Journal of Gastrointestinal Surgery 28 (2024) 1083–1088

Contents lists available at ScienceDirect

Journal of Gastrointestinal Surgery

journal homepage: www.jogs.org

Original Article

Postoperative delayed emptying after total, subtotal, or distal gastrectomy for gastric cancer: a population-based study

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ARTICLE INFO

Article history:
Received 20 January 2024
Received in revised form 26 March 2024
Accepted 27 April 2024
Available online 3 May 2024

Keywords:
Delayed conduit emptying
Delayed gastric emptying
Gastrectomy
Gastric adenocarcinoma
Postoperative complication

ABSTRACT

Background: This study aimed to examine the rate of delayed emptying and other 90-day postoperative complications after total, subtotal, and distal gastrectomies for gastric adenocarcinoma in a population-based setting.
Methods: This study included all patients who underwent total, subtotal, or distal gastrectomy for gastric cancer in Finland in 2005–2016, with follow-up until December 31, 2019. Logistic regression provided the odds ratios with 95% CIs of 90-day mortality. The results were adjusted for age, sex, year of surgery, comorbidities, pathologic stage, and neoadjuvant therapy.
Results: A total of 2058 patients underwent total (n = 1227), subtotal (n = 450), or distal (n = 381) gastrectomy. In the total, subtotal, and distal gastrectomy groups, the rates of 90-day delayed emptying were 1.7%, 1.3%, and 2.1% in the whole cohort and 1.6%, 1.8%, and 3.5% in the subgroup analysis of R0 resections, respectively. The resection type was not associated with the risk of delayed emptying. Subtotal gastrectomy was associated with a lower risk of major complications and reoperations, whereas distal gastrectomy was associated with a lower risk of anastomotic complications.
Conclusion: The extent of resection did not affect delayed emptying, whereas fewer postoperative complications were observed after subtotal or distal gastrectomy than after total gastrectomy.

Introduction

Gastric cancer is the third leading cause of cancer deaths and the fifth most frequently diagnosed cancer worldwide annually [1]. Surgery with D2 lymphadenectomy and R0 resection combined with perioperative therapy is considered the standard treatment for

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https://doi.org/10.1016/j.gassur.2024.04.026

gastric adenocarcinoma [2]. Partial gastrectomy instead of total gastrectomy can be selected when a satisfactory proximal resection margin can be obtained [2].

Gastric cancer surgery is associated with high rates of postoperative complications ranging from 18.3% to 36.0% [3,4]. Delayed emptying (delayed conduit emptying after total gastrectomy and delayed gastric emptying after subtotal or distal gastrectomy) is one of the major complications after gastrectomy for gastric cancer, with an incidence rate of 4.2% to 25.0% [4–6]. Delayed emptying is characterized by the stasis of gastric contents causing epigastric fullness, nausea, and vomiting, leading to delays in oral intake and prolonged hospital stay [6], and may affect overall survival [4]. The underlying causes of delayed emptying are unclear, and studies have speculated a link between delayed emptying and vagal nerve dissection, reconstruction technique (Roux stasis syndrome), reconstruction route (antecolic vs retrocolic), the size of the remnant stomach, and patients' multiple comorbidities [6]. A study of 266 patients with gastric cancer who underwent Roux-en-Y distal gastrectomy found that a tumor located in the lower third of the stomach was associated with delayed emptying [7]. In addition, the same finding was observed in a study of 412 patients undergoing distal gastrectomy with different reconstruction routes for gastric cancer [6]. Furthermore, this study showed that the resected area was significantly larger in the delayed emptying group than in the nondelayed emptying group [6].

There is a lack of large, population-based studies comparing delayed emptying after total, subtotal, and distal gastrectomies for gastric cancer. The main aim of this study was to examine the rate of delayed emptying after total, subtotal, and distal gastrectomies for gastric adenocarcinoma in a population-based setting. The secondary aim was to report other 90-day postoperative complications after total, subtotal, or distal gastrectomy.

Materials and methods

Study design

This was a population-based, nationwide, and retrospective cohort study from Finland that included total, subtotal, and distal gastrectomies for gastric adenocarcinoma. All other resection types were excluded. Patients with other histologic types of gastric malignancies were excluded because they were not comparable in terms of treatment and prognosis. The study period was from January 1, 2005, to December 31, 2016, with follow-up until December 31, 2019 [8]. Patients undergoing total, subtotal, or distal gastrectomy were compared according to delayed emptying and other 90-day postoperative complications and reoperations. The study was approved by the regional ethical review board in Oulu, Finland; the Finnish national health officials; and hospital districts [9].

Data collection

A retrospective comparison of long-term survival in different surgical operations is prone to bias in single-center studies. The Finnish National Esophago-Gastric Cancer Cohort (FINEGO) includes all patients with esophageal and gastric cancers diagnosed in Finland between 1987 and 2016 [8]. The FINEGO database contains information from the Finnish Cancer Registry, Finnish National Institute for Health and Welfare registries, Care Register for Health Care, and Hospital Discharge Registry. The Finnish Cancer Registry is 87.0% complete for gastric cancer, and the Hospital Discharge Registry is 92.7% complete for gastric cancer [10]. Surgically treated patients were identified using the Nordic MedicoStatistical Committee surgical codes. Identification using both registries by searching for cancer diagnoses and operation codes allows near 100% completeness of eligible patient identification. After the identification of cases, available information, including age, sex, comorbidity [11], surgery, and other variables, were collected from the Finnish Cancer Registry, Finnish National Institute for Health and Welfare registries, Care Register for Health Care, and Hospital Discharge Registry [8]. Medical reports were obtained from the respective healthcare units and reviewed by specialized surgeons, providing accurate information on tumor location, histology, and stage; type of resection; neoadjuvant treatment; and complications. All-cause mortality data were obtained from the 100% complete death registry, held by Statistics Finland until December 31, 2019 [12].

Exposures

Patients undergoing subtotal or distal gastrectomy were considered the study exposure group, and patients undergoing total gastrectomy were considered the control group.

The type of gastrectomy was defined by resection lines. In total gastrectomy, the resection line was made in the distal esophagus. In subtotal gastrectomy, the resection line was situated in the upper third of the stomach, resulting in a gastric pouch similar to gastric bypass surgery and/or an intact gastric fundus. In distal gastrectomy, the resection line was situated in the line between the upper and middle third of the stomach or in the middle third of the stomach, usually from the lesser curvature to the watershed line of the large curvature.

Outcomes

The primary outcome of the study was the rate of delayed emptying after total, subtotal, or distal gastrectomy. According to the Esophagectomy Complications Consensus Group (ECCG) classification [13], delayed emptying was designated as a requirement of nasogastric drainage over 7 days (delayed conduit emptying after total gastrectomy and delayed gastric emptying after subtotal or distal gastrectomy). The secondary outcomes were the rates of other 90-day postoperative complications (anastomotic complication, bleeding, small bowel obstruction, ileus, pancreatic fistula, intra-abdominal abscess, major complication, and reoperation), as defined in the ECCG classification [13].

Statistical analysis

The analyses followed a detailed a priori study protocol. IBM SPSS software (version 26.0; IBM Corporation) was used for all analyses. Follow-up times were calculated from the date of surgery to the time of death or the end of follow-up, whichever occurred first. Survival was calculated using the life table method, visualized with Kaplan-Meier curves. Logistic regression provided odds ratios (ORs) with 95% CIs. To avoid confounding, adjustments for 6 known prognostic factors were made: age (continuous), sex (male/female), year of the surgery (continuous), comorbidity (Charlson Comorbidity Index 0, 1, or ≥2 [excluding the gastric cancer under treatment]) [11]), pathologic stage (stage 0-I, II, III, or IV, according to the eighth edition American Joint Committee on Cancer/International Union Against Cancer staging of gastric cancer [14]), and neoadjuvant therapy (yes/no). Furthermore, analysis that included only R0 resections was performed. Patients with completely missing exposure or outcome data were excluded from the analysis.

Results

Patients

Gastrectomy for gastric adenocarcinoma was performed in 2196 patients during 2005–2016. Of the 2196 patients, 2063 underwent total, subtotal, or distal gastrectomy. Of note, 5 patients with missing

Table 1
Clinical variables in 2058 patients who underwent gastrectomy for gastric adenocarcinoma in Finland from 2005 to 2016

Variable	Whole cohort, N = 2058	Total gastrectomy, n = 1227	Subtotal gastrectomy, n = 450	Distal gastrectomy, n = 381
Age, y	70 (62-78)	68 (60-76)	72 (64-80)	75 (67-82)
Sex				
Male	1141 (55.4)	678 (55.2)	254 (56.4)	209 (54.9)
Female	917 (44.6)	550 (44.8)	196 (43.6)	172 (45.1)
Charlson comorbidity index				
0	1030 (50.0)	664 (54.1)	201 (44.7)	165 (43.3)
1	626 (30.4)	366 (29.8)	142 (31.5)	118 (31.0)
≥2	402 (19.5)	197 (16.1)	107 (23.8)	98 (25.7)
Tumor location				
Proximal (including cardia)	215 (10.4)	212 (17.3)	3 (0.7)	0 (0.0)
Middle	878 (42.7)	690 (56.2)	124 (27.5)	64 (16.8)
Distal	964 (46.8)	325 (26.5)	323 (71.8)	316 (82.9)
Missing	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)
Neoadjuvant treatment				
Yes	1758 (85.4)	224 (18.3)	56 (12.4)	13 (3.4)
No	293 (14.2)	999 (81.4)	391 (86.9)	368 (96.6)
Missing	7 (0.3)	4 (0.3)	3 (0.7)	0 (0.0)
Pathologic stage				
0-I	508 (24.7)	273 (22.2)	132 (29.3)	103 (27.0)
II	580 (28.2)	351 (28.6)	130 (28.9)	99 (26.0)
III	714 (34.7)	476 (38.8)	136 (30.2)	102 (26.8)
IV	215 (10.4)	104 (8.5)	45 (10.0)	66 (17.3)
Missing	41 (2.0)	23 (1.9)	7 (1.6)	11 (2.9)
Radicality				
R0	1495 (72.6)	928 (75.6)	340 (75.6)	227 (59.6)
R1	165 (8.0)	122 (9.9)	22 (4.9)	21 (5.5)
R2	160 (7.8)	71 (5.8)	37 (8.2)	52 (13.6)
Palliative intent	158 (7.7)	57 (4.7)	31 (6.9)	70 (18.4)
Missing	80 (3.9)	49 (4.0)	20 (4.4)	11 (2.9)
90-d Complications				
Delayed emptying	35 (1.7)	21 (1.7)	6 (1.3)	8 (2.1)
Anastomotic complication	98 (4.8)	72 (5.9)	16 (3.5)	10 (2.6)
Bleeding	75 (3.6)	44 (3.6)	14 (3.1)	17 (4.5)
Small bowel obstruction	14 (0.7)	8 (0.7)	5 (1.1)	1 (0.3)
Ileus	102 (5.0)	52 (4.2)	21 (4.7)	29 (7.6)
Pancreatic fistula	14 (0.7)	13 (1.1)	0 (0.0)	1 (0.3)
Intra-abdominal abscess	160 (7.8)	107 (8.7)	35 (7.8)	18 (4.7)
Major complication	340 (16.5)	219 (17.8)	62 (13.8)	59 (15.5)
Reoperation	160 (7.8)	106 (8.6)	24 (5.3)	30 (7.9)

Data are presented as median (IQR) or number (percentage).

exposure or primary outcome data were excluded. Total gastrectomy was performed in 1227 patients (59.6%), subtotal gastrectomy in 450 patients (21.9%), and distal gastrectomy in 381 patients (18.5%). The median age of all patients was 70 years. Most study patients had pathologic stage III diseases and distally located tumors. R0 resection was achieved in 72.6% of the patients, and palliative resections were performed in 7.7% of the study patients. Patient characteristics are described in Table 1.

Primary outcome

The rates of delayed emptying were 1.7% after total gastrectomy, 1.3% after subtotal gastrectomy, and 2.1% after distal gastrectomy. The type of resection was not associated with the risk of 90-day delayed emptying in the crude analysis (OR: 0.78 [95% CI, 0.31–1.94] for subtotal gastrectomy and 1.23 [95% CI, 0.54–2.80] for distal gastrectomy, compared with total gastrectomy) (Table 2) or in the adjusted analysis (OR: 0.65 [95% CI, 0.26–1.65] for subtotal and 0.88 [95% CI, 0.37–2.09] for distal gastrectomy, compared with total gastrectomy) (Table 2). In the subgroup analysis of R0 resections, the rates of delayed emptying were 1.6% after total gastrectomy, 1.8% after subtotal gastrectomy, and 3.5% after distal gastrectomy, and the results were similar to those of the main analysis (Table 3).

Secondary outcomes

The rates of 90-day complications are shown in Table 1. The rates of major complications were 17.8% after total gastrectomy, 13.8% after subtotal gastrectomy, and 15.5% after distal gastrectomy. In multivariate analysis, subtotal gastrectomy was associated with a lower risk of major complications (OR, 0.70; 95% CI, 0.51–0.96) than total gastrectomy, whereas distal gastrectomy was not (Table 2). The reoperation rates in the total, subtotal, and distal gastrectomy groups were 8.6%, 5.3%, and 7.9%, respectively. Subtotal gastrectomy was associated with a lower risk of reoperations in the adjusted analysis (OR, 0.56; 95% CI, 0.35–0.91) than total gastrectomy, whereas distal gastrectomy was not (Table 2).

Distal gastrectomy, but not subtotal gastrectomy, was associated with a lower risk of anastomotic complications in the adjusted analysis (OR, 0.43; 95% CI, 0.21–0.85) than total gastrectomy (Table 2). In the subgroup analysis of R0 resections, distal gastrectomy was associated with a lower risk of anastomotic complications in the adjusted analysis (OR, 0.27; 95% CI, 0.10–0.77) and a lower risk of intra-abdominal abscesses in the adjusted analysis (OR, 0.46; 95% CI, 0.46–0.95) than total gastrectomy (Table 3).

Discussion

This population-based, nationwide study showed that the type of gastric resection (total, subtotal, or distal) was not associated with the risk of delayed emptying. Lower risks of major complications and reoperations were observed after subtotal gastrectomy, and lower risks of anastomotic complications were observed after distal gastrectomy.

The main strength of this population-based study is the complete identification and 100% complete follow-up of all the study patients diagnosed with gastric adenocarcinoma in Finland. The population-

Table 2
The 90-day complications after total, subtotal, or distal gastrectomy for gastric adenocarcinoma, expressed as odd ratios with 95% CIs

Variable	Number of patients N = 2058	Total gastrectomy N = 1227	Subtotal gastrectomy n = 450	Distal gastrectomy n = 381
Delayed emptying				
All patients (crude)	2058	1.00 (Reference)	0.78 (0.31-1.94)	1.23 (0.54-2.80)
All patients (adjusted)[a]	2058	1.00 (Reference)	0.65 (0.26-1.65)	0.88 (0.37-2.09)
Anastomotic complication				
All patients (crude)	2058	1.00 (Reference)	0.59 (0.34-1.03)	0.43 (0.22-0.85)
All patients (adjusted)[a]	2058	1.00 (Reference)	0.59 (0.33-1.03)	0.43 (0.21-0.85)
Bleeding				
All patients (crude)	2058	1.00 (Reference)	0.86 (0.47-1.59)	1.26 (0.71-2.23)
All patients (adjusted)[a]	2058	1.00 (Reference)	0.77 (0.40-1.45)	1.14 (0.62-2.08)
Small bowel obstruction				
All patients (crude)	2058	1.00 (Reference)	1.71 (0.56-5.26)	0.40 (0.50-3.22)
All patients (adjusted)[a]	2058	1.00 (Reference)	1.82 (0.58-5.73)	0.36 (0.04-3.02)
Ileus				
All patients (crude)	2058	1.00 (Reference)	1.11 (0.66-1.86)	1.86 (1.16-2.98)
All patients (adjusted)[a]	2058	1.00 (Reference)	0.97 (0.57-1.66)	1.56 (0.94-2.58)
Pancreatic fistula				
All patients (crude)	2058	1.00 (Reference)	N/A[b]	0.25 (0.03-1.89)
All patients (adjusted)[a]	2058	1.00 (Reference)	N/A[b]	0.30 (0.04-2.41)
Intra-abdominal abscess				
All patients (crude)	2058	1.00 (Reference)	0.88 (0.59-1.31)	0.52 (0.31-0.87)
All patients (adjusted)[a]	2058	1.00 (Reference)	0.96 (0.64-1.44)	0.60 (0.35-1.03)
Major complication				
All patients (crude)	2058	1.00 (Reference)	0.74 (0.54-1.00)	0.84 (0.62-1.15)
All patients (adjusted)[a]	2058	1.00 (Reference)	0.70 (0.51-0.96)	0.79 (0.57-1.10)
Reoperation				
All patients (crude)	2058	1.00 (Reference)	0.60 (0.38-0.94)	0.64 (0.59-1.38)
All patients (adjusted)[a]	2058	1.00 (Reference)	0.56 (0.35-0.91)	0.82 (0.52-1.28)

N/A, not available.
[a] Adjustment for age (continuous), sex (male/female), year of the surgery (continuous), comprehensive complication index (0, 1, or ≥2 [excluding the gastric cancer under treatment]), pathologic stage (stage 0-I, II, III, or IV), and neoadjuvant therapy (yes/no).
[b] Not calculated because of 0 events in the group.

based study design reduced selection bias, and the study analysis was performed according to the a priori study protocol to minimize the risk of chance findings. The large size of the FINEGO cohort is another strength, enabling survival and regression analysis in subgroups. The Finnish national registries are based on independent and automatic reporting of diagnosis and procedure codes from the hospitals to the hospital discharge registry and clinicians reporting new cancer cases, enabling dependable patient identification with

Table 3
The 90-day complications after R0 resected total, subtotal, or distal gastrectomy for gastric adenocarcinoma, expressed as odd ratios with 95% CIs

Variable	Number of patients, N = 1495	Total gastrectomy, N = 928	Subtotal gastrectomy, n = 340	Distal gastrectomy, n = 227
Delayed emptying				
All patients (crude)	1495	1.00 (Reference)	1.09 (0.42-2.84)	2.22 (0.93-5.31)
All patients (adjusted)[a]	1495	1.00 (Reference)	0.97 (0.37-2.58)	1.67 (0.66-4.26)
Anastomotic complication				
All patients (crude)	1495	1.00 (Reference)	0.70 (0.38-1.27)	0.29 (0.10-0.81)
All patients (adjusted)[a]	1495	1.00 (Reference)	0.68 (0.37-1.26)	0.27 (0.10-0.77)
Bleeding				
All patients (crude)	1495	1.00 (Reference)	0.76 (0.36-1.61)	1.43 (0.71-2.87)
All patients (adjusted)[a]	1495	1.00 (Reference)	0.60 (0.27-1.33)	1.11 (0.53-2.34)
Small bowel obstruction				
All patients (crude)	1495	1.00 (Reference)	2.06 (0.46-9.24)	N/A[b]
All patients (adjusted)[a]	1495	1.00 (Reference)	1.97 (0.42-9.19)	N/A[b]
Ileus				
All patients (crude)	1495	1.00 (Reference)	1.73 (0.95-3.16)	2.67 (1.46-4.90)
All patients (adjusted)[a]	1495	1.00 (Reference)	1.54 (0.83-2.89)	2.46 (1.28-4.73)
Pancreatic fistula				
All patients (crude)	1495	1.00 (Reference)	N/A[b]	N/A[b]
All patients (adjusted)[a]	1495	1.00 (Reference)	N/A[b]	N/A[b]
Intra-abdominal abscess				
All patients (crude)	1495	1.00 (Reference)	0.92 (0.60-1.44)	0.36 (0.17-0.76)
All patients (adjusted)[a]	1495	1.00 (Reference)	1.03 (0.66-1.62)	0.46 (0.21-0.95)
Major complication				
All patients (crude)	1495	1.00 (Reference)	0.76 (0.54-1.09)	0.78 (0.52-1.18)
All patients (adjusted)[a]	1495	1.00 (Reference)	0.71 (0.49-1.03)	0.73 (0.47-1.12)
Reoperation				
All patients (crude)	1495	1.00 (Reference)	0.69 (0.41-1.17)	0.83 (0.47-1.47)
All patients (adjusted)[a]	1495	1.00 (Reference)	0.64 (0.37-1.11)	0.73 (0.40-1.36)

N/A, not available.
[a] Adjustment for age (continuous), sex (male/female), year of the surgery (continuous), comprehensive complication index (0, 1 or ≥2 [excluding the gastric cancer under treatment]), pathologic stage (stage 0-I, II, III, and IV) and neoadjuvant therapy (yes/no).
[b] Not calculated because of 0 events in the group.

high coverage [10]. The results were adjusted for known remarkable potential confounders (age, sex, year of the surgery, comprehensive complication index, pathologic stage, and neoadjuvant therapy), although some unknown bias or confounding may have occurred because of the observational nature of the study. Furthermore, the complication data was comprehensively collected and categorized by specialized surgeons, increasing the quality of the current study. In contrast, because of the retrospective nature of the study, there is a possibility that some complications may have been missed during the review of the patient records.

In this current population-based nationwide cohort, the rates for delayed emptying were 1.3% to 2.1% after total or partial gastrectomy in the whole cohort and 1.6% to 3.5% in patients with R0 total or partial gastrectomy. The resection type was not associated with the risk of 90-day delayed emptying in the main analysis or in the subgroup analysis of patients who underwent R0 resection. To the best of our knowledge, this is the first study comparing the rates of 90-day delayed emptying after different resection types in a population-based nationwide setting. In a study of 223 laparoscopic distal gastrectomies, the incidence rate of delayed gastric emptying was 2.2% [15]. Furthermore, a study of 2652 patients undergoing radical distal gastrectomy found an incidence rate of 2.3% for delayed gastric emptying [16], although higher incidence rates ranging from 4.2% to 25.0% have been reported [4–6]. The high variation in incidence rates may be due to different definitions of delayed emptying in the literature and in practice [15]. Clinically diagnosed delayed emptying can be a mild condition that causes nausea, early satiety, and postprandial bloating passing by in a few days without invasive approaches, although the most severe situations can lead to deferred oral intake, gastric tube application, and even reoperations [15,17]. The underlying causes of delayed emptying after gastrectomy are unclear but are likely to be multifactorial. Of note, 1 previous study classified the possible risk factors for postoperative gastric stasis into 3 categories, including the general physical condition of the patients, surgery-related factors, and characteristics of gastric cancer [16]. Age, poor nutritional status, preoperative pyloric obstruction, massive blood loss, postoperative intra-abdominal infection, and mental factors have been shown to be independent risk factors for postoperative gastric stasis [16,18,19]. In addition, residual stomach volume, anastomosis in the greater curvature and vagal nerve dissection or damage, reconstruction technique, and reconstruction route have been identified as risk factors [6,16,18,19]. In our study, the rate of 90-day delayed emptying was the highest in patients undergoing distal gastrectomy (2.1% in the whole cohort and 3.5% in the subgroup of patients who underwent R0 resection). Patients who underwent distal gastrectomy were older and had more comorbidities than those in the other groups, and the proportions of R2 and palliative resections were the highest in this group. This supports the earlier findings of patient-related factors e.g. comorbidities and advanced gastric cancer seem to have an effect on delayed emptying. However, there was no statistical difference in the rate of delayed emptying among different resections in our study.

In previous studies, gastric cancer surgery has been associated with high rates of postoperative complications ranging from 9% to 46% [3,4,20]. A population-based benchmark study from Sweden and the Netherlands with 1930 patients undergoing total (n = 880) or partial (n = 1050) gastrectomy showed a complication rate of 35.2% and an anastomotic leakage rate of 4.2%, but the rates according to resection type were not reported [20]. A previous study of 239 patients who underwent total (n = 126) or subtotal (n = 113) gastrectomy suggested no association between resection type and complication rate [4]. In the current study, the rate of major surgical complications varied from 13.8% to 17.8%, and the rate of anastomotic leakage varied from 2.6% to 5.9% among different resection types. Lower risks of major complications and reoperations were observed after subtotal gastrectomy, and lower risks of anastomotic complications were observed after distal gastrectomy than after total gastrectomy. Therefore, it seems beneficial to limit the level of resection to the stomach when possible. It has been shown that gastrectomy with D2 lymphadenectomy is associated with significantly higher postoperative mortality, morbidity, and complication and reoperation rates [4,21]. It could also be speculated that more extensive lymphadenectomy known to be associated with higher postoperative morbidity and mortality were performed more often with total gastrectomies than with subtotal or distal gastrectomies in which there were more R2 and palliative resections. Nevertheless, in the subgroup analysis of patients who underwent R0 resection, lower risks of anastomotic complications and intra-abdominal abscesses were observed after distal gastrectomies than after total gastrectomies, suggesting that minor resection may result in less postoperative complications. The complication rates in our nationwide study are in line with or even lower than those reported in earlier published literature. These results favor subtotal gastrectomy over total gastrectomy in situations in which extending the resection to the esophagus can be avoided from an oncologic perspective. Future studies should examine the differences between subtotal gastrectomy and total gastrectomy in more detail.

Conclusion

The level of resection was not associated with delayed emptying in this population-based nationwide study. However, subtotal and distal gastrectomies may result in fewer postoperative complications than total gastrectomy.

Ethics approval

The study was approved the regional ethical review board in Oulu, Finland.

Author contributions

OH and JHK conceived and designed the study; JHK is the guarantor of the study, analyzed the data, and supervised the study; AJ, OH, and JHK drafted the manuscript; all authors acquired the data, performed the experiments, and critically reviewed, edited, and approved the manuscript.

Funding

This study was funded by the Turku University Foundation (AJ), the Finnish-Norwegian Medical Foundation (AJ), the Finnish Cultural Foundation (AJ), the Mary and Georg C. Ehrnrooth Foundation (AJ and OH), the Instrumentarium Science Foundation (OH), the Finnish State Research Funding (OH), the Finnish Cancer Foundation (JHK), the Päivikki and Sakari Sohlberg Foundation (JHK), and the Sigrid Juselius Foundation (JHK).

Data availability

The study data cannot be made publicly available because of laws and regulations. The data are available upon reasonable request from JHK, given that the registry holders' permissions to use the data are obtained.

Declaration of competing interest

The authors declare no competing interests.

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