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審査学位論文
（博　士）

Hyperglycemia 3 days after esophageal cancer surgery is associated with an increased risk of postoperative infection

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Short Title: Hyperglycemia by esophagectomy

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Abstract

***Purpose*:** Postoperative hyperglycemia is associated with infectious complications after various types of surgery. Our objective was to determine whether postoperative blood glucose levels up to 1 week after highly invasive esophageal cancer surgery are associated with the incidence of postoperative infections (POIs).

***Methods*:** We conducted a retrospective chart review of 109 consecutive thoracic esophageal squamous cell cancer patients who underwent invasive esophagectomy with thoracotomy and laparotomy. The incidence of POIs and risk factors for POIs, including postoperative blood glucose levels, were evaluated.

***Results*:** Of the 109 patients, 37 (34.0%) developed POIs. Clinically, 73.0% of the POIs became evident on or after postoperative day 4 (median, 5.25 days; interquartile range, 3.00–9.25 days). On and after postoperative day 3, chronological changes in blood glucose levels were significantly different between two groups of patients with or without POIs, as indicated by repeated measures ANOVA (P = 0.006). Multivariate logistic regression analysis results showed that an increased blood glucose concentration on postoperative day 3 was a significant risk factor for POIs.

***Conclusions*:**

Our findings suggested that postoperative hyperglycemia on postoperative day 3 was a predictive factor of POIs after highly invasive esophageal cancer surgery.

Key words: esophagectomy, hyperglycemia, postoperative complications

Introduction

Improvements in surgical techniques, such as minimally invasive thoracoscopic and laparoscopic approaches, as well as perioperative management for thoracic esophageal cancer surgery have facilitated faster recovery and reduced complication rates after esophagectomy.[1-3] Meanwhile, the use of preoperative chemotherapy or chemoradiotherapy (CRT) has continued to increase with the aim to improve locoregional control and survival rates following esophageal cancer surgery.[4] Esophagectomy after preoperative therapy is often invasive because of the systemic or locoregional influence of chemo- and radiotherapeutic agents and is often associated with postoperative complications (POCs) including infections. Several studies have reported an increase in the incidence of postoperative infections (POIs), such as pneumonia as well as anastomotic leakage, mediastinitis, and surgical site infections (SSIs), in patients who received CRT followed by esophagectomy.[4-7] Furthermore, Bosset et al.[4] reported that postoperative mortality due to respiratory insufficiency, mediastinal infection, or sepsis in the combined treatment group was significantly greater than that in the surgery-alone group. Therefore, it is important to identify

predictive factors of POIs after highly invasive esophageal cancer surgery.

Higher perioperative glucose levels have been reported to be associated with complications after various types of cardiac, general, vascular, and orthopedic surgeries.[8-14] In these reports, the period of postoperative blood glucose monitoring varied from 12 h to 1 week. Vriesendorp et al.,[15] in the study on esophageal cancer surgery, monitored postoperative glucose values for up to 48 h after surgery and reported that early postoperative hyperglycemia after esophagectomy did not affect the incidence of POI or length of hospital stay. Therefore, we hypothesized that postoperative blood glucose levels longer than 48 h after esophageal cancer surgery were associated with the incidence of POI. Thoracic esophagectomy requiring both thoracotomy and laparotomy is the most invasive surgery for esophageal cancer, which may require a longer recovery period because of surgical stress compared with other procedures. In the present study, we investigated the association between postoperative blood glucose levels up to 1 week after surgery and the incidence of POIs in thoracic esophageal cancer patients who underwent highly invasive procedures with thoracotomy and laparotomy. The primary goal was to identify risk factors for POIs

after esophageal cancer surgery, and secondary goals were to clarify the association between hyperglycemia and POIs; chronological changes of blood glucose levels; the influence of glucose tolerance and insulin therapy; and cutoff values predicting POIs, including sites of infections.

Materials and Methods

Subjects

In this study, we retrospectively evaluated treatment outcomes of 109 thoracic esophageal cancer patients who underwent thoracic esophagectomy from January 1999 to December 2005 at the Department of Surgery, Iwate Medical University, Morioka, Japan. Details of the surgical procedure have been described previously.[16] In brief, the surgical procedure consisted of subtotal esophagectomy, three-field lymph node dissection, and gastric tube reconstruction by right-sided thoracotomy, laparotomy, and bilateral cervical approaches. Patients who underwent esophagectomy by thoracoscopic and/or laparoscopic approaches, which were adopted by our institution in 2006, were not included in this study because our goal was to focus on the predictive factors of

POCs after highly invasive esophagectomy. In all cases, jejunostomy tubes were placed intraoperatively.

Perioperative Management and Data Collection

One week before surgery, the administration of 5% glucose solution (lipid emulsion, 30%; calories, 10–14 kcal/kg/day) was initiated at a dose of 50 mL/kg/day. Oral nutritional intake was maintained until 1 day before surgery. Intravenous hyperalimentation was used for patients having difficulty with oral intake. On the basis of the favorable results of our previous randomized study on the effects of preoperative corticosteroid administration on postoperative morbidity in patients undergoing esophageal cancer surgery, 70 patients received preoperative methylprednisolone infusion within 30 min of the start of surgery.

Postoperatively, all patients received continuous infusion of Ringer's acetate solution with 5% glucose (Veen D; Nikken Chemicals, Tokyo, Japan) through peripheral intravenous catheters and continuous enteral feeding through jejunostomy tubes. Continuous enteral feeding was started 24–48 h after surgery at 5-10 kcal/kg/day

initially; the quantity of nutrition was progressively increased (i.e., 25, 50, and 75% of full strength on postoperative days 2, 3, and 4-5, respectively) up to the full strength (30 kcal/kg/day) on postoperative days 6-7. Peripheral solution was infused at approximately 2 mL/kg/h (10 kcal/kg/day) by postoperative day 7. Oral intake started after postoperative day 7. Antimicrobial prophylaxis was administered for an average of 3 days.

Blood glucose levels were measured every 12 h until 72 h after surgery and thereafter every 24 h by postoperative day 7 at the Central Clinical Laboratory of Iwate Medical University. Rapid-acting insulin was subcutaneously administered to patients with blood glucose levels of >250 mg/dL (>13.9 mmol/L), and a subcutaneous insulin injection was repeatedly administered to those with a maintained blood glucose level of >250 mg/dL beginning 2 h after injection. Blood glucose levels were measured every 2 h until the levels were below 250 mg/dL. Clinical data was retrieved from the clinical information database system of Iwate Medical University or patient medical charts.

Endpoints and Patient Variables

The American Diabetes Association[17] criteria were used to define three types of glucose tolerance: diabetes mellitus (DM), pre-diabetes (pre-DM), and normal. The DM group consisted of patients who were receiving diabetes treatment or diagnosed with DM, whereas the pre-DM group consisted of patients with impaired fasting glucose levels and/or impaired glucose tolerance.

POCs were defined according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0).[18] Definitions by the Centers for Disease Control and Prevention and the National Healthcare Safety Network[19,20] were used to diagnose POIs. Complications related to surgical procedures were assessed according to the Clavien–Dindo classification grading system,[21] and other complications were classified as per CTCAE v4.0.

Risk factors for POIs analyzed in this study included age, gender, American Society of Anesthesiologists Physical Status Classification (ASA-PS classification), body mass index (BMI), preoperative therapy, preoperative methylprednisolone administration, surgical duration, intraoperative blood loss, pathological tumor-node-metastasis (pTNM) classification,[22] glucose tolerance, and blood glucose

levels both preoperatively and on postoperative days 1, 3, 5, and 7. Moreover, blood glucose levels were monitored every 12 h until 60 h after surgery (postoperative day 3). Logistic regression analysis was used to assess the influence of these factors on POIs. On each postoperative day, receiver operating characteristic (ROC) curve analysis was performed to determine blood glucose cutoff levels to predict the risk of POIs.

Statistical Analysis

Descriptive and statistical analyses were performed. For normally distributed quantitative variables, data are presented as means ± standard deviations. For non-normally distributed variables, data are presented as medians and interquartile ranges. Risk factors for POIs were determined by univariate and multivariate analyses. The chi-squared test and Fisher's exact test were used for categorical variables. Quantitative variables were compared using the unpaired *t*-test, Welch's *t*-test, Mann–Whitney U-test, and Kruskal–Wallis test. Differences in postoperative chronological changes in the clinical laboratory test results between the two patient groups were analyzed using analysis of variance for repeated measures (repeated measures ANOVA).

Simple and multivariate logistic regression analyses were used to identify the risk factors of POIs. Variables significant at the 0.20 level in univariate analysis were used for multivariate logistic analysis. Variables significant at the 0.05 level were retained in the final model. For quantitative variables, ROC curve analysis was used to determine the value demonstrating the highest accuracy to predict POIs. Area under the ROC curve (AUC) analysis was used to determine the probability that the variable under study could distinguish among different outcomes.

A probability (*P*) value of <0.05 was considered statistically significant. In some cases, blood glucose data were missing for at least one timepoint. Statistical analysis was performed using IBM® SPSS® statistical software (version 20.0; IBM-SPSS, Inc., Chicago, IL, USA).

Results

POCs

No patient died within 30 days of surgery. Of the 109 patients, POCs were observed in

71 (65.1%), and 37 (34.0%) developed POIs. For analysis, these 37 patients were defined as the POI group and the others as the non-POI group. The sites and rates of POIs were as follows: pneumonia (n = 21, 19.3%), SSI (n = 10, 9.2%), catheter-associated bloodstream infection (n = 2, 1.8%), cholecystitis (n = 2, 1.8%), and methicillin-resistant *Staphylococcus aureus* (MRSA) enteritis (n = 4, 3.7%). SSIs included esophageal anastomotic leakage (n = 3, 2.8%), reconstructive gastric tube necrosis (n = 1, 0.9%), intra-abdominal abscess due to pancreatic fistula (n = 1, 0.9%), and wound infection (n = 5, 4.6%) (Table 1). Two patients had multiple infections: one with pneumonia and SSI and the other with MRSA enteritis and SSI. Clinically, 75.7% (28/37) of the POIs became evident on or after postoperative day 4 (median, 5.25 days; interquartile range, 3.00–9.25 days).

Baseline Patient Characteristics and POIs

Baseline patient characteristics are shown in Table 2. POIs were observed more frequently in elderly patients than in younger patients (P = 0.07). No significant difference between the POI and non-POI groups was observed with regard to gender,

ASA-PS classification, BMI, glucose tolerance, preoperative therapy, preoperative methylprednisolone, preoperative nutrition, surgical duration, intraoperative blood loss, pTNM classification, or postoperative nutrition.

Chronological Changes in Blood Glucose Levels in Patients with or without POCs

Comparisons of chronological changes in blood glucose levels between the POI and non-POI groups showed significant differences. On postoperative day 1, blood glucose levels among the two patient groups were similar. The POI group had significantly higher blood glucose levels on postoperative days 3 and 5 compared to the non-POI group. The average blood glucose levels of patients in the POI group were maintained at >150 mg/dL until postoperative day 7, whereas those in the non-POI group already decreased by postoperative day 3 and were maintained at <150 mg/dL (Fig. 1a).

Chronological changes in postoperative blood glucose levels differed among the three groups of patients categorized by glucose tolerance. In the normal glucose tolerance group, the blood glucose levels of patients in the POI group were significantly higher on postoperative days 3 and 5 than those in the non-POI group but decreased to

the same level by postoperative day 7 (Fig. 1b). In the DM and pre-DM groups, significant differences in postoperative changes in glucose levels were observed only on postoperative day 5 in the pre-DM group between the POI and non-POI groups. However, the glucose levels of patients in the POI group tended to be higher than those of patients in the non-POI group (Fig. 1c, d). In the DM group, glucose levels continuously increased until postoperative day 7 in both the POI and non-POI groups (Fig. 1d). Semidiurnal evaluation of blood glucose levels until 60 h after surgery demonstrated that patients in the POI group had significantly higher blood glucose levels at or after 48 h than those in the non-POI group (Fig. 2).

Of the 109 patients, 19 (17%) were administered rapid-acting insulin (Humulin R®; Eli Lilly and Company, Indianapolis, IN, USA) by postoperative day 7: 10% (5/49) in the normal group, 10% (4/39) in the pre-DM group, and 48% (10/21) in the DM group. There was no significant difference in the incidence of POIs among the three groups of glucose tolerance types (Table 3). There was no significant association between patients weight and the total amounts of insulin injected until postoperative day 7 (Spearman's r = -0.065, P=0.523). In addition, we classified 109 patients into 2

groups based on the amount of enteral feeding received during the 7 postoperative days: >7,000 and <7,000 kcal. Significant difference was not observed between these two groups in terms of the total amounts of insulin injected in the days (P=0.444).

Risk Factors for POIs

Because 73% of the POIs became clinically evident on or after postoperative day 4, simple logistic regression analysis was performed to assess the aforementioned baseline patient characteristics and blood glucose levels on postoperative day 3 to identify candidate predictive factors of POIs. The variables significant at the 0.20 level in univariate analysis were age, BMI, and blood glucose level on postoperative day 3. Multivariate logistic regression analysis of these variables showed that age and blood glucose levels on postoperative day 3 were identified as predictive factors of POIs (Table 4). ROC curve analysis was performed to determine blood glucose cutoff levels predictive of POIs. The most discriminatory blood glucose cutoff value to predict POIs was 139.5 mg/dL [AUC, 0.623, P = 0.04, 95% confidence interval (CI), 0.507–0.740]. Next, we classified the 109 patients into two groups according to blood glucose levels

below or above 140 mg/dL on postoperative day 3. The incidence of nonsurgical site infections (38.5%), particularly pneumonia (28.8%), in patients with blood glucose levels of >140 mg/dL on postoperative day 3 was significantly higher than that (15.7 and 10.5%, respectively) in patients with blood glucose levels of <140 mg/dL (Table 5).

Discussion

Multivariate analysis revealed that age and blood glucose levels on postoperative day 3 were predictive factors of POIs (Table 4). Previous studies have reported that an increased incidence of POIs, including pneumonia, was observed in elderly patients after various surgeries including esophagectomy, thoracotomy, and general surgery.[23, 24] In this study, however, no significant differences were observed between a reference group (age range, 40–59 years) and the eldest group (age range, 70–79 years). Therefore, age may not be an appropriate predictive factor of POI onset after esophageal cancer surgery. Many studies have also demonstrated a correlation between postoperative blood glucose levels and POI onset following general and gastroenterological surgery.[25-27] In terms of esophageal cancer surgery, however,

Vriesendorp et al.[15] reported that early postoperative hyperglycemia did not affect the incidence of POIs. In that study, approximately one-half of patients with esophageal adenocarcinoma underwent transhiatal esophagectomy. In the present study, we searched for predictive factor of POIs by focusing on thoracic esophageal squamous cell carcinoma patients who underwent highly invasive procedures with thoracotomy and laparotomy while excluding those who underwent thoracoscopic and laparoscopic surgery; we found a significant correlation between postoperative blood glucose levels and POIs. In addition, it appeared that the discrepancy between our results and those reported by Vriesendorp et al. was due to the difference in the period of blood glucose monitoring after surgery. In our present study, there was no significant difference in blood glucose levels between the POI and non-POI groups until postoperative day 2 as well as the previous report (Fig. 2). However, the POI group showed significantly higher blood glucose levels after 48 h (postoperative day 3) than did the non-POI group. Our current findings present the first evidence of an association between postoperative blood glucose levels and the incidence of POIs after esophageal cancer surgery.

It is well known that glucose intolerance has a significant role in the

development of POIs. In the present study, however, the incidence of POIs was not increased in DM patients and no significant difference was observed in blood glucose levels between the POI and non-POI groups at all timepoints. Dronge et al.[28] reported that good preoperative glycemic control (HbA1c levels < 7.0%) in major noncardiac surgery was associated with a decrease in infectious complications across various surgical procedures. Because all patients in the DM group in our study received preoperative therapy for DM, preoperative glycemic control may also decrease the incidence of POIs in highly invasive esophageal cancer surgery. With regard to chronological changes in postoperative blood glucose levels, patients in the DM group showed a sustained elevation of glucose levels until postoperative day 7, which was different from that observed in other groups. However, it may take longer to recover from surgical stress following invasive esophageal cancer surgery. Therefore, the differences in blood glucose levels between the POI and non-POI groups may not have been evident in the DM group because the ability to metabolize glucose could not be restored until postoperative day 7.

It is also well known that corticosteroid administration can cause an elevation

in blood glucose levels and an increased incidence of infections. Although a significant increase in blood glucose levels was observed in the methylprednisolone administration group (n = 70) compared with the non-administration group (n = 39) on the day of surgery, glucose levels did not differ between the two groups after postoperative day 1 (P = 0.63, repeated measures ANOVA, Fig. 3). Furthermore, the incidence of POIs did not differ between the two groups; these findings were in accordance with those of our previous study.[16] The results of the present study demonstrated that these preoperative factors associated with postoperative glucose levels, glucose intolerance, and corticosteroid administration were not associated with an increased incidence of POIs after esophageal cancer surgery.

ROC curve analysis showed that the most discriminatory blood glucose level on postoperative day 3 to predict the risk of POI was 139.5 mg/dL. Ata et al.[25] showed that the SSI rates in general surgery and colorectal surgery were increased in patients with postoperative blood glucose levels of 140 mg/dL within 24 h. Eshuis et al.[26] also reported that early postoperative hyperglycemia (≥140 mg/dL) was associated with postoperative infectious complications and the most discriminatory

cutoff blood glucose level was 141 mg/dL, as determined by ROC curve analysis. Therefore, it appeared that the optimal blood glucose cutoff level to predict the risk of POIs was commonly around 140 mg/dL, irrespective of the type of surgery, although opinions on the appropriate time for evaluation varied according to the type of surgery. In terms of esophageal cancer surgery, interestingly, the incidence of nonsurgical infectious complications, particularly pneumonia, was significantly higher in patients with blood glucose levels of >140 mg/dL on postoperative day 3 (Table 5).

It remains unclear whether postoperative hyperglycemia is the result or the cause of POIs. Furthermore, it remains controversial whether intensive insulin therapy is suitable to reduce POCs including POIs.[29-31] Therefore, further studies will be required to evaluate the efficacy of postoperative glycemic control therapies for POIs after esophageal cancer surgery.

Conclusion

The study findings suggested that postoperative hyperglycemia on postoperative day 3 could be a predictive factor of the risk of POIs after highly invasive esophageal cancer

surgery, and evaluation of postoperative hyperglycemia may contribute to better outcomes for patients with occult POIs through earlier detection and management of infections.

Conflict of Interest There are no potential conflicts of interest to disclose.

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Figure 1

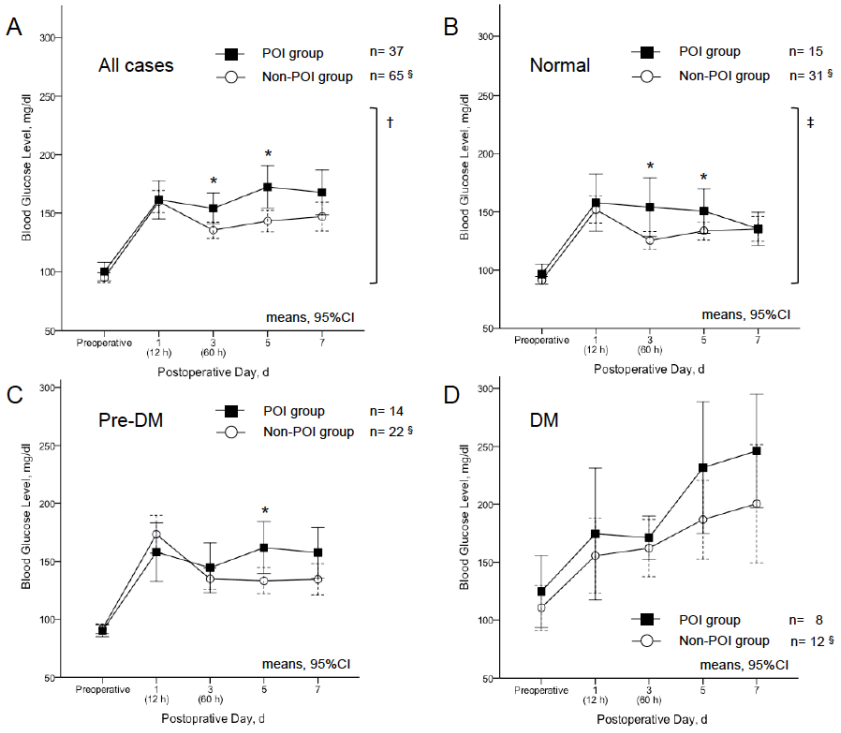

Figure 1. Chronological changes in the blood glucose level in relation to glucose tolerance and POIs. A, all cases; B, normal group; C, pre-DM group; D, DM group. POI, Postoperative infection; CI, Confidence interval; DM, diabetes mellitus.

*$P < 0.05$.

†$P = 0.006$, repeated measures ANOVA.

‡$P = 0.02$, repeated measures ANOVA.

§Cases with missing values for blood glucose levels were excluded from the list.

Figure 2

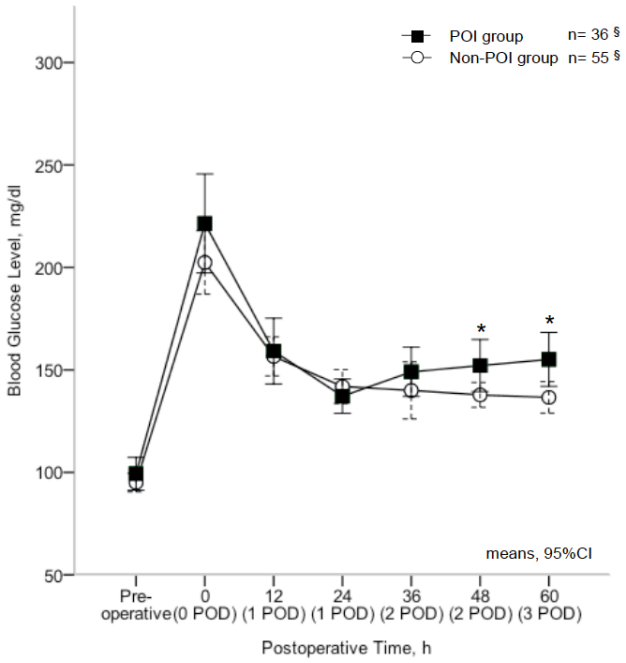

Figure 2. Chronological changes in blood glucose levels with or without postoperative complications within the first 60 h after surgery.

POI, Postoperative infection; POD, Postoperative day; CI, Confidence interval.

* $P < 0.05$.

§The cases with missing values for blood glucose levels were excluded from the list.

Figure 3

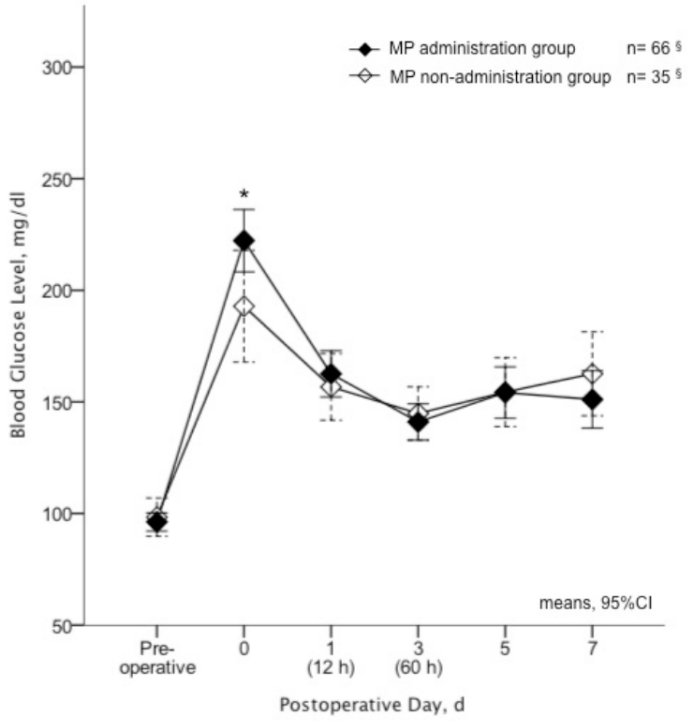

Figure 3. Chronological changes in blood glucose levels with or without preoperative administration of methylprednisolone.

MP, Preoperative methylprednisolone; CI, Confidence interval.

* $P < 0.05$.

§Cases with missing values for blood glucose levels were excluded from the list..

Table 1. Postoperative complications

Any complication[a]	No.	Grade (No.)		Infectious complication CDC/NHSN criteria[b]	Postoperative day when infection was revealed, median (range)
Surgical complications					
Chylothorax	5	II[c]			
Hoarseness	2	I[c]			
Recurrent laryngeal nerve palsy	4				
		I[c] (1)			
		II[c] (1)			
		IVa[c] (2)			
Anastomotic stricture	2	IIIa[c]			
Jejunal obstruction	2	IIIb[c]			
Wound infection	5	I[c]	→	SSI - Superficial incisional primary SSI	10 (8–14)
Esophageal anastomotic leak	3				
		II[c] (1)	→	SSI - Deep incisional primary SSI	11
		IIIa[c] (1)	→	SSI - Deep incisional primary SSI	14
		IIIb[c] (1)	→	SSI - Organ/space SSI (SSI-MED)	14
Reconstructive gastric tube necrosis	1	IVa[c]	→	SSI - Organ/space SSI (SSI-MED)	8
Pancreatic fistula	3				
		I[c] (2)			
		IIIb[c] (1)	→	SSI - Organ/space SSI (SSI-IAB)	22
Nonsurgical complications					
Supraventricular tachycardia	11	2 or 3[d]			
increased AST/ALT	22	2 or 3[d]			
increased Blood bilirubin	9	2 or 3[d]			
Ileus	1	3[d]			
Interstitial pneumonia	1	3[d]			
SIADH	1	3[d]			
Pneumonia	21	2 or 3 or 4[d]	→	Clinically defined pneumonia	4 (2–11)
Catheter-associated bloodstream infection	2	2[d]	→	Laboratory-confirmed bloodstream infection	2, 3
MRSA enteritis	4	2 or 3[d]	→	Gastrointestinal system infection-Gastroenteritis	5 (2–8)
Cholecystitis	2	2[d]	→	Gastrointestinal system infection-Intraabdominal	7, 11

Abbreviations: SIADH, Syndrome of inappropriate secretion of antidiuretic hormone; SSI, surgical site infection; SSI-MED, SSI-mediastinitis; SSI-IAB, SSI-intra-abdominal.
[a]There is some overlapping
[b]CDC/NHSN, Centers for Disease Control and Prevention/National Healthcare Safety Network - Surveillance Definition of Healthcare-Associated Infection and Criteria for Specific Types of Infections in the Acute Care Setting
[c]Clavian–Dingo Grade
[d]CTCAE Grade

Table 2. Baseline Patient Characteristics and the Incidence of POIs

Characteristic		Postoperative Infections		
		No	Yes	*P*
Gender, No. (%)				
Male	99 (90.8)	65 (65.7)	34 (34.3)	1.00
Female	10 (9.2)	7 (70.0)	3 (30.0)	
Age, No. (%)				
<60 years	39 (35.8)	30 (76.9)	9 (23.1)	0.07
≧60 years	70 (64.2)	42 (60.0)	28 (40.0)	
ASA-PS classification, No. (%)				
I	52 (47.7)	33 (63.5)	19 (36.5)	0.59
II	57 (52.3)	39 (68.4)	18 (31.6)	
Body mass index, No. (%)				
<18.5	13 (11.9)	9 (69.2)	4 (30.8)	
18.5-24.9	84 (77.1)	58 (69.0)	26 (31.0)	0.18
≧25.0	12 (11.0)	5 (41.7)	7 (58.3)	
Glucose tolerance, No. (%)				
Normal	49 (44.9)	34 (69.4)	15 (30.6)	
Pre-DM	39 (35.8)	25 (64.1)	14 (35.9)	0.78
DM	21 (19.3)	13 (61.9)	8 (38.1)	
Preoperative therapy, No. (%)				
No	92 (84.4)	60 (65.2)	32 (34.8)	0.68
Yes		12 (70.6)	5 (29.4)	
Chemoradiotherapy	8 (7.3)	7	1	
Chemotherapy	9 (8.3)	5	4	
Preoperative methylprednisolone, No. (%)				
No	39 (35.8)	23 (59.0)	16 (41.0)	0.24
Yes	70 (64.2)	49 (70.0)	21 (30.0)	
Preoperative parenteral nutrition, No. (%)				
No	97 (89.0)	65 (67.0)	32 (33.0)	0.54
Yes	12 (11.0)	7 (58.3)	5 (41.7)	
pStage (TNM[a]), No. (%)				
0	0 (0)	0	0	
IA	13 (11.9)	10	3	
IB	12 (11.0)	8	4	
IIA	10 (9.2)	6	4	
IIB	9 (8.3)	5	4	0.85
IIIA	21 (19.3)	12	9	
IIIB	11 (10.1)	9	2	
IIIC	14 (12.8)	10	4	
IV	19 (17.4)	12	7	
Postoperative nutrition during the first 7 postoperative days, No. (%)				
Enteral	101 (92.7)	70 (69.3)	31 (30.7)	0.33
Enteral / Parenteral[b]	5 (4.6) [c]	2 (40.0)	3 (60.0)	
Operative length, median [IQR], min.	370.0 [329.5–412.5]	362.5 [325.0–410.0]	370.0 [340.0–422.5]	0.55
Operative blood loss, median [IQR], mL.	549.0 [377.5–703.5]	551.0 [368.0–684.5]	542.0 [390.0–872.5]	0.44

Abbreviations: ASA-PS, American Society of Anesthesiologists Physical Status; SD, standard deviation; IQR, Interquartile range; pStage, pathological stage.

[a]UICC classification[22]

[b]Nutrition management was changed from enteral nutrition to parenteral nutrition

[c]Three patients with MRSA enteritis in the POI group were excluded because parenteral nutrition was administrated after detection of the infectious complication

Table 3. Glucose Intolerance and Insulin Therapy

Variable	Normal (n = 49)	Pre-DM (n = 39)	DM (n = 21)	*P*
Administration of Insulin[a], No. (%)	5 (10)	4 (10)	10 (48)	0.001
Insulin Dose[a], mean (SD), IU	0.82 (2.5)	1.49 (5.6)	44.52 (73.6)	<0.001

Abbreviations: ASA, American Society of Anesthesiologists; SD, standard deviation; DM, diabetes mellitus.
[a]During the first 7 postoperative days

Table 4. Risk Factors Associated with Postoperative Infection by Logistic Regression Analysis

Variable	Unjusted OR (95%CI)	*P* Value	Adjusted OR (95%CI)	*P*
Gender				
Female	Reference			
Male	1.22 (0.30–5.02)	0.78		
Age, years				
40–59	Reference		"Reference"	
60–69	2.68 (1.03–6.89)	0.04	3.87 (1.31–11.46)	0.01
70–79	1.57 (0.51–4.82)	0.43	1.98 (0.56–7.07)	0.29
ASA–PS classification				
I	Reference			
II	0.80 (0.36–1.77)	0.59		
Body mass index				
<18.5	Reference			
18.5–24.9	1.01 (0.29–3.58)	0.99		
≥25.0	3.15 (0.61–16.31)	0.17		
Preoperative therapy				
No	Reference			
Yes	0.78 (0.25–2.41)	0.67		
Preoperative methylprednizolone				
No	Reference			
Yes	0.62 (0.27–1.40)	0.25		
Operative time, min				
<370	Reference			
≧370	1.24 (0.56–2.75)	0.59		
Operative blood loss, mL				
<550	Reference			
≧550	0.95 (0.43–2.09)	0.89		
pStage (TMN)				
I	Reference			
II	1.87 (0.53–6.60)	0.33		
III	1.24 (0.43–3.62)	0.69		
IV	1.50 (0.42–5.38)	0.53		
Glucose intolerance				
Normal	Reference			
Pre-DM	1.27 (0.52–3.10)	0.60		
DM	1.40 (0.48–4.07)	0.54		
Blood glucose level in the 3rd postoperative day, mg/dL				
80–119	Reference		Reference	
120–159	1.14 (0.39–3.28)	0.82	0.99 (0.32–3.09)	0.99
160–189	2.86 (0.86–9.55)	0.09	3.68 (1.01–13.45)	0.05
≥190	7.33 (1.48–36.24)	0.02	6.76 (1.22–37.35)	0.03

Abbreviations: OR, odds ratio; CI, confidence interval; ASA-PS, American Society of Anesthesiologists Physical Status; DM, diabetes mellitus.

Table 5. Infectious Complications and Blood Glucose Level on Postoperative Day 3

Infectious Complications[a]	Blood Glucose Level, mg/dl (POD 3)		*P*
	<140 n = 57 (%)	≥140 n = 52 (%)	
Surgical complications	7 (12.3)	3 (5.8)	0.33
SSI - Superficial incisional primary SSI	3 (5.3)	2 (3.8)	1.00
SSI - Deep incisional primary SSI	2 (3.5)	0 (0)	0.50
SSI - Organ/space SSI (SSI-MED)	1 (1.8)	1 (1.9)	1.00
SSI - Organ/space SSI (SSI-IAB)	1 (1.8)	0 (0)	1.00
Nonsurgical complications	9 (15.7)	20 (38.5)	0.01
Clinically defined pneumonia	6 (10.5)	15 (28.8)	0.03
Laboratory-confirmed bloodstream infection	1 (1.8)	1 (1.9)	1.00
Gastrointestinal system infection - Gastroenteritis	1 (1.8)	3 (5.8)	0.35
Gastrointestinal system infection - Intra-abdominal	1 (1.8)	1 (1.9)	1.00

Abbreviations: POD, postoperative day; SSI, surgical site infection; SSI-MED, SSI-mediastinitis; SSI-IAB, SSI-intra-abdominal.

[a]There is some overlapping