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Retrospective Study

How to examine the anastomotic integrity intraoperatively in totally laparoscopic radical gastrectomy? Methylene blue testing prevents technical defect-related anastomotic leaks

IMBT Prevents postoperative anastomotic leaks

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Abstract

BACKGROUND

Intraoperative methylene blue testing (IMBT), air leak testing, or endoscopy is used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer. Totally laparoscopic radical gastrectomy has been widely used to treat gastric cancer in the last few decades. However, reports on testing anastomotic integrity in totally laparoscopic radical gastrectomy are limited.

AIM

To explore the effects of IMBT on the incidence of postoperative anastomotic leaks (PALs) and identify the risk factors for PALs in totally laparoscopic radical gastrectomy.

METHODS

From January 2017 to December 2019, patients who underwent totally laparoscopic radical gastrectomy in the Shaanxi Provincial People's Hospital are retrospectively analyzed and grouped according to whether or not they experience an IMBT. The patients were divided into the IMBT group and the control group. If the IMBT is positive, an intraoperative suture is required to reinforce the anastomosis. The difference in the incidence of PALs is compared, and the risk factors are investigated.

RESULTS

This study consist of 513 patients, 211 in the IMBT group and 302 in the control group. Positive IMBT is shown in 7 patients (3.3%) in the IMBT group, and no PAL occurred in these patients after suture reinforcement, a multivariate analysis showed that risk factors for predicting a positive IMBT are body mass index (BMI) >25kg/m^2 (HR=8.357, P = 0.009), operation time >4h (HR=55.881, P = 0.002), and insufficient surgical experience (HR=15.286, P = 0.010). Moreover, 15 patients (2.9%) developed PALs in 513 patients, and the rates of

PALs are significantly lower in the IMBT group than in the control group (2 of 211 patients (0.9%) vs. 13 of 302 patients (4.3%), P = 0.0026). Further analysis demonstrated that preoperative complications (HR=13.128, *P* = 0.017), totally laparoscopic total gastrectomy (HR=9.075, *P* = 0.043), and neoadjuvant chemotherapy (HR=7.150, *P* = 0.008) are independent risk factors for PALs.

CONCLUSION

IMBT is an effective method to evaluate the integrity of anastomosis during totally laparoscopic radical gastrectomy; thus, preventing technical defect-related anastomotic leaks. Preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are independent risk factors for PALs.

Key Words: Anastomotic leak; Gastric neoplasms; Totally laparoscopic radical gastrectomy; Methylene blue; Risk factors

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Core Tip: We reviewed the outcomes of 513 consecutive patients with gastric cancer who underwent totally laparoscopic radical gastrectomy with and without intraoperative methylene blue testing at Shaanxi Provincial People's Hospital from January 2017 to December 2019. We found that intraoperative methylene blue testing is an effective method to evaluate the integrity of anastomosis during totally laparoscopic radical gastrectomy and could reduce the incidence of postoperative anastomotic leaks. Preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are independent risk factors for postoperative anastomotic leaks.

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide, ranking fifth for incidence and third for mortality[1]. Totally laparoscopic radical gastrectomy has been widely used to treat gastric cancer[2-4]. Postoperative anastomotic leak (PAL) is a severe complication, and occurs in 1.7%-5.7% of patients with gastric cancer[5-7]. These complications could prolong hospital stay, increase medical expenses, cause poor quality of life, and subsequently worsen the long-term survival of patients[8-10].

It is well known that the defects of intraoperative anastomotic techniques are closely related to PALs[11-13]. Therefore, some PALs might be avoided if insufficiently integral anastomoses were immediately reinforced. Intraoperative methylene blue testing (IMBT), intraoperative air leak test, or intraoperative endoscopy is used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer[6,14-15]. However, to the best of our knowledge, no study has assessed the integrity of anastomosis during totally laparoscopic radical gastrectomy. Compared with open surgery, totally laparoscopic radical gastrectomy have the disadvantages of two-dimensional images, poor hand-eye coordination, limited operating space, fulcrum effect, and lack of haptic feedback[16-17]. Furthermore, according to the ERAS guidelines, abdominal drains should not routinely be placed after gastrectomy, which requires high-quality anastomosis[18-19]. Thus, a reliable anastomosis leak test is vital during totally laparoscopic radical gastrectomy.

In this study, we used IMBT to check the anastomotic integrity of esophagojejunostomy or gastrojejunostomy during totally laparoscopic radical gastrectomy. This is the first study to assess the anastomotic integrity during totally laparoscopic radical gastrectomy. We aim to explore the effects of IMBT on the incidence and the risk factors for PALs.

MATERIALS AND METHODS

Patients

We performed a retrospective review of patients who underwent totally laparoscopic radical gastrectomy from January 2017 to December 2019. In our department, some surgeons think IMBT is useful, while others are skeptical regarding its effects. Thus, two groups are formed: an IMBT group and a control group. Staging of the tumor was performed following the eighth edition of the AJCC Guidelines for gastric cancer[20]. This study is approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

The inclusion criteria are : (1) patients who underwent totally laparoscopic radical gastrectomy for gastric cancer and adenocarcinoma of the gastroesophageal junction from January 2017 to December 2019; (2) gastric cancer or adenocarcinoma of the gastroesophageal junction diagnosed *via* endoscopy and pathological identification; and (3) patients whose surgical and demographic data is complete and reliable. The exclusion criteria are : (1) patients who underwent totally laparoscopic distal gastrectomy that used Billroth-I anastomosis; (2) those who were converted to open surgery; (3) those who were found to have distant metastases intraoperatively; (4) those who did not undergo radical resection; and (5) those who gave up treatment or were transferred to another hospital.

Surgical Methods and Postoperative Management

All surgeries are performed laparoscopically. Totally laparoscopic total gastrectomy is reconstructed *via* an overlap anastomosis[21], and totally laparoscopic distal gastrectomy is reconstructed *via* a Billroth-II anastomosis[22]. Lymph node dissection is performed according to the Japanese Gastric Cancer Treatment Guidelines 2014 (ver. 4)[23]. This study used a 45-mm linear stapler (Johnson Company, USA) for the overlap anastomosis and a 60-mm linear stapler (Johnson Company, USA) for the Billroth-II anastomosis. In our department, we preferred the Billroth II anastomosis and Roux-en-

Y esophagojejunostomy rather than the Billroth I anastomosis. A Billroth I anastomosis needs to preserve a large residual stomach, leading to insufficient tumor margins and significant anastomotic tension when the tumor location is relatively high and the diameter is large. In China, most gastric cancer cases are found in advanced stages, and the diameter of the tumor is often large compared to Japan and Korea[24-26]. In addition, Billroth I anastomosis has a greater risk of remnant gastritis and reflux esophagitis[27-28].

Postoperative management is conducted according to the Japanese Gastric Cancer Treatment Guidelines (ver.4)[23]: the nasogastric tube is removed on postoperative day one, and the abdominal drainage tube removed on postoperative day five without symptoms or inflammatory reactions. Abdominal CT, gastrointestinal tract angiography, or endoscopy is performed when an anastomotic leak is suspected.

Methylene Blue Testing Technique

For the patients that underwent totally laparoscopic total gastrectomy, we performed IMBT as follows (Figure 1A): after the digestive tract's reconstruction（Fig.2A and A'）, the nasogastric tube (18F) is delivered 5 cm from the distal end of the anastomotic stoma, gauze is wrapped around the anastomosis, and then the jejunum is clamped using an intestinal clamp 5 cm distal to the anastomosis. Next, normal saline is injected through the nasogastric tube to rinse and observe whether continuous bright red liquid flows out of the nasogastric tube when pumping back. If the liquid is detected, we look for and stop the bleeding and then flush repeatedly until the clear liquid is pumped back out. Next, we dissolve 2 mL (20mg) methylene blue into 50 mL normal saline and inject it through the nasogastric tube in order to make the methylene blue liquid disperse evenly around the anastomosis (Figure 2B and B'). Finally, we observe whether the gauze around the anastomosis is stained blue, if there is blue staining (Figure 3), we find the leak according to the blue-stained site, suture it, and then change the gauze and repeat the process.

For the patients who underwent totally laparoscopic distal gastrectomy, IMBT is performed as follows (Figure 1B): the nasogastric tube (18F) is indwelled 5 cm from the distal end of the anastomotic stoma after the digestive tract's reconstruction (Figure 2C and C'). Next, we wrap the anastomosis with gauze, and close it with clamps 5 cm distal to the anastomosis. Then normal saline is flushed through the nasogastric tube; the needle was pumped back to observe whether there is bright red liquid flowing out of the nasogastric tube. If red liquid is present we look for and stop the bleeding. The flushing is repeated until the clear liquid is extracted from the nasogastric tube. Next, 5 mL (50mg) methylene blue is dissolved into 500 mL normal saline and injected through the nasogastric tube in order to evenly distribute the methylene blue liquid around the anastomosis (Figure 2D and D'). Finally, if blue liquid is present we repeat the above procedures.

Definition

We defined preoperative complications as one or more of the following anemia, malnutrition, diabetes, or pulmonary dysfunction. The World Health Organization's definition of anemia is used to define anemia, patients with Hb concentration of <12 g/dL in women and <13 g/dL in men is defined as anemia[29]. Malnutrition is defined by the European Society of Clinical Nutrition and Metabolism (ESPEN) criteria[30], which suggests two methods used to diagnose malnutrition. Method one: Body mass index (BMI) <18.5 kg/m^2. Method two: Unintentional weight loss combined with a low age-related BMI (<20 kg/m^2 in <70 years or <22 kg/m^2 in ≥70 years) or low fat-free mass index (FFMI) (<17 kg/m^2 in men and <15 kg/m^2 in women). Positive IMBT is defined as the visualization of methylene blue on the gauze surrounding the anastomosis. PAL is defined as meeting one of the following criteria: (1) Gastrointestinal contents or bile-like fluid drained from the abdominal drainage tube. (2) Gastrointestinal radiography shows leakage of the contrast medium from the drainage tube. (3) Methylene blue is extracted from the abdominal drainage tube after the oral administration of methylene blue. (4) Abdominal CT examination shows that

the gastrointestinal wall is incomplete, revealing gas and fluid leaks around the anastomosis. (5) Anastomotic leaks are found under endoscopy after surgery.

Statistical Analysis

Analysis was performed by the statistic software SPSS for Windows Version 25.0 (SPSS Inc., Chicago, Illinois, U.S.A.). Measurement data is expressed as `x±s (normal distribution) and median (non-normal distribution). Count data is expressed as examples (rate). A univariate analysis was performed by the Chi-square test or a Fisher's exact test when appropriate. In univariate analysis, the variables with $P < 0.05$ were included in multivariate analysis. A multivariate analysis was conducted by the logistic regression model. $P < 0.05$ is considered to be statistically significant.

RESULTS

From January 2017 to December 2019, a total of 513 patients that underwent totally laparoscopic radical gastrectomy were analyzed retrospectively (211 patients in the IMBT group and 302 patients in the control group). Complete data of the intraoperative and postoperative findings is shown in Figure 4. The baseline of the patients in the two groups is consistent, as shown in Table 1.

The Risk Factors Analysis of Positive IMBT

Seven patients (3.3%) had positive intraoperative methylene blue testing in the IMBT group, as detailed in Table 2. These cases were managed by additional suturing, none had a PAL, and the postoperative hospital stays were 10.3±1.1 days. Univariate analysis showed that surgeons with insufficient surgical experience (<50 cases of totally laparoscopic radical gastrectomy) have a higher rate of positive IMBT (14.3% vs. 2.1%, $P = 0.021$). Other risk factors include operation time >4 h, neoadjuvant chemotherapy, and a body mass index (BMI) >25kg/m^2 ($P = 0.008$; 0.033; 0.021), as shown in Table 3 and 4. A multivariate analysis identified BMI >25kg/m^2, operation time >4 h, and insufficient

surgical experience as independent risk factors for positive IMBT (P = 0.009; P = 0.002; P = 0.010), as detailed in Table 5.

Comparison of The Incidence of PALs

PAL occurred in 15 (2.9%) patients, including 2 in the IMBT group and 13 in the control group. The rate of PALs is significantly lower in the IMBT group than in the control group (2 of 211 patients (0.9%) vs. 13 of 302 patients (4.3%), P = 0.0026).

The Risk Factors Analysis of PALs

The clinical characteristics of the patients with anastomotic leaks is shown in Table 6. The diagnosis time of PALs is 5.8±2.0 days after surgery, postoperative hospital stays is 19.3±3.5 days, and the abdominal drainage tube placement time is 17.3±3.2 days. All 15 patients improved and were discharged from the hospital, and no one died. In a univariate analysis, patients with BMI > 25 kg/m^2 (8.8% vs. 2.4%, P = 0.025), preoperative complications (8.1% vs. 2.0%, P = 0.018), totally laparoscopic total gastrectomy (6.8% vs. 1.9%, P = 0.046), and neoadjuvant chemotherapy (9.8% vs. 2.9%, P = 0.028) are associated with PALs, as shown in Table 3 and 4. Multivariate analysis showed that preoperative complications (HR=13.128, P = 0.017), totally laparoscopic total gastrectomy (HR=9.075, P = 0.043), and neoadjuvant chemotherapy (HR=7.150, P = 0.008) are independent risk factors for PALs (Table 5).

DISCUSSION

Anastomotic leaks are among the most common and severe complications after totally laparoscopic radical gastrectomy and are the main risk factor for a patients' postoperative death[8-10]. The integrity of the anastomosis, which is closely related to the anastomotic technique, is a prerequisite for tissue healing and is essential for preventing anastomotic leaks[6,12]. In totally laparoscopic radical gastrectomy, we used IMBT to check the integrity of the anastomosis. The results showed that IMBT reduces the

incidence of PALs, which is consistent with the intraoperative methylene blue testing results in an open total gastrectomy[14].

Several methods are available to assess the integrity of the anastomosis. An intraoperative air leak test was proposed by Kanaji to check anastomotic integrity during an open radical gastrectomy[6] and showed that this test reduces the occurrence of postoperative anastomotic leaks; however, the intraoperative air leak test did not show the exact site of the leaks and only depicted the approximate area. Celik *et al*[14] showed a low incidence of anastomotic leaks in the methylene blue testing group (3.7% vs. 14.4%, $P = 0.007$) in which methylene blue is injected *via* a nasogastric tube to check the integrity of the anastomosis during an open total gastrectomy. Some researchers[31] who performed an intraoperative endoscopic examination during laparoscopic gastric bypass surgery showed a low incidence of anastomotic leaks (0 vs. 8%, $P = 0.0412$) and a low reoperation rate (0 vs. 8%, $P = 0.0412$). However, it is a challenge to find gastroscopic instruments as well as an experienced endoscopist. Our study confirmed that IMBT is an important method for assessing anastomotic integrity in totally laparoscopic radical gastrectomy, which detects anastomoses and pinpoints the areas of the leaks. Furthermore, we examined the anastomosis during totally laparoscopic distal gastrectomy, whereas previous studies focused on esophagojejunal anastomotic leaks after a totally gastrectomy.

This study found seven IMBT-positive patients whose anastomosis is reinforced with sutures, and none of them developed PALs. Our study indicated that patients with an operative time >4 h, a BMI >25 kg/m^2, and insufficient surgical experience have a higher risk of positive IMBT. Previous studies have shown that technically relevant factors such as prolonged operative time, excessive BMI, and inexperience of the surgeon are strongly associated with the occurrence of PALs[6,32-33]. Therefore, we recommend performing IMBT in patients with these high-risk factors.

However, two patients (0.9%) with negative IMBT developed PALs in this study, meaning that the cause of the anastomotic leaks is complex. This study found that patients with preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are at a higher risk for PALs. Previous studies have indicated that anemia, malnutrition, and pulmonary insufficiency are also strongly associated with the occurrence of PALs[13,32,34], and are consistent with the results of our study. Kawamura *et al*[35] showed that the rate of anastomotic leaks is significantly higher in the laparoscopic total gastrectomy group (5.0 %) than in the laparoscopic distal gastrectomy group (1.2%), which is consistent with our study. However, there is still controversy about whether neoadjuvant chemotherapy leads to PALs. Gorur *et al*[36] reported that chemotherapy affects cell proliferation and the formation of collagenous fiber, which is a key component of anastomotic healing. Some studies reported that neoadjuvant chemotherapy does not increase the risk of PALs[37, 38]. Our study suggested that neoadjuvant chemotherapy is a risk factor for PALs. We hypothesized that patients undergoing neoadjuvant chemotherapy have increased tissue toughness and adhesion within the abdominal cavity, resulting in increased surgical damage; thus, leading to PALs. Therefore, we should pay close attention to patients with the above-mentioned risk factors.

This study has its limitations. First, it is a single-center retrospective study, which needs to be further confirmed by a multicenter, randomized controlled study with a larger sample size. Second, our study did not compare the intraoperative methylene blue testing, intraoperative air leak test, and intraoperative endoscopy. Finally, the methylene blue testing could not prevent PALs caused by non-technical factors.

CONCLUSION

In summary, IMBT can find technical defects within an anastomosis, and suturing can reduce the incidence of anastomotic leaks after totally laparoscopic radical

gastrectomy. Independent risk factors associated with PAL include preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy.

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