of clinical, in laparoscopic gastrectomy, total omentectomy is time-consuming and poses a risk of injury to the adjacent organs, greater blood loss, higher risk of abdominal abscesses, ascites, anastomotic leakage, ileus, wound infections and particularly the spleen and colon [15, 16]. Many retrospective studies had reported that partial omentectomy might be an oncologically safe procedure compared to total omentectomy. Also, Kurokawa et al. 2018' reported randomized controlled trial that Bursectomy did not provide a survival advantage over non-bursectomy. D2 dissection with omentectomy alone should be done as a standard surgery for resectable cT3-T4a gastric cancer [10, 17]. In Western, Jongerius et al. 2016 reported OMEGA trial which is arguing that the incidence of metastases in the greater omentum is low thus, omentectomy as part of a radical gastrectomy may be omitted.

1.3 Changes in the Scale of Lymph Node Dissection

Lymph node dissection (LND) is the most controversial topic in surgery for gastric cancer. While surgeons in Japan performed extended LND in the West commonly prefer a more limited one [18].

The rationale behind lymphadenectomy is based on the lymphatic spread of cancer. Gastric cancer frequently metastasizes to regional lymph nodes, even in the early stages of the disease. The regional lymph nodes were categorized into four groups: N1, N2, N3 and N4. The extent of lymphadenectomy was expressed using the letter R. The standard LND was R2, which included the removal of all the lymph nodes in groups N1 and N2. Extended LND had been performed by Japanese surgeons since the 1980s for tumors invading the subserosa, serosa and adjacent structures. However, a large-scale prospective study concerning the long-term benefit of para-aortic LND had not been performed until the study by Sasako et al. in 2008 [19]. The interim analysis of this trial showed similar short-term results. The five-year survival rates after D2 LND alone and D2 lymphadenectomy plus para-aortic LND were 69.2% and 70.3%, respectively. The five-year recurrence-free survival rates were 62.6% and 61.7%, respectively. No improvement was observed in overall or recurrence-free survival after D2 lymphadenectomy plus para-aortic LND, and recurrence rates in the lymph nodes were similar [17, 18].

The most important and largest-scale studies in the Western world were published in 1995 and 1996. The Dutch Gastric Cancer Trial [20] and the Medical Research Council (MRC) Trial [21] published early results after D1 and D2 LND. Both trials found significantly higher morbidity and mortality rates after D2 dissection. However, especially in the MRC trial, the higher morbidity was largely attributed to the pancreatic resections and splenectomies that were done as a part of D2 dissection for middle and upper tumors. In 1999, the long-term results of these two prospective randomized trials were published [22] and no long-term survival advantages were found after D2 LND.

In 2011, major revised points in the new Japanese classification and gastric cancer treatment guidelines [23] were summarized the grade of lymph node metastasis was expressed in terms of the number of metastatic nodes for the first time. In addition, the extent of LND definition was revised as D3 LND was not defined in neww classification due to the lack of survival benefit.

The 2015 NCCN guidelines state that D2 LND is considered a recommended, but not a required procedure. In the guidelines, D1 or modified D2 LND with the aim of harvesting at least 15 lymph nodes is recommended. In addition, the guidelines suggest that D2 LND should be performed by experienced surgeons in high volume center, rather confusing.

1.4 Background knowledges of Gastric Cancer

Epidemiology

Over one million cases of gastric cancer are diagnosed each year around the world. Stomach cancer is the 5th most commonly diagnose cancer in the world and the 7th most prevalent [24]. The cumulative risk of developing gastric cancer from birth to age 74 is 1.87% in males and 0.79% in females worldwide [25]. In developed countries, gastric cancer is 2.2 times more likely to be diagnosed in males than females. In developing countries, this ratio is 1.83. There is no country where it is the most diagnosed cancer in females.

Gastric cancer is more frequently diagnosed in developed nations. The average incidence rate among high-middle Human Development index (HDI) nations is 20 per 100,000 for males, while the average rate among low-middle HDI nations is 6.6 per 100,000.

The incidence of gastric cancer is highly variable by region and culture [24]. Incidence rates are highest in Eastern and Central Asia and Latin America. In East Asia, the average incidence of gastric cancer is 32.1 per 100,000. In North America, this incidence is 5.6 per 100,000. The rate is lowest in North and East Africa, with only 4.7 annual diagnoses per 100,000. South Korea has the highest national incidence with almost 60 per 100,000 new cases annually [26, 27]. Although declining in incidence, non-cardia gastric cancer continues to be diagnosed twice as often as cardia gastric cancer [28].

Gastric cancer accounts for 783,000 deaths each year, making it the third most deadly cancer among males worldwide and 8.3% of all cancer deaths are attributable to gastric cancer.

Etiology

Gastric cancers are overwhelmingly adenocarcinomas (90%). Gastric adenocarcinoma is a malignant epithelial tumor, originating from glandular epithelium of the gastric mucosa. Histologically, there are two major types of gastric adenocarcinoma (Lauren classification): 1) well-differentiated or intestinal type, and 2) undifferentiated or diffuse type. The intestinal type is more common in males, blacks, and older age groups, whereas the diffuse type has a more equal male-to-female ratio and is more frequent in younger individuals [29, 30]. Diffuse type adenocarcinoma tumor cells are discohesive and secrete mucus, which is delivered in the interstitium, producing large pools of mucus. It is poorly differentiated. If the mucus remains inside the tumor cell, it pushes the nucleus to the periphery and it called signet-ring cell [31].

Intestinal type tumors predominate in high-risk geographic areas, such as East Asia, Eastern Eruope, central and South America, and account for much of the international variation of gastric cancer. Diffuse type adenocarcinomas of the stomach have a more uniform geographic distribution [32]. A decline in the

incidence of the intestinal type tumors in the corpus of the stomach accounts for most of the recent decrease in gastric cancer rates worldwide. In contrast, the incidence of diffuse type gastric carcinoma, particularly the signet ring type, has been increasing.

Signet ring cell carcinoma is a form of adenocarcinoma whose histologic diagnosis is based on the microscopic findings: The predominant component is scattered malignant cells containing intracytoplasmic mucin, which occupies more than 50% of tumors. Signet ring cell carcinoma is thought to be distinct biologic entities originating from different sources of carcinogenesis. Recently, a large-volume study from the US demonstrated that SRC does not necessarily portend a worse prognosis [33].

The second most common types of gastric cancer are lymphomas (MALTomas or MALT lymphoma) which around 5% of gastric malignancies.

Current Trends

In the 1930s, gastric cancer was the most common cause of cancer death in US and Europe. During the past 70 years, mortality rates have fallen dramatically in all developed countries. However, in the past 30 years, the incidence of gastric cardia adenocarcinoma rose by five to six folds in developed countries. Gastric cardia tumor now account for nearly half of all stomach cancers among men from US and UK [28].

There has also been a rising trend in esoapageal adenocarcinoma, in which obesity, gastroesophageal reflux disease (GERD), and Barrett's esophagus are major etiologic factors. Gastric cardia cancers share certain epidemiologic features with adenocarcinomas of the distal esophagus and gastroesophageal junction, suggesting that they represent a similar disease entity [34].

The incidence of gastric cancer has steadily declined worldwide over the past 50 years. These declines preceded the successful reduction of H. *pylori* infection and are likely attributable to changes in food preservation, such as less pickling of vegetables, and less smoking and processing of meat [27].

The second major factor in gastric cancer decline has been the success in preventing and treating H. *pylori* infections in much of the developing world. As many as 90% of cases of non-cardia gastric cancer are attributable to H. *pylori*, which explains why the incidence of why the incidence has declined in step with declining infection rates [35]. Likewise, a decline in the incidence of the intestinal type tumor which in the corpus of the stomach accounts for most of the recent decrease in gastric cancer rates worldwide. In contrast, the incidence of diffuse type gastric carcinoma, particularly the signet ring type, has been increasing. Meanwhile, during that same period, cardia-subtype gastric cancers have increased 7 fold, especially in the developed world [36].

1.5 The History of Gastric Cancer Surgery

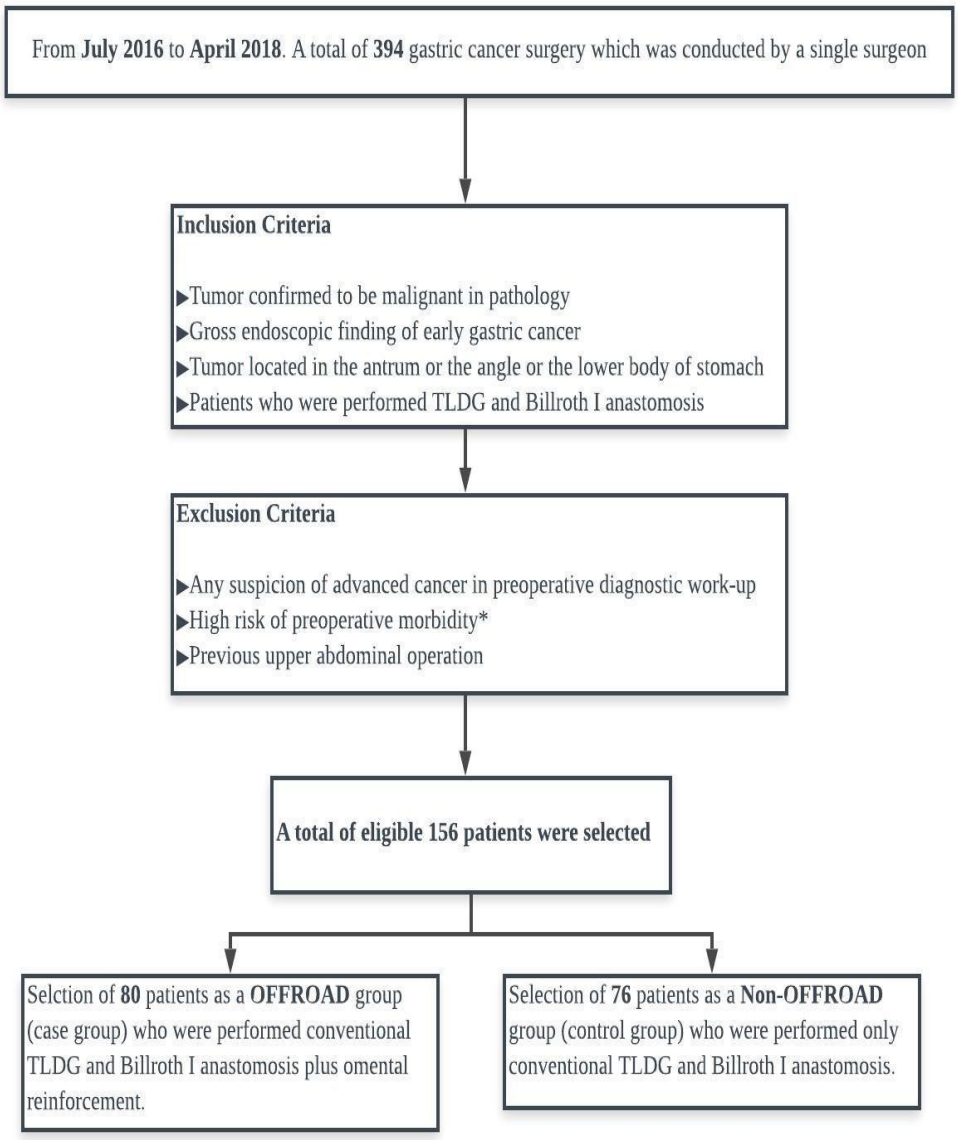
Gastric cancer is a disease that may be traced throughout history and the development of modern civilization. The first documented cases of gastric cancer date back to as early as 1600 BC when it was described in the Ebers Papyrus and in the Hippocrates reports related by Galen in the second century AD in Rome [37]. Galen discussed the etiology as an entity that attacked the body through the skin. Hippocrates had direct experience only of external tumors, because in the Egyptian, Greek, and Roman civilizations corpses could not be utilized for medical anatomical studies. As studies continued, the first anatomic description was made by Cruveilhier in 1835 who described the natural history, likely its course to one of the most well-known figures of world history, Napoleon Bonaparte, who was thought to have a family history of the disease and reportedly died from gastric cancer in 1821. The official history of gastric cancer surgery began 40 years later, when on the 9th of April, 1879, Jules Emile Pean, a French surgeon, performed the first gastric resection for cancer. Unfortunately the patient died on the 5th postoperative day [38]. The first successful operation, a subtotal resection with gastroduodenal anastomosis was performed in 1881, by Theodor Billroth in Vienna. Sixteen years later, in 1897, Karl Schlatter performed the first total gastrectomy in Zurich.

2. Methods

2.1 Study population

The study population comprises 156 patients diagnosed with early gastric cancer and underwent totally-laparoscopic distal gastrectomy (TLDG) at National Cancer Center, department of Gastric Cancer between July 2016 and April 2018 by a single surgeon (K.Y.W.). The aforementioned patients had a common denominator for TLDG plus delta anastomosis, which is the surgery of highest rate in our institution currently. The selection criteria of this case control study are presented in flow chart **(Fig.1)**. All patients' data were collected retrospectively. Inclusion criteria include follows: 1) Tumor confirmed to be malignant in pathology, 2) Gross endoscopic finding of early gastric cancer, 3) Tumor located in the antrum or the angle or the lower body of stomach 4) Patients who were performed TLDG and Billroth I anastomosis. Patients with any suspicion of advanced cancer in preoperative diagnostic work-up, high risk of preoperative morbidity: grade IV or higher American Society of Anesthesiologists (ASA) score [39] and history of previous upper abdominal operation were excluded. Then, a total of 156 patients were divided into 80 of OFFROAD group (OG: case group), and 76 of Non-OFFROAD group (NOG: control group)**.**

Figure 1. Flow chart of the Case-Control study



***American Society of Anesthesiologists (ASA) grade IV or higher[39].**

2.2 Patient demographics

All patients' demographics including age, sex, pathological histology, tumor location and size, preoperative ASA score and postoperatively confirmed pathologic stages were transcribed.

2.3 Variables indicate initial success of surgery and overall course of recovery.

Short-term operative outcomes were collected including operating time, estimated blood loss, length of stay, body weight change (comparison of preoperative and discharge-period value), first flatus day and pain score of the third day after surgery measured by numerical rating scale (NRS) for evaluate initial success of surgery and overall course of recovery

2.4 Monitoring surgical complications and inflammatory reactions

Data of compromising events during OFFROAD procedure and surgical complications including postoperative ileus, pneumonia, surgical site infection, delayed gastric emptying and anastomotic leakage or stricture of both groups were collected.

In order to monitor flap necrotic change and inflammatory reactions which could provoked due to manipulation of omentum during OFFROAD, we measured patient's inflammatory markers: serum white blood cell (WBC) and C-reactive protein (CRP) concentrations on postoperative day (POD) one, three and five. We also tried to observe the temporal changes of inflammatory marker concentrations in both groups using box plots.

2.5 Definition of Anastomotic Leakage and Surveillance protocols

Anastomotic leakage (AL) was defined as follows: 1) when AL were found in our routine esophago-gastroduodenoscopy (EGD) surveillance which was conducted on POD#2 for every case. Or 2) when if AL was found in the results of diagnostic EGD performed when patients showed suspicious clinical

manifestations of **peritonitis** (High fever over 38.3 degrees [40], abrupt abdominal pain that was not previously shown and sudden increase in serum WBC concentration which is greater than 100 cells/mL). When AL occurred, immediate abdominal computed tomography (CT) plus EGD were conducted and we compared different clinical features between both groups.

Anastomotic stenosis was defined as anastomotic narrowing that could not accommodate the insertion of 10mm endoscope with presence of symptoms suggesting stricture (dysphagia, inability to progress from the liquid to solid diet, nausea, vomiting and/or epigastric pain).

2.6 Surgical procedure of OFFROAD

The process of OFFROAD was consistently conducted as follows. After finishing TLDG and Billroth I anastomosis with partial omentectomy, the residual omentum was mobilized upward to cover widely the stomach. Then it was divided vertically using energy device and made it into two wings. After locating the left side wing beneath the anastomosis and the right side wing on the surface of the anastomosis (both wings were made to wrap entire anastomosis site) we fixed them with endo-clips.

2.7 Statistical analyses

Nominal data were calculated with the $\chi 2$ test and Fisher's exact test for the qualitative data. Comparisons between the two groups were made by the t-test for independent samples in case of normal data distribution and the Mann-Whitney U test in case of abnormal data distribution. P value of <0.05 was regarded as significant. The SPSS statistical software package 20.0 was used for statistical testing.

3. Results

3.1 Clinicopathologic features

The clinical and pathologic characteristics of the two groups are provided in **table 1**. There were no significant differences between the groups including age, sex, histology, tumor location and size, ASA score and postoperative pathologic findings.

Table 1. Patients' Clinicopathologic factors

	Non OFFROAD group (n=76)	OFFROAD group (n=80)	P value
Age (years)	59.66 ± 11.61	60.60 ± 9.69	0.513
Sex			0.189
Male	55 (72.4%)	50 (62.5%)	
Female	21 (27.6%)	30 (37.5%)	
Histology			0.197
Differentiated	59 (77.6%)	61 (76.3%)	
Undifferentiated	17 (22.4%)	19 (23.7%)	
Location			0.622
Antrum	40 (52.6%)	42 (52.5%)	
Lower body	36 (47.4%)	38 (47.5%)	
Tumor size (cm)	3.2 ± 2.02	3.2 ± 1.69	0.421
ASA score*			0.642
1	24	31	
2	41	39	
3	11	10	
pT category			0.428
T1	61 (80.3%)	67 (83.8%)	
T2	8 (10.5%)	6 (7.5%)	
≥T3	7 (9.2%)	7 (8.7%)	
pN category			0.499
N0	62 (81.6%)	62 (77.5%)	
N1	9 (11.8%)	10 (12.5%)	
≥ N2	6 (6.6%)	8 (10.0%)	
pStage			0.280
I	68 (89.5%)	69 (86.3%)	
II	4 (5.3%)	9 (11.3%)	
≥ III	4 (5.3%)	2 (2.4%)	

*American Society of Anesthesiologists (ASA) grade IV or higher[39].

3.2 Short-term operative outcomes

The short term operative outcomes are presented in **table 2**. The operating time was comparable in the two groups. The mean duration of OFFROAD procedure was shorter than five minutes. There were no significant differences in estimated blood loss, length of stay, body weight change and first flatus days. The postoperative pain score was significantly lower in OG compared to NOG (NRS; 3.43±1.19 vs 2.94±0.90, *P=0.004*).

Table 2. Short term operative outcome

	Non OFFROAD group (n=76)	OFFROAD group (n=80)	P value
Operating time (minutes)	217 ± 35.08	197 ± 32.70	0.101
Estimated blood loss (mL)	45 ± 62.02	42 ± 51.21	0.734
Length of hospital stay (days)	9.82 ± 6.06	10.60 ± 7.20	0.464
Body weight change (%) *	-3.26 ± 1.38	-5.10 ± 0.69	0.109
First flatus time (days)	3.67 ± 1.02	3.53 ± 0.99	0.367
Postoperative pain score (NRS of POD#3)	3.43 ± 1.19	2.94 ± 0.90	**0.004**

***comparison between preoperative and pre-discharge period.**

3.3 Comparison of Sugrical Complications

The surgical complications are listed in **table 3**. There was one case of immediate bleeding during OFFROAD procedure. Mild to moderate postoperative complications occurred in three patients (3.95%) in NOG (1 postoperative ileus, 1surgical site infection, 1 delayed gastric emptying) and six patients (7.50%) in OG (postoperative ileus in one patient, pneumonia in one, surgical site infection in one and delayed gastric emptying in three). The incident rate of all postoperative complications was not significantly different between both groups.

AL was shown in three patients in each group, and there was no significant difference in incidence (NOG: OG, 3.95 vs. 3.75 %). Anastomotic strictures occurred in control group (OG) only. According to the Clavien-Dindo classification of surgical complications, the distribution of severity was similar between the two groups (*p=0.608*).

Table 3. Surgical complications

	Non OFFROAD group (n=76)	OFFROAD group (n=80)	P value
Omental bleeding during OFFROAD procedure	N/A	1 (1.25%)	
Mild to moderate postoperative Complications			
Postoperative ileus	1 (1.32%)	1 (1.25%)	0.971
Pneumonia	0	1 (1.25%)	0.330
Wound problem	1 (1.32%)	1 (1.25%)	0.971
Delayed gastric emptying	1 (1.32%)	3 (3.75%)	0.338
Severe Postoperative Complications*			
Anastomotic leakage	3 (3.95%)	3 (3.75%)	0.949
Anastomotic stricture	0	1 (1.25%)	0.330

*** Clavien-Dindo classification grade III or higher; requiring surgical, endoscopic or radiological intervention[14].**

3.4 Comparison of Inflammatory marker levels

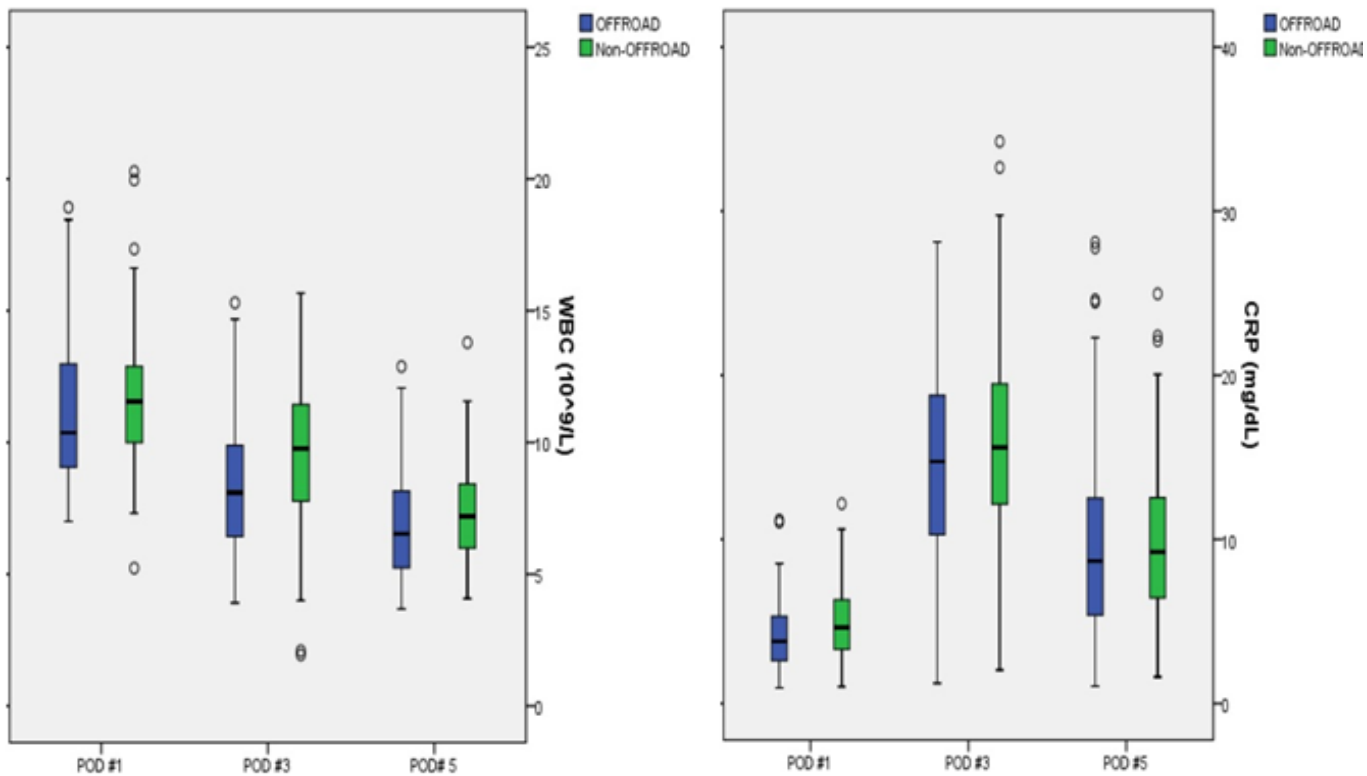
The serum WBC and CRP concentrations were measured on POD one, three and five **table 4.** In order to monitor flap necrotic changes and inflammatory reactions which could be provoked due to manipulation of omentum during OFFROAD.

The inflammatory maker levels of WBC and CRP were comparable between both groups **(Fig.2)**. The Serum WBC count on POD 1 was significantly lower in OG (NOG: OG, 11.8±1.7 vs. 10.8±2.4; *P=0.02*). However, no significant difference was observed in others.

Table 4. Comparison of laboratory test between Non OFFROAD and OFFROAD patients

	Non-OFFROAD patients (N=76)	OFFROAD patients (N=80)	P Value
White blood cell (10^9/L)			
POD #1	11.8 ± 2.7	10.8 ± 2.4	**0.02**
POD #3	9.3 ± 3.0	8.6 ± 2.4	0.12
POD #5	7.3 ± 1.7	6.9 ± 2.0	0.16
C-reactive protein (mg/L)			
POD #1	4.8 ± 2.3	4.4 ± 1.9	0.16
POD #3	16.6 ± 6.8	15.9 ± 5.6	0.51
POD #5	10.2 ± 5.2	10.9 ± 5.8	0.48

Fig.2 Box plots for inflammatory marker levels of both groups.



Serum WBC levels of both groups showed gradual decline as time flows after surgery. Serum CRP levels of both groups recorded peak at POD #3 and gradually decreased from POD #5.

3.5 Clinical features in Anastomotic Leakage Cases between the two groups.

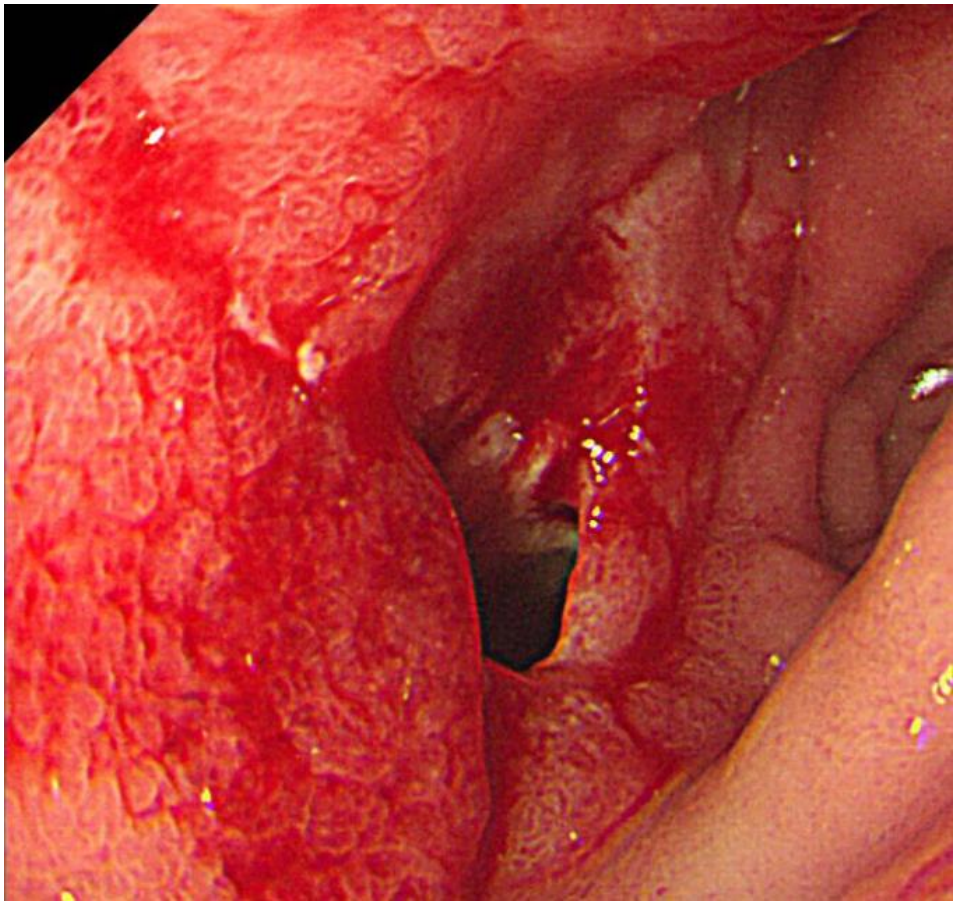
Table 5. describes different clinical manifestations when AL occurred in both groups. All patients of control group (NOG) had every three symptoms of peritonitis (High fever over 38.3 degrees, abrupt abdominal pain that was not previously shown, and sudden increase in WBC concentration which is greater than 100 cells/mL). In contrary, each patient in case group (OG) showed only one symptom (fever or abdominal pain) of peritonitis. There was no death in the entire cohort.

When patients showed one of the features of peritonitis, immediate CT scan and diagnostic EGD were performed and those images are described in **Fig.3** and **Fig.4**. Unlike control group (NOG), EGD and CT scan findings on case group (OG) showed omental flap sealed leakage hole and there were only localized inflammatory changes.

Table 5. Clinical manifestations in anastomotic leakage cases between the two groups

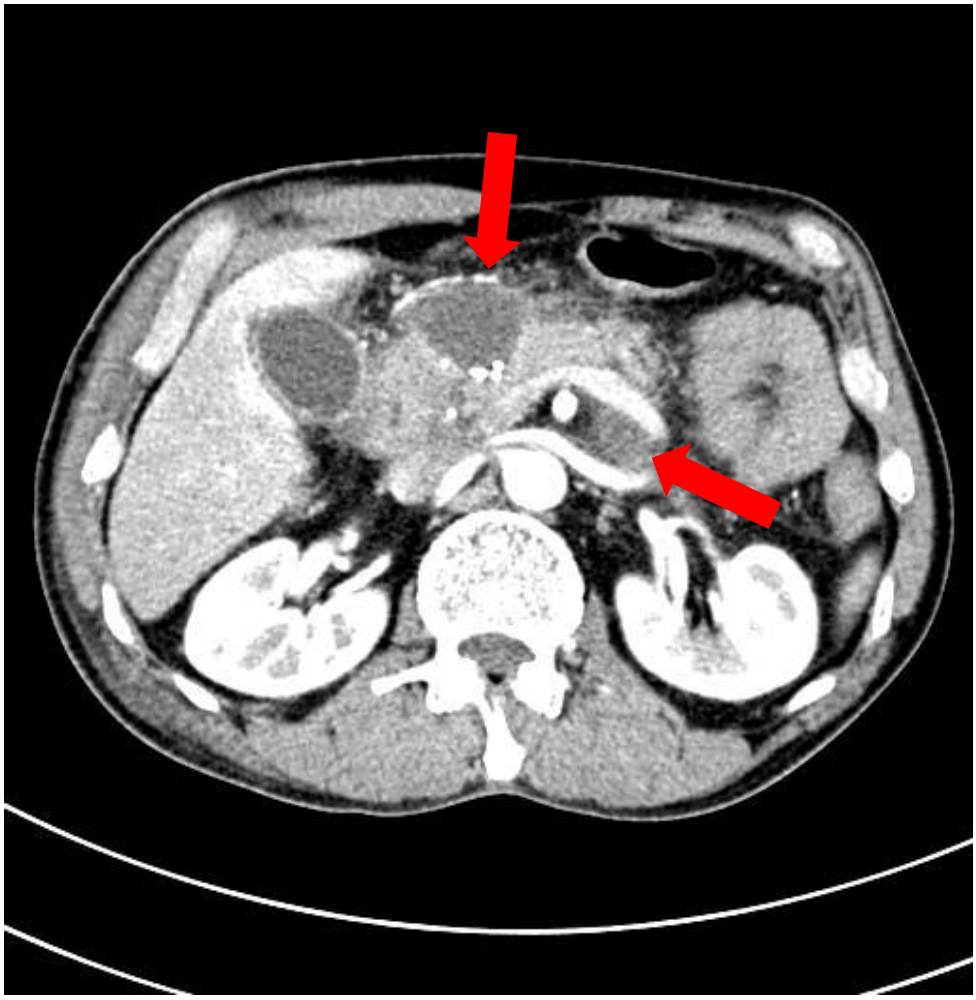
	Non-OFFROAD patients (N=3)	OFFROAD patients (N=3)
Features of peritonitis		
1. Fever(>38.3)	3/3 (100%)	1/3 (33.3%)
2. Onset of abrupt abdominal pain	3/3 (100%)	1/3 (33.3%)
3. WBC and CRP Increases	3/3 (100%)	1/3 (33.3%)
The number of symptoms each patient had	3	1
Mortality	0	0

Fig 3-A. Findings of Non OFFROAD group; Esophago-Duodenoscopy performed when Anastomotic Leakage occur



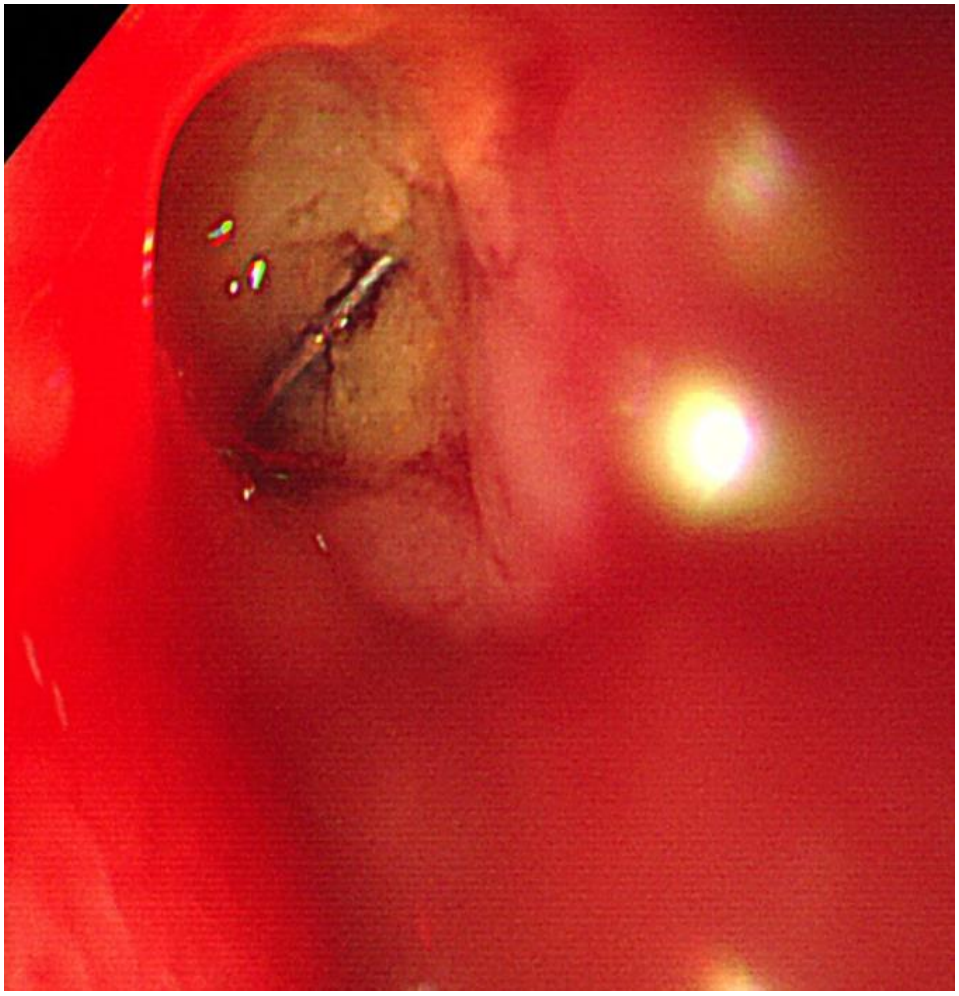
*Leakage hole which communicated with peritoneal cavity was observed by EGD diagnosis in Non-OFFROAD group.

Fig 3-B Findings of Non OFFROAD group; Computed Tomography scan performed when Anastomotic Leakage occur



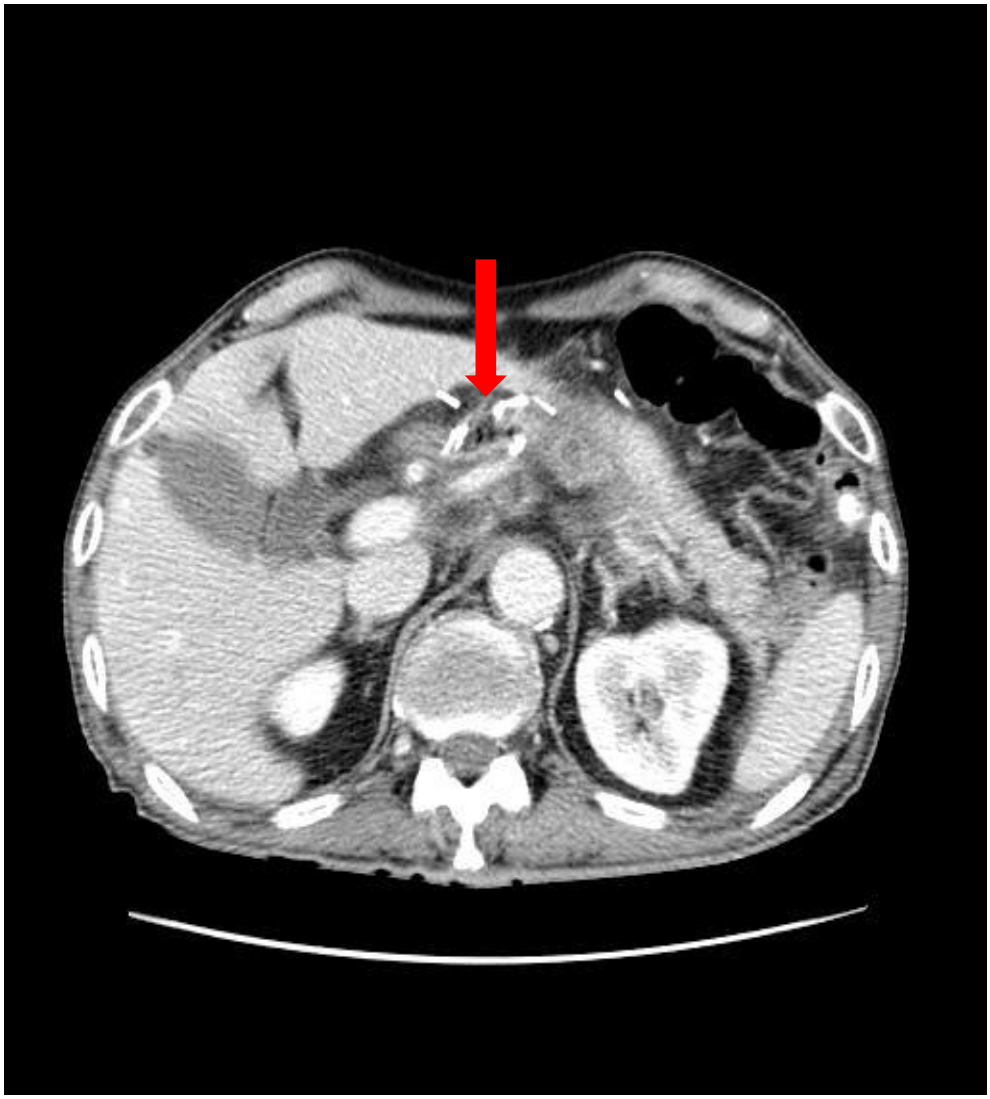
*Aggravated peritonitis and intra-abdominal abscess around anastomosis site (red arrow) were found through CT scan in Non-OFFROAD group.

Fig 4-A. Findings of OFFROAD group; Esophago-duodenoscopy performed when Anastomotic Leakage occur



*The surface of the omental flap was observed through leakage hole in OFFROAD group.

Fig 4-B. Findings of OFFROAD group; Computed Tomography scan performed when Anastomotic Leakage occur



*Complicated fluid collection was rarely found and only peritoneal free air around anastomosis site was confirmed (red arrow) in OFFROAD group.

4. Discussion

4.1 Summary

In presented study, total of 156 patients diagnosed with EGC underwent gastrectomy plus OFFROAD procedure. The mean duration of OFFROAD procedure was shorter than five minutes. There were no significant differences in 'Short-term outcomes' and 'Surgical complications' except that the pain score in POD #3 and serum WBC concentration in POD #1 were lower in OG than NOG. Among 76 of control group (NOG) and 80 of case group (OG), 3.95% and 3.85% of AL occurred, respectively and there was no difference in incidence. However, clinical features of both groups were in contrast when AL occurs. Unlike all patients of NOG manifested every three features of peritonitis, each patient of OG manifested only one symptom (fever or abdominal pain) of peritonitis. Inferred from the results of our study, OFFROAD could not prevent AL itself. However OFFROAD was able to prevent peritonitis aggravated from anastomotic leakage.

Although there was additional procedure, OG had a shorter operating time (197±32.70 min) than NOG (217±35.08 min) in result. It is interpreted that because OG is distributed temporally later and is affected by the surgical technique improves over time. The results were different from our hypothesis that manipulation of omentum would promote inflammatory reaction. Rather, OG showed less inflammatory change in serum WBC and pain score than NOG.

However, because statistical significance is only proved in part, it is limited to evaluate the anti-inflammatory effect of OFFROAD.

4.2 Timely relevance of studies using residual omentum

From the early 2000s, it has been reporting that the partial omental resection which preserves the physiological function of omentum shows no oncological inferiority compared to the former standard complete omentectomy[10, 11, 14, 16, 41]. Considering these current paradigmatic shifts, attempting anastomotic reinforcement by utilizing residual omentum has a timely relevance, especially in the field of gastric cancer surgery.

4.3 Previous studies and the value of OFFROAD

OFFROAD is the first study to investigate the reinforcement of anastomosis using omentum in the field of gastric cancer surgery. Until recently, studies have been led by physicians in the field of esophageal and colorectal cancer surgery. In esophageal surgery, DAI et al. in 2006, Bhat et al. in 2005 and Sepesi in 2012 reported that the occurrence of AL could be controlled significantly by omental reinforcement [42-44]. In colorectal surgery, Tocchi et al. 1997' and Nasiri et al. 2017' reported significant positive effects. However, Merad et al. in 1998 and Ozben et al. in 2016 reported incompatible data [45-47]. Of the studies that

reinforced anastomosis with omentum, this study firstly conducted routinely EGD and measured inflammatory marker levels. Also, immediate CT scan and EGD were additively performed together in the situation of AL occurs.

4.4 Versatile usefulness of omentum

Omentum has been utilized clinically as a mere physical barrier so far [4, 48, 49], but clearly there exist further versatility based on previous studies. Some histopathological studies demonstrated neo-vascularizing effects of omentum [5] and that difficulties in future secondary intra-abdominal surgery could be avoided by preventing anastomosis site to form adhesions with nearby organs [6, 7]. Considering oncological viewpoint, to enhance anastomosis site blood perfusion possibly not only promotes anastomotic healing but also magnify the effect of adjuvant chemotherapy [8, 9]. Additional study is needed to assess the versatile usefulness of OFFROAD other than a role of simple physical barrier.

4.5 Possible complications and Limitations of OFFROAD

Since OFFROAD requires additional manipulation after completion of regular surgery, following two complications had to be considered. 1) Necrotic change of omental flap was a possible complication of OFFROAD and it could occur when excessive tensions were imposed on the flap or ometal feeding vessels were

damaged. Intraoperatively, care was taken to avoid excessive tension on omental flap and to preserve omental feeding vessels and we had monitored every patient's serum WBC and CRP concentrations. There were no suspicious findings observed as a result. 2) There existed a risk of postoperative omental bleeding from OFFROAD. Of the 80 cases in case group (OG), one patient which was our second case showed postoperative omental bleeding. Since this case, where the bleeding has stopped spontaneously without tracing a bleeding source, we have made efforts to preserve omental feeding vessels more delicately and the event was not repeated.

This study has some limitations: 1) Designed as a case-control study without prospective cohort, the level of evidence is insufficient. 2) All patients in this study were in laparoscopic setting without laparotomy, because of high proportion of laparoscopic approaches for managing EGC. However, there is no reason to limit this procedure to particular surgical approach, when considering its fundamental principles.

6. Conclusion

The safety and feasibility of OFFROAD has been observed. It might migate peritonitis aggravated from anastomotic leakage. Additional large-scale study is needed to assess the versatile usefulness of OFFROAD other than a role of simple physical barrier.

BIBLIOGRAPHY

1. Bruce, J., et al., *Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery.* Br J Surg, 2001. **88**(9): p. 1157-68.
2. Sierzega, M., et al., *Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach.* Br J Surg, 2010. **97**(7): p. 1035-42.
3. Kim, Y.W., et al., *Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial.* Ann Surg, 2008. **248**(5): p. 721-7.
4. McLean, D.H. and H.J. Buncke, Jr., *Autotransplant of omentum to a large scalp defect, with microsurgical revascularization.* Plast Reconstr Surg, 1972. **49**(3): p. 268-74.
5. Shah, S., et al., *Cellular basis of tissue regeneration by omentum.* PLoS One, 2012. **7**(6): p. e38368.
6. Ellis, H., et al., *Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study.* Lancet, 1999. **353**(9163): p. 1476-80.
7. Thompson, J.N. and S.A. Whawell, *Pathogenesis and prevention of adhesion formation.* Br J Surg, 1995. **82**(1): p. 3-5.
8. Bridges, E. and A.L. Harris, *Vascular-promoting therapy reduced tumor growth and progression by improving chemotherapy efficacy.* Cancer Cell, 2015. **27**(1): p. 7-9.
9. Chauhan, V.P., et al., *Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels.* Nat Commun, 2013. **4**: p. 2516.
10. Kurokawa, Y., et al., *Bursectomy versus omentectomy alone for resectable gastric cancer (JCOG1001): a phase 3, open-label, randomised controlled trial.* Lancet Gastroenterol Hepatol, 2018. **3**(7): p. 460-468.
11. Haverkamp, L., et al., *The Oncological Value of Omentectomy in Gastrectomy for Cancer.* J Gastrointest Surg, 2016. **20**(5): p. 885-90.
12. Ha, T.K., et al., *Omentum-preserving gastrectomy for early gastric cancer.* World J Surg, 2008. **32**(8): p. 1703-8.
13. Okines, A., et al., *Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2010. **21 Suppl 5**: p. v50-4.
14. Japanese Gastric Cancer, A., *Japanese gastric cancer treatment guidelines 2014 (ver. 4).* Gastric Cancer, 2017. **20**(1): p. 1-19.

15. Kim, M.C., et al., *Comparative study of complete and partial omentectomy in radical subtotal gastrectomy for early gastric cancer.* Yonsei Med J, 2011. **52**(6): p. 961-6.
16. Kim, D.J., J.H. Lee, and W. Kim, *A comparison of total versus partial omentectomy for advanced gastric cancer in laparoscopic gastrectomy.* World J Surg Oncol, 2014. **12**: p. 64.
17. Eom, B.W., et al., *Role of bursectomy for advanced gastric cancer: result of a case-control study from a large volume hospital.* Eur J Surg Oncol, 2013. **39**(12): p. 1407-14.
18. Sano, T., et al., *Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy--Japan Clinical Oncology Group study 9501.* J Clin Oncol, 2004. **22**(14): p. 2767-73.
19. Sasako, M., et al., *D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer.* N Engl J Med, 2008. **359**(5): p. 453-62.
20. Bonenkamp, J.J., et al., *Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients.* Lancet, 1995. **345**(8952): p. 745-8.
21. Cuschieri, A., et al., *Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group.* Lancet, 1996. **347**(9007): p. 995-9.
22. Bonenkamp, J.J., et al., *Extended lymph-node dissection for gastric cancer.* N Engl J Med, 1999. **340**(12): p. 908-14.
23. Japanese Gastric Cancer, A., *Japanese classification of gastric carcinoma: 3rd English edition.* Gastric Cancer, 2011. **14**(2): p. 101-12.
24. Guggenheim, D.E. and M.A. Shah, *Gastric cancer epidemiology and risk factors.* J Surg Oncol, 2013. **107**(3): p. 230-6.
25. Bray, F., et al., *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA Cancer J Clin, 2018. **68**(6): p. 394-424.
26. Irino, T., et al., *Gastric Cancer in Asia: Unique Features and Management.* Am Soc Clin Oncol Educ Book, 2017. **37**: p. 279-291.
27. Balakrishnan, M., et al., *Changing Trends in Stomach Cancer Throughout the World.* Curr Gastroenterol Rep, 2017. **19**(8): p. 36.
28. Pera, M., et al., *Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction.* Gastroenterology, 1993. **104**(2): p. 510-3.
29. Correa, P., et al., *Pathology of gastric carcinoma in Japanese populations: comparisons between Miyagi prefecture, Japan, and Hawaii.* J Natl Cancer Inst, 1973. **51**(5): p. 1449-59.

30. Lauren, P., *The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification.* Acta Pathol Microbiol Scand, 1965. **64**: p. 31-49.
31. Chon, H.J., et al., *Differential Prognostic Implications of Gastric Signet Ring Cell Carcinoma: Stage Adjusted Analysis From a Single High-volume Center in Asia.* Ann Surg, 2017. **265**(5): p. 946-953.
32. Munoz, N., et al., *Histologic types of gastric carcinoma in high- and low-risk areas.* Int J Cancer, 1968. **3**(6): p. 809-18.
33. Taghavi, S., et al., *Prognostic significance of signet ring gastric cancer.* J Clin Oncol, 2012. **30**(28): p. 3493-8.
34. Brown, L.M. and S.S. Devesa, *Epidemiologic trends in esophageal and gastric cancer in the United States.* Surg Oncol Clin N Am, 2002. **11**(2): p. 235-56.
35. Rawla, P. and A. Barsouk, *Epidemiology of gastric cancer: global trends, risk factors and prevention.* Prz Gastroenterol, 2019. **14**(1): p. 26-38.
36. Karimi, P., et al., *Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention.* Cancer Epidemiol Biomarkers Prev, 2014. **23**(5): p. 700-13.
37. De Usobiaga, E., *[History of gastric cancer].* Rev Esp Enferm Apar Dig, 1970. **30**(2): p. 226-36.
38. Santoro, E., *The history of gastric cancer: legends and chronicles.* Gastric Cancer, 2005. **8**(2): p. 71-4.
39. Wolters, U., et al., *ASA classification and perioperative variables as predictors of postoperative outcome.* Br J Anaesth, 1996. **77**(2): p. 217-22.
40. O'Grady, N.P., et al., *Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America.* Crit Care Med, 2008. **36**(4): p. 1330-49.
41. Kodera, Y., et al., *Quantitative detection of disseminated cancer cells in the greater omentum of gastric carcinoma patients with real-time RT-PCR: a comparison with peritoneal lavage cytology.* Gastric Cancer, 2002. **5**(2): p. 69-76.
42. Dai, J.G., et al., *Wrapping of the omental pedicle flap around esophagogastric anastomosis after esophagectomy for esophageal cancer.* Surgery, 2011. **149**(3): p. 404-10.
43. Bhat, M.A., et al., *Use of pedicled omentum in esophagogastric anastomosis for prevention of anastomotic leak.* Ann Thorac Surg, 2006. **82**(5): p. 1857-62.
44. Sepesi, B., et al., *Omental reinforcement of the thoracic esophagogastric anastomosis: an analysis of leak and reintervention rates in patients*

undergoing planned and salvage esophagectomy. J Thorac Cardiovasc Surg, 2012. **144**(5): p. 1146-50.
45. Tocchi, A., et al., *Prospective evaluation of omentoplasty in preventing leakage of colorectal anastomosis.* Dis Colon Rectum, 2000. **43**(7): p. 951-5.
46. Ozben, V., et al., *Does omental pedicle flap reduce anastomotic leak and septic complications after rectal cancer surgery?* Int J Surg, 2016. **27**: p. 53-7.
47. Nasiri, S., et al., *The Effect of Omentoplasty on the Rate of Anastomotic Leakage after Intestinal Resection: A Randomized Controlled Trial.* Am Surg, 2017. **83**(2): p. 157-161.
48. Turner-Warwick, R.T., E.J. Wynne, and M. Handley-Ashken, *The use of the omental pedicle graft in the repair and reconstruction of the urinary tract.* Br J Surg, 1967. **54**(10): p. 849-53.
49. Lanter, B. and R.A. Mason, *Use of omental pedicle graft to protect low anterior colonic anastomosis.* Dis Colon Rectum, 1979. **22**(7): p. 448-51.

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