Received: 26 April 2021 | Revised: 18 June 2021 | Accepted: 22 June 2021

DOI: 10.1002/ags3.12488

ORIGINAL ARTICLE

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

The impact of pancreas compression time during minimally invasive gastrectomy on the postoperative complications in gastric cancer

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Abstract

Aim: Pancreas compression during minimally invasive gastrectomy causes blunt injury to the pancreas and leads to postoperative complications. However, the extent of practical compression associated with the incidence of postoperative complications remains unknown. This study aimed to evaluate the impact of pancreas compression, particularly the duration of compression, on short-term outcomes in minimally invasive gastrectomy for gastric cancer.

Methods: This study included 178 patients who underwent laparoscopic or robotic gastrectomy at the Shizuoka Cancer Center in 2018. The total time of pancreas compression during gastrectomy was measured using video-reviews, and the correlation between the time and surgical outcomes was evaluated.

Results: A duration of 3 min was selected as the cutoff value of pancreas compression time to predict high drain amylase concentration on postoperative day 1 (≥1000 U/L). The incidence of clinically relevant pancreatic fistula (1.5% vs 12.4%, $P = .011$) and all postoperative complications (12.3% vs 30.1%, $P = .010$) were significantly higher in the longer-compression group than in the shorter-compression group. The multivariable analysis identified longer compression as the only independent risk factor for postoperative complications.

Conclusion: More than a few minutes of pancreas compression during minimally invasive gastrectomy was associated with a higher incidence of postoperative complications.

KEYWORDS

drain amylase concentration, gastric cancer, minimally invasive surgery, pancreas compression, postoperative complications

1 | INTRODUCTION

Minimally invasive gastrectomy has been developed as an alternative treatment for early gastric cancer patients.[1] With proof of its efficacy as well as safety demonstrated by phase III trials,[2-4] laparoscopic gastrectomy is now regarded as a standard treatment for early gastric cancer. For further advancement, robotic gastrectomy is increasingly widespread as a procedure with the potential for improving safety.[5-8]

Meanwhile, previous nationwide prospective cohort studies noted a higher incidence of postoperative pancreatic fistula after laparoscopic gastrectomy in comparison with conventional open surgery.[9,10] Certainly, a direct cutting or thermal injury can cause pancreatic fistula[11]; however, the most problematic cause is a blunt injury induced by pancreas compression due to laparoscopic forceps with or without a gauze/sponge that is specific to minimally invasive surgery in comparison with open surgery.[12] Especially at the time of suprapancreatic lymph node dissection, frequent pancreas compressions occur to secure the surgical field.[13]

Instead of a direct pancreas compression, an approach of "Pancreas-compressionless gastrectomy," in which the assistant controlled the position of the pancreas by pulling the mesentery along the inferior border of the pancreas or nerves surrounding the suprapancreatic major arteries, was reported as a safe and useful method for preventing postoperative infectious complications due to pancreatic damage.[12] A robotic approach using an articulated arm was also reported as a solution for this problem.[14] However, despite these methods it seems to be difficult to eliminate the direct pancreas compression completely. Linear forceps are apt for compressing the parenchyma of the pancreas even when pulling away the surrounding tissues, such as a nerve or mesentery. An angled robotic arm can also push the caudal pancreas due to the restricted viewing angle of the rigid da Vinci endoscope (Intuitive, Sunnyvale, CA). If it is difficult to realize gastrectomy without any pancreas compression, then it is important to clarify how much compression is related to the incidence of complications involving the pancreas.

Therefore, this study aimed to evaluate the impact of pancreas compression, particularly the duration of pancreas compression, on short-term clinical outcomes in patients with gastric cancer who underwent minimally invasive gastrectomy.

2 | METHODS

This retrospective study included 189 consecutive patients who underwent laparoscopic or robotic gastrectomy for gastric cancer at the Shizuoka Cancer Center (Japan) from January 2018 to December 2018. Eleven patients whose operation recording videos were not available were excluded. For the remaining 178 patients, the total time of pancreas compression during suprapancreatic lymph node dissection was measured using the information obtained during video review. The clinical, surgical, and pathological findings were obtained from a prospectively maintained database and from individual patient medical records, when necessary.

2.1 | Surgical indication and procedure

Laparoscopic or robotic gastrectomy with either D1+ or D2 lymphadenectomy was performed according to the latest guidelines.[15] There was no difference in indication between laparoscopic and robotic surgery. While robotic surgery was expected as a procedure with the potential for improving safety, its scientific evidence was inadequate. We explained the features of both approaches and possible complications. The surgical approach was determined according to the patient's preference. The endoscopic surgical skill qualification system: a qualified surgeon of the Japanese Society for Endoscopic Surgery (JSES) performed or assisted in all the laparoscopic surgeries. All robotic procedures were performed by qualified surgeons using the da Vinci Si or Xi Surgical System. Other attending surgeons were experienced surgeons who were all board-certificated surgeons of the Japanese Surgical Society.

The suprapancreatic lymph node dissection (lymph node stations No. 7, 8a, 9, and 11p) was performed following the methods reported by Tsujiura et al.[12] The pancreas was pulled caudally to secure the surgical field of view by some methods; one is directly compressing the pancreas with a gauze/sponge, another is rolling back the pancreas by pulling the root of the transverse mesocolon with a gauze/sponge, and the other is pulling the root of the transverse mesocolon or pulling the nerve fibers surrounding the common hepatic and splenic arteries by forceps, which is known as "pancreas-compressionless gastrectomy."[12] Because we had a transition period to the latter method in this study period, some of the methods were adopted depending on the situation. At the end of the operation, a Blake drain was inserted on the suprapancreatic area.

2.2 | Measurement of pancreas compression duration

We reviewed all videos and measured the time duration of pancreas compression during the suprapancreatic lymph node dissection without any information on the short-term outcome in each patient. Prior to the main analysis, we randomly selected three videos and compared the pancreas compression time investigated by three researchers (K.I., M.H., and K.F.) to clarify the data reliability. The average of the standard deviations of the time, among the three researchers, was only ±1.7 min. Therefore, we adopted the data investigated by one researcher (K.I.) in all the other videos. Pancreas compression was defined as follows: when the pancreas was compressed with a gauze/sponge, compression time was counted at all strengths and at any part of the pancreas (Figure S1a). Rolling back the pancreas by pulling the root of the transverse mesocolon with a gauze/sponge was not regarded as pancreas compression, as long as the inferior border of the pancreas could be seen. When the pancreas was compressed unintentionally during just rolling back the pancreas, we counted the compression time. When the pancreas was directly compressed with forceps, the compression time was counted when the compression was thicker than the thickness of one forceps (approximately 5 mm, Figure S1b). The total time of compression was evaluated in each video. From the sum data, the compression time was expressed in minutes, rounding down to the nearest decimal.

2.3 | Definition of outcomes

The amylase concentration in the drainage fluid was measured on postoperative day (POD) 1 in all the patients. In this study we defined the concentration of 1000 U/L or more as a high drain amylase concentration because it was reported as a risk factor for pancreas-related intra-abdominal abscess.[16,17] Pancreatic fistula was defined as grade B or C, according to the International Study Group on Pancreatic Fistula (ISGPF) definition.[18] Postoperative complications were defined as any adverse event corresponding to Clavien–Dindo (CD) classification grade II or higher that occurs within 30 d of gastrectomy.[19] If a patient had more than one type of complication, the complication with the highest grade was used for the analysis. We administered antibiotics prophylactically within 24 h after operation in all patients. We resumed the antibiotics treatment only when we recognized obvious signs of bacterial infection, such as fever, purulent drainage fluids, the elevation of inflammatory markers, and the images of fluid collection. We did not administer additional prophylactic antibiotics just for a high drain amylase concentration.

2.4 | Statistical analyses

To analyze correlations, a scatterplot and receiver operating characteristic (ROC) curve were drawn, and Spearman's rank correlation coefficient was calculated. All continuous variables are presented as medians (range). For comparison between two groups, we used Fisher's exact test and the Mann–Whitney *U*-test, as appropriate. Univariable and multivariable analyses of risk factors were performed using logistic regression analysis. A multiple linear regression model was used for the analysis of continuous variables.

All *P*-values < .05 were considered statistically significant. All statistical analyses were conducted using EZR statistical software package (Eazy R, Saitama Medical Center, Jichi Medical University, Japan[20]), which is a graphical interface for R (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Patient characteristics and surgical data are summarized in Table 1. Clinical stage I patients accounted for the majority of the study population. Approximately one-fourth of all patients underwent robotic gastrectomy.

TABLE 1 Patient characteristics and surgical data

Variables	N = 178
Age (years), median (range)	70 (33–87)
Sex	
Male	131
Female	47
BMI (kg/m^2), median (range)	22.7 (15.7–35.2)
ASA-PS	
1	40
2	126
3	12
Serum albumin level (g/dl)	
Median (range)	4.2 (2.7–5.2)
Clinical T category	
T1	139
T2	35
T3	4
Clinical N category	
N0	172
N1	4
N2	2
Clinical stage	
I	168
IIA	6
IIB	4
Approach	
Laparoscopy	132
Robot	46
Extent of resection	
Distal	138
Pylorus-preserving	11
Proximal	16
Total	13
Extent of lymph node dissection	
D1+	126
D2	52
Performed or assisted by a nonqualified surgeon[a]	
Yes	151
No	27

Abbreviations: ASA-PS, American Society of Anesthesiologists Performance Status; BMI, body mass index.

[a]Nonqualified surgeon of Endoscopic Surgical Skill Qualification System of the Japanese Society for Endoscopic Surgery.

The histogram of pancreas compression time is shown in Figure 1. We completed surgery without any compression in 44 patients. There was a weak correlation between pancreas compression time and drain amylase concentration on POD 1 ($R = 0.337$, $P < .001$) (Figure 2). Figure 3 shows the ROC curve for the prediction of high

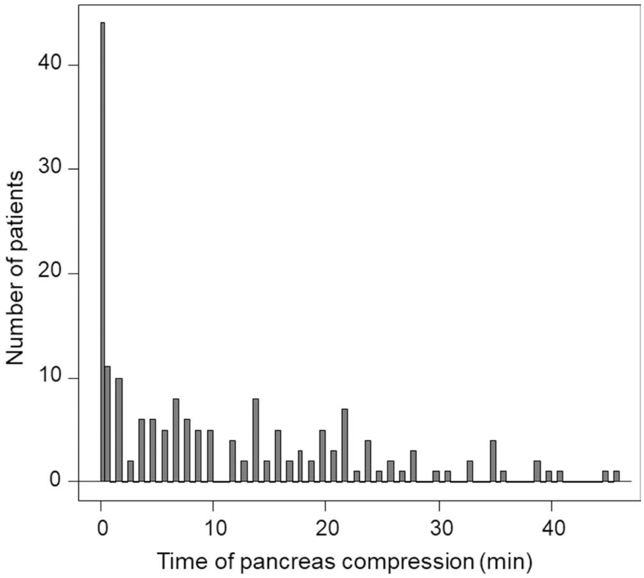

FIGURE 1 The frequency histogram of pancreas compression time. The surgery was completed without any compression in 44 patients

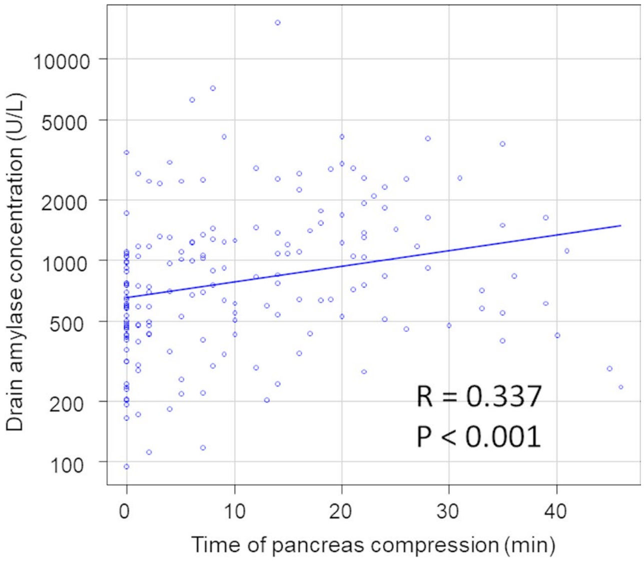

FIGURE 2 The scatterplot of the correlation between pancreas compression time and drain amylase concentration on postoperative day 1. The vertical axis of the plot is scaled logarithmically. There was a weak correlation (R = 0.337, $P < .001$)

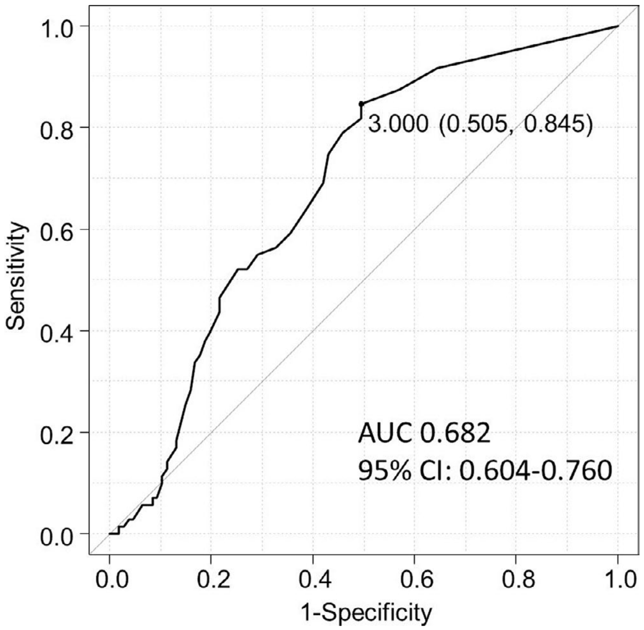

FIGURE 3 The receiver operating characteristic curve for the prediction of high drain amylase concentration (1000 U/L or more) on postoperative day 1 based on the pancreas compression time. We determined 3 min as the cutoff value of the pancreas compression time because the sum of sensitivity and specificity was maximum at that point. AUC: area under the curve; CI: confidence interval

drain amylase concentration on POD 1 (1000 U/L or more) according to pancreas compression time. We identified 3 min as the cutoff value of the pancreas compression time because the sum of sensitivity and specificity was maximum at that point.

To evaluate the impact of pancreas compression on short-term outcomes, all of the 178 patients were divided into two groups: the shorter-compression group (S group, n = 65), in which patients had <3 min compression, and the longer-compression group (L group, n = 113), in which patients had ≥3 min of compression (Table S1). Comparison of short-term outcomes between the S and the L groups is shown in Table 2 and Table 3. The incidence of clinically relevant pancreatic fistula (ISGPF grade B or C; 1.5% vs 12.4%, $P = .011$), all postoperative complications (12.3% vs 30.1%, $P = .010$), and surgical complications (6.2% vs 17.7%, $P = .039$) were significantly higher in the L group than in the S group.

In the multivariable logistic regression analysis, longer pancreas compression time was identified as the only independent risk factor for all postoperative complications (odds ratio: 2.54, 95% confidence interval: 1.01–6.37, $P = .047$) (Table 4).

We performed multiple linear regression analysis to identify specific factors associated with pancreas compression time. Laparoscopic gastrectomy ($P < .001$), male gender ($P = .002$), and patients with advanced cT grade ($P = .010$) were significantly associated with longer compression time (Table 5). The pancreas compression time was significantly shorter in robotic gastrectomy than in laparoscopic gastrectomy (median; 1 min vs 10 min, $P < .001$).

4 | DISCUSSION

This study demonstrated that longer pancreas compression time during minimally invasive gastrectomy increased the incidence of postoperative complications in gastric cancer patients. Although previous studies indicated that the harmful effect of pancreas compression during gastrectomy, how much time of compression causes blunt injury to the pancreas was still uncertain. To the best of our

TABLE 2 Short-term outcomes according to the duration of pancreas compression

	S group (n = 65)	L group (n = 113)	*P* value
Operative time (min), median (range)	271 (159–582)	274 (134–696)	.702
Estimated blood loss (ml), median (range)	10 (0–267)	17 (0–402)	.109
D-AMY on POD 1 (U/L), median (range)	534 (95–3439)	1050 (118–15 238)	<.001*
Clinically relevant pancreatic fistula,[a] n (%)	1 (1.5)	14 (12.4)	.011*
All postoperative complications, n (%)			
≥Grade II	8 (12.3)	34 (30.1)	.010*
≥Grade III	1 (1.5)	6 (5.3)	.425
Surgical complications, n (%)			
≥Grade II	4 (6.2)	20 (17.7)	.039*
≥Grade III	1 (1.5)	6 (5.3)	.425

Note: S group: shorter-compression group in which patients had less than 3 min compression. L group: longer-compression group in which patients had 3 min or more of compression. The severity of postoperative complications was graded based on the Clavien–Dindo classification.
Abbreviations: D-AMY, drain amylase concentration; POD, postoperative day.
[a]Grade B or C according to the International Study Group on Pancreatic Fistula (ISGPF) definition.
*Statistically significant.

TABLE 3 Details of postoperative complications

	S group (n = 65)	L group (n = 113)	*P* value
Surgical complications			
Anastomotic leakage	1 (1.5)	5 (4.4)	.418
Intra-abdominal abscess	1 (1.5)	5 (4.4)	.418
Bleeding	0 (0.0)	2 (1.8)	.534
Anastomotic stenosis	1 (1.5)	0 (0.0)	.365
Delayed gastric emptying	1 (1.5)	5 (4.4)	.418
Ileus	0 (0.0)	3 (2.7)	.301
Nonsurgical complications			
Acute cholecystitis	0 (0.0)	1 (0.9)	1.000
Pneumonia	0 (0.0)	3 (2.7)	.301
Pulmonary embolism	0 (0.0)	1 (0.9)	1.000
Elevation of liver enzyme	2 (3.1)	4 (3.5)	1.000
Unexplained abdominal pain	0 (0.0)	2 (1.8)	.534
Nausea	0 (0.0)	1 (0.9)	1.000
Rash	1 (1.5)	3 (2.7)	1.000
Delirium	1 (1.5)	1 (0.9)	1.000
Hypertension	0 (0.0)	1 (0.9)	1.000
Dizziness	0 (0.0)	1 (0.9)	1.000

Note:: Data are shown as n (%). S group: shorter-compression group in which patients had less than 3 min compression. L group: longer-compression group in which patients had 3 min or more compression.

knowledge, this is the first study to provide evidence that more than a few minutes of pancreas compression is associated with a higher incidence of postoperative complications.

In this study, longer pancreas compression was significantly associated with the incidence of clinically relevant pancreatic fistula (ISGPF grade B or C) and all postoperative complications or surgical complications. The multivariable analysis identified longer pancreas compression as the only independent risk factor for all postoperative complications, rather than the well-known risk factors such as male gender, obesity, or the degree of lymphadenectomy.[21,22] This was the case because a high concentration of drain amylase level due to longer pancreas compression raised the risk of postoperative complications. Moreover, extracting the pancreas compression time as an independent factor might weaken the impact of previously reported risk factors on the incidence of postoperative complications because their risks might partially come from longer pancreas compression time. A high concentration of drain amylase is commonly thought to be a risk for intra-abdominal infectious complications, such as anastomotic leakage or abscess, or a risk for clinically relevant pancreatic fistula.[16,17,23-25] Clinically relevant pancreatic fistula, which is classified into grade B or C based on ISGPF definition, includes not only abdominal infectious complications, but also complications that change the management of the expected postoperative pathway, such as bleeding, etc. As per previous reports, pancreatic fistula causes local inflammation and enteroparalysis, and it may lead to delayed gastric emptying, ileus, pseudoaneurysm, or pneumonia.[26-29] These features can explain the higher incidence of clinically relevant pancreatic fistula and all complications in the L group than in the S group.

A previous study using large-animal models supported the idea that a direct pancreas compression caused blunt pancreas injury leading to pancreatic juice leakage.[30] In this previous study, the predicted pancreas compression time to injure the pancreas was set at 15 min. However, the present study showed the association between ≥3 min of pancreas compression and more postoperative complications. This result suggests that we could better handle the pancreas more carefully than how it was done before. Some methods have been considered for avoiding pancreas compression during the suprapancreatic dissection in laparoscopic gastrectomy. Placing the ports more cranially helps the linear forceps to get over the pancreas. Head-up tilt of the operation table enables pulling the pancreas caudally by the force of gravity. Rolling back the pancreas

TABLE 4 Risk factors for all postoperative complications

	Univariable			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Pancreas compression time (min)						
≥3	3.07	1.32–7.12	.009*	2.54	1.01–6.37	.047*
<3	1			1		
Age (years)						
≥75	1.05	0.50–2.18	.906			
<75	1					
Sex						
Male	1.71	0.73–4.02	.219	1.29	0.51–3.26	.598
Female	1			1		
BMI (kg/m^2)						
≥25	2.00	0.96–4.18	.066	1.62	0.75–3.53	.221
<25	1			1		
ASA-PS						
3	1.09	0.28–4.21	.906			
≤2	1					
Clinical T category						
≥2	1.15	0.51–2.62	.734			
1	1					
Clinical N category						
≥1	0.64	0.07–5.63	.687			
0						
Extent of lymph node dissection						
D2	1.71	0.82–3.55	.150	1.62	0.75–3.49	.217
D1+	1			1		
Approach						
Laparoscopy	1.65	0.70–3.88	.253	1.11	0.44–2.83	.827
Robot	1			1		
Performed or assisted by a nonqualified surgeon[a]						
Yes	1.93	0.63–5.95	.250	1.70	0.53–5.44	.369
No	1			1		

Abbreviations: ASA-PS, American Society of Anesthesiologists Performance Status; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a]Nonqualified surgeon of Endoscopic Surgical Skill Qualification System of the Japanese Society for Endoscopic Surgery.

*Statistically significant.

by pulling, not the pancreas, but the root of the transverse mesocolon can avoid compression. Changing the point of grasp and pull, as reported in "Pancreas-compressionless gastrectomy," may also be effective.[12] However, pancreas compression is unavoidable in some cases because of the linear shape of the forceps used in laparoscopic surgery, which prevents getting over the pancreas depending on its anatomical position.[31] Inevitable compression can also happen when just rolling back the pancreas is inadequate to secure the surgical field.

We expect robotic gastrectomy to become a promising solution. We adopted multiple linear regression analysis. The pancreas compression time was considered a continuous value to identify the factors that can reduce that time as much as possible. This analysis revealed that laparoscopic gastrectomy, male gender, and patients with advanced cT grade were significantly associated with longer compression time. Robotic gastrectomy has the potential to develop gastrectomy that avoids compressing the pancreas and further reduces the incidence of postoperative complications. The articulated arm of the robot was suggested to make the dissection of the suprapancreatic lymph nodes easier.[32] Lower concentration of drain amylase or lower postoperative morbidity rate in robotic gastrectomy than those in conventional laparoscopic gastrectomy was reported in previous studies.[14,33] Nevertheless, robotic surgery has not yet been fully implemented for gastrectomy with no

TABLE 5 Multiple linear regression analysis of relationships between clinical characteristics and pancreas compression time

	β	95% CI	SE	*P* value
Age (years)				
≥75	0.92	−2.58 to 4.42	1.77	.603
<75				
Sex				
Male	5.61	2.01 to 9.22	1.83	.002*
Female				
BMI (kg/m^2)				
≥25	3.26	−0.32 to 6.85	1.82	.075
<25				
ASA-PS				
3	−1.74	−8.19 to 4.71	3.27	.595
≤2				
Clinical T category				
≥2	7.56	1.81 to 13.32	2.91	.010*
1				
Clinical N category				
≥1	6.77	−2.47 to 16.01	4.68	.150
0				
Extent of lymph node dissection				
D2	−4.14	−9.50 to 1.21	2.71	.128
D1+				
Approach				
Laparoscopy	7.60	3.95 to 11.25	1.85	<.001*
Robot				
Performed or assisted by a nonqualified surgeon[a]				
Yes	−1.72	−6.21 to 2.76	2.27	.448
No				

Note: β: regression coefficient.

Abbreviations: ASA-PS, American Society of Anesthesiologists Performance Status; BMI, body mass index; CI, confidence interval; SE, standard error.

[a]Nonqualified surgeon of Endoscopic Surgical Skill Qualification System of the Japanese Society for Endoscopic Surgery.

*Statistically significant.

pancreas compression. The restricted viewing angle of the rigid scope forces a robotic arm or an assistant's forceps to compress the pancreas. Compressing with a robotic arm tends to impose a strong pressure because of the lack of the sense of touch. That may be because there was no significant difference in the incidence of postoperative complications between robotic gastrectomy and laparoscopic gastrectomy, regardless of the shorter compression time in robotic gastrectomy. Further technical or technological development is desired. According to this multiple linear regression analysis, we identified two other confounding factors, male gender and advanced tumor, that affect the pancreas compression time. Patient characteristics and surgical data in the S group and the L group are shown in Table S1. There were more male patients (55.4% vs 84.1%, $P < .001$), patients with higher body mass index (median; 21.8 vs 23.3, $P = .013$), those who received laparoscopic surgery (53.8% vs 85.8%, $P < .001$) in the L group. We may have a risk of longer pancreas compression in these patients.

It is difficult to suggest which method of securing the surgical field is better to avoid pancreas compression, such as rolling back the pancreas with a gauze/sponge or the "pancreas-compressionless gastrectomy" method. Because some of the methods were adopted depending on the situation, we could not compare outcomes among the methods. Although we tried to analyze according to the most used method in each surgery, there was no difference in the incidence of postoperative complications or clinically relevant pancreatic fistula. This study only shows that reducing the pancreas compression time is important for a safer procedure in either method.

We additionally conducted the same analyses using the maximum duration time of compression at once in each surgery, not the total time of compression. There was a very weak correlation between the maximum duration time of compression at once and drain amylase concentration on POD 1 (R = 0.297, $P < .001$). That was weaker than the correlation between the total time of compression and drain amylase concentration. The cutoff value of the maximum duration time of compression at once for the prediction of high drain amylase concentration on POD 1 (1000 U/L or more) was 2 min. Incidence of clinically relevant pancreatic fistula (1.6% vs 12.0%, $P = .021$), all postoperative complications (13.1% vs 29.1%, $P = .025$) were significantly higher in the longer compression group than in the shorter group. These differences were also smaller than the differences in the two groups according to the total time of compression. This result may suggest that the duration time of compression at once is less meaningful for predicting the degree of blunt injury than the total time of compression. In most videos, pancreas compression was intermittent because we often changed the location of the forceps to secure the appropriate surgical field in each scene. It may make the association between the compression time and outcomes weaker.

In univariable and multivariable analysis for the incidence of postoperative complications and pancreas compression time, the attendance of a nonqualified surgeon of the Endoscopic Surgical Skill Qualification System of JSES as an operator or an assistant had no significant impact (Tables 4 and 5). That may be because all nonqualified surgeons were trainees for qualified surgeons and similarly well-experienced in gastric surgery. The high quality of controlling surgery by attending qualified surgeons also may explain the result.

This study has some limitations. First, this is a retrospective study performed at a single institute. Second, other factors can affect injury of the pancreas. Our study lacked an evaluation of the strength of pancreas compression, as it was obtained only by visual observation during video review. We focused only on pancreas compression but not on the direct injury caused by cutting or thermal injury. Moreover, we reviewed videos only during suprapancreatic lymph node dissection. Pancreas compression and injury during infrapyloric lymph node dissection also might affect the results. These limitations may explain why some patients with only a small pancreas compression time had a high drain amylase concentration or postoperative complications. A weak correlation between the pancreas compression time and drain amylase concentration can also be explained.

In conclusion, more than a few minutes of pancreas compression during minimally invasive gastrectomy was associated with a higher incidence of postoperative complications in gastric cancer patients. It is ideal for dissecting the suprapancreatic lymph nodes without any pancreas compression.

ACKNOWLEDGMENTS

We thank Editage (www.editage.com) for English language editing.

DISCLOSURE

Funding: The authors declare that no external funding was received for this study.

Conflict of Interest: The authors declare no Conflicts of Interest for this article.

Author contributions: The authors meet all the criteria of the International Committee of Medical Journal Editors (ICMJE).

Ethical statement: The protocol for this research project was approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Institutional Review Board of the Shizuoka Cancer Center, Approval No. J2019-173. Informed consent was substituted by the informed opt-out procedure because of the retrospective nature of the study, and anonymous clinical data were used for the analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Itamoto K, Hikage M, Fujiya K, Kamiya S, Tanizawa Y, Bando E, et al. The impact of pancreas compression time during minimally invasive gastrectomy on the postoperative complications in gastric cancer. Ann Gastroenterol Surg. 2021;5:785–793. https://doi.org/10.1002/ags3.12488