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Original Article

Impact of splenectomy on long-term outcomes after gastrectomy for gastric cancer: a population-based study

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ABSTRACT

Background: No national studies comparing long-term survival after total or partial gastrectomy with splenectomy due to injury or oncologic reasons or spleen preservation exist. This study aimed to examine the 5-year overall survival (OS) of patients with gastric adenocarcinoma who underwent total or partial gastrectomy with splenectomy due to injury or oncologic reasons or spleen preservation in a population-based nationwide setting.
Methods: This study included all patients undergoing total or partial gastrectomy with splenectomy or spleen preservation for gastric adenocarcinoma in Finland from 2005 to 2016, with follow-up until December 31, 2019. A total of 2196 patients with gastric cancer diagnosis and total or partial gastrectomy were identified in the registries. Of these patients, 2118 were applicable for this study. Cox proportional hazard models provided hazard ratios (HRs) with 95% CIs of 5-year OS. The results were adjusted for age, sex, year of operation, comorbidities, tumor location, pathologic stage, and neoadjuvant therapy.
Results: The observed 5-year OS rates were 38.7% in patients with no or minor spleen injury, 39.7% in patients with splenectomy due to injury, and 30.8% in patients with splenectomy due to oncologic reasons (P = .032). Patients who underwent R0 gastrectomy with splenectomy due to oncologic reasons had higher 5-year mortality (the adjusted model HR, 1.26; 95% CI, 1.01–1.56) than patients who underwent spleen preservation.
Conclusion: The OS was worst in patients who underwent gastrectomy with splenectomy due to oncologic reasons, highlighting the poor prognosis in patients with advanced gastric cancer. Splenectomy due to injury does not compromise the prognosis.

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Introduction

Gastric cancer is one of the leading causes of cancer-related death worldwide [1], and its management is primarily based on the tumor stage [2,3]. Upfront surgery is performed only in patients with early-stage disease [2]. For stage ≥ IB disease, a multidisciplinary approach involving R0 resection with D2 lymphadenectomy for medically fit patients combined with neoadjuvant treatment improves outcomes and is considered a standard treatment [2]. According to the Japanese Gastric Cancer Treatment Guidelines, D2 lymphadenectomy also includes lymph nodes along the peripheral splenic artery (the splenic hilar nodes) [4] because of findings of even 10% to 20% of metastatic lymph nodes in the splenic hilum in proximal tumors [5,6]. Splenic hilar nodal dissection without splenectomy requires a highly skilled operative technique, and despite this, splenectomy is often necessary [6]. In cases in which a tumor infiltrates the spleen or pancreas, splenectomy or pancreatosplenectomy is needed to achieve R0 resection [5], although high morbidity and mortality rates have been reported after this extensive operation [7–10].

The role of prophylactic splenectomy for gastric cancer remains controversial, and cure strategies differ between Japan and Europe [6,8]. A recent meta-analysis of 6431 patients from 18 studies found increased postoperative morbidity without improvement in survival after prophylactic splenectomy for advanced gastric cancer in the upper third tumors [8]. In a study of 1074 patients who underwent gastrectomy for proximal tumors, splenectomy was a poor prognostic factor for overall survival (OS) and disease-free survival (DFS) [11]. In addition, the same study included propensity score–matched analysis of 229 patients who underwent splenectomy or pancreatosplenectomy and found splenectomy as an independent poor prognostic factor associated with significantly worse OS and DFS [11]. However, there is a lack of large, population-based Western studies comparing long-term survival after total or partial gastrectomy with splenectomy or spleen preservation.

Here, we collected data on intraoperative complications in patients who underwent total or partial gastrectomy and recorded the cause of splenectomy (due to injury or due to oncologic reasons) during the operation. The primary aim of this study was to examine the 5-year OS of patients with gastric adenocarcinoma who underwent total or partial gastrectomy with splenectomy due to injury or oncologic reasons or spleen preservation. The secondary aim was to compare 90-day mortality between the groups.

Materials and methods

Study design

This was a population-based, nationwide, and retrospective cohort study in Finland that included patients who underwent total or partial gastrectomy for gastric adenocarcinoma. Patients with other histologic types of gastric malignancies were excluded because they were not comparable in terms of treatment and prognosis. Patients with Siewert II tumors and those who underwent wedge resections were excluded. The study period was from January 1, 2005, to December 31, 2016, with follow-up until December 31, 2019 [12]. The patients who underwent total or partial gastrectomy with splenectomy were compared with patients who underwent spleen-preserving gastrectomy with 5-year OS as the main outcome. The study was approved by the regional ethical review board of the Finnish national health officials and hospital districts in Oulu, Finland [13].

Data collection

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 [12]. The FINEGO database contains information from the Finnish Cancer Registry, Finnish National Institute for Health and Welfare Registries, Care Register for Healthcare, and Hospital Discharge Registry. The Finnish Cancer Registry and the Hospital Discharge Registry are 87.0% and 92.7% complete for gastric cancer, respectively [14]. Surgically treated patients were identified using NOMESCO (The Nordic Medico-Statistical Committee) surgical codes. The identification using both registries by searching for cancer diagnoses and operation codes allows nearly 100% completeness on eligible patient identification. After the identification of cases, available information, including age, sex, comorbidity [15], surgery, and other variables, were collected from the Finnish Cancer Registry, Finnish National Institute for Health and Welfare Registries, Care Register for Healthcare, and Hospital Discharge Registry [12]. Medical reports were obtained from the respective healthcare units and reviewed by specialized surgeons, providing accurate information on the type of resection; tumor location, histology, and stage; and neoadjuvant treatment. Furthermore, data on intraoperative complications were collected separately, and the reason (injury vs oncologic) for splenectomy was determined. All-cause mortality data were obtained from a 100% complete death registry held by Statistics Finland until December 31, 2019 [16].

Exposures

Patients who underwent total or partial gastrectomy with splenectomy were considered the study exposure group, and those who underwent spleen-preserving total or partial gastrectomy were considered the control group.

Outcomes

The primary outcome of the study was to evaluate the 5-year OS of patients with gastric adenocarcinoma who underwent total or partial gastrectomy with splenectomy due to injury or oncologic reasons or spleen preservation. The secondary outcome was 90-day mortality.

Statistical analysis

The analyses followed a detailed a priori study protocol. The IBM SPSS software (version 26.0; IBM) 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 and visualized using Kaplan-Meier curves. Cox proportional hazard models provided hazard ratios (HRs) with 95% CIs. To avoid confounding, adjustments for 7 known prognostic factors were made: age (continuous), sex (male/female), year of the surgery (continuous), comorbidity (Charlson Comorbidity Index [CCI] [15] 0, 1, or ≥ 2 [excluding gastric cancer under treatment]), tumor location (proximal, middle, or distal), 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 [17]), and neoadjuvant therapy (yes/no). Analysis was performed comparing patients who underwent splenectomy for any reason, those who underwent spleen preservation and splenectomy due to injury, those who underwent splenectomy due to oncologic reasons, and those who underwent spleen preservation. Furthermore, the analysis of three subgroups was performed: (i) patients with Siewert III tumors in which splenic hilar nodal dissection is considered important, (ii) those with R0 resections, and (iii) those with stage III to IV diseases. In addition, the adjustments for the subgroups were performed as described above. Patients with completely missing medical records were excluded from the main analysis.

Results

Patients

A total of 2196 patients with gastric cancer diagnosis and total or partial gastrectomy were identified in the registries. Of these patients, 2118 were eligible for this study. Of the 2118 patients, 193 (9.1%) had minor splenic injury not needing splenectomy during the operation. Splenectomy due to injury was performed in 55 patients (2.6%), and splenectomy due to oncologic reasons was performed in 240 patients (11.3%).

Most patients included in the study were men, had distal gastric adenocarcinoma, and had pathologic stage III disease. R0 resection was achieved in 72.3% of patients. Tumors were more often located in the corpus in the splenectomy group (64.6%) than in the spleen preservation group (39.8%). The baseline characteristics are presented in Table 1.

Primary outcomes

The observed 5-year OS rates were 32.5% in patients who underwent splenectomy and 38.7% in patients who underwent spleen-preserving gastrectomy (P = .011) (Fig. 1). After adjustment for confounding factors, gastrectomy with splenectomy was not significantly associated with the 5-year overall mortality (adjusted HR, 1.12; 95% CI, 0.96–1.32) (Table 2) compared with spleen-preserving gastrectomy. HRs with 95% CIs for 5-year overall mortality in the predefined subgroups are presented in Table 2. Gastrectomy with splenectomy and R0 resection was associated with a higher 5-year mortality in the crude model (HR, 1.41; 95% CI, 1.17–1.70) and adjusted model (HR, 1.26; 95% CI, 1.03–1.55) than spleen-preserving gastrectomy (Table 2).

Table 1
Clinical variables in 2118 patients who underwent total or partial gastrectomy for gastric adenocarcinoma in Finland from 2005 to 2016.

Variable	Whole cohort (N = 2118)	Gastrectomy and spleen preservation (n = 1823)	Gastrectomy with splenectomy (n = 295)
Age (y), median (IQR)	71 (62–78)	71 (62–79)	68 (60–75)
Sex, n (%)			
Male	1172 (55.3)	1022 (56.0)	150 (50.8)
Female	946 (44.7)	801 (44.0)	145 (49.2)
Charlson Comorbidity Index, n (%)			
0	1057 (49.9)	889 (48.8)	168 (56.9)
1	646 (30.5)	564 (30.9)	82 (27.8)
≥2	415 (19.6)	370 (20.3)	45 (15.3)
Tumor location, n (%)			
Proximal	196 (9.3)	142 (7.8)	54 (18.2)
Middle	917 (43.3)	726 (39.8)	191 (64.6)
Distal	1005 (47.5)	955 (52.4)	50 (17.2)
Neoadjuvant treatment, n (%)			
Yes	295 (13.9)	222 (12.2)	73 (24.7)
No	1816 (85.7)	1595 (87.5)	221 (75.0)
Missing	7 (0.3)	6 (0.3)	1 (0.3)
Pathologic stage, n (%)			
0-I	519 (24.5)	469 (25.7)	50 (16.9)
II	603 (28.5)	520 (28.5)	83 (28.1)
III	730 (34.5)	597 (32.7)	133 (45.1)
IV	226 (10.7)	204 (11.2)	22 (7.5)
Missing	40 (1.9)	33 (1.8)	7 (2.4)
Radicality			
R0	1531 (72.3)	1318 (72.3)	213 (72.2)
R1	173 (8.2)	139 (7.6)	34 (11.5)
R2	160 (7.6)	148 (8.1)	12 (4.1)
Palliative intent	170 (8.0)	158 (8.7)	12 (4.1)
Missing	84 (3.9)	60 (3.3)	24 (8.1)

Furthermore, the observed 5-year OS rates were 38.7% in patients with no or minor spleen injury, 39.7% in patients who underwent splenectomy due to injury, and 30.8% in patients who underwent splenectomy due to oncologic reasons (P = .032) (Fig. 2). In the crude model, gastrectomy with splenectomy due to oncologic reasons was associated with higher 5-year mortality (HR, 1.24; 95% CI, 1.05–1.46) (Table 3) than spleen-preserving gastrectomy. Gastrectomy with splenectomy due to oncologic reasons and R0 resection was associated with higher 5-year mortality (crude model HR, 1.46; 95% CI, 1.18–1.77; adjusted model HR, 1.26; 95% CI, 1.01–1.56) (Table 3) than spleen preservation.

Secondary outcomes

The 90-day OS rates were 92.9% in patients who underwent splenectomy and 92.8% in patients who underwent spleen-preserving gastrectomy (P = .972). Gastrectomy with splenectomy was not significantly associated with the 90-day overall mortality in the whole cohort or in the predefined subgroups compared with spleen-preserving gastrectomy (Table 4). Furthermore, the 90-day OS rates were 92.8% in patients with no or minor injury, 87.3% in patients who underwent splenectomy due to injury, and 94.2% in patients who underwent splenectomy due to oncologic reasons (P = .193).

HRs with 95% CIs for 90-day overall mortality are presented in Tables 4 and 5. In subgroup analysis of patients with stage III and IV diseases, gastrectomy with splenectomy due to injury was associated with a higher 90-day overall mortality (adjusted HR, 2.63; 95% CI, 1.04–6.61) (Table 5) than spleen preservation.

Discussion

In this population-based nationwide cohort study, the observed 5-year OS was higher in patients who underwent spleen-preserving gastrectomy than in those who underwent splenectomy. Furthermore, the observed 5-year OS was worst in patients who underwent gastrectomy with splenectomy due to oncologic reasons, emphasizing a worse prognosis in patients with advanced diseases. Splenectomy due to injury does not compromise long-term survival.

The main strength of this nationwide population-based study is the complete identification and 100% complete follow-up of all the study patients diagnosed with gastric adenocarcinoma in Finland. The Finnish national registries are based on clinicians reporting new cancer cases to the Finnish Cancer Registry and also independent and automatic reporting of diagnosis and procedure codes from the hospitals to the hospital discharge registry, thereby permitting reliable patient identification with high coverage [14]. In addition, the sample size of the FINEGO database was considered sufficient to enable survival and regression analyses in smaller subgroups of patients. Furthermore, the observed CIs still contain clinically significant differences in point estimates. Therefore, even larger studies and meta-analyses are needed for confirmation. The study analysis was performed according to a priori study protocol to minimize the risk of chance findings. Furthermore, the results were adjusted for known potential confounders (age, sex, year of the surgery, CCI, tumor location, pathologic stage, and neoadjuvant therapy), whereas some unknown confounding or bias may have occurred because of the observational nature of the study.

To the best of our knowledge, this is the first study to report outcomes after splenectomy due to injury or oncologic reasons in patients who underwent total or partial gastrectomy for gastric cancer. The observed 5-year OS rates were 32.5% in patients who underwent splenectomy and 38.7% in patients who underwent spleen-preserving gastrectomy. In previous studies, the 5-year overall survival has varied widely, from 16.9% to 77.3% after gastrectomy with splenectomy and from 33.8% to 81.0% after gastrectomy with spleen preservation [8]. The effect of splenectomy on

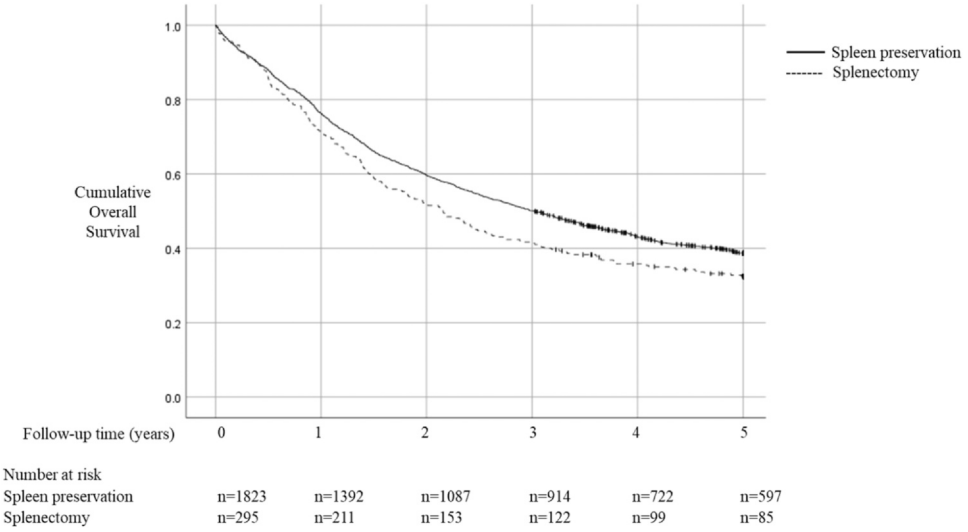

Figure 1. The observed 5-year overall survival curves between patients who underwent gastrectomy with splenectomy and those who underwent spleen-preserving gastrectomy.

Table 2
Risk of 5-year overall mortality after total or partial gastrectomy for gastric adenocarcinoma between the whole cohort and subgroups expressed as hazard ratios with 95% CIs.

Variable	No. of patients	Gastrectomy and spleen preservation	Gastrectomy with splenectomy
All patients (crude)	2118	1.00 (reference)	1.22 (1.05–1.41)
All patients (adjusted)[a]	2072	1.00 (reference)	1.12 (0.96–1.32)
Siewert III tumors			
All patients (crude)	196	1.00 (reference)	1.45 (0.99–2.13)
All patients (adjusted)[a]	193	1.00 (reference)	1.11 (0.73–1.69)
R0 resections			
All patients (crude)	1531	1.00 (reference)	1.41 (1.17–1.70)
All patients (adjusted)[a]	1507	1.00 (reference)	1.26 (1.03–1.55)
Patients with stage III-IV diseases			
All patients (crude)	956	1.00 (reference)	0.95 (0.79–1.15)
All patients (adjusted)[a]	955	1.00 (reference)	1.05 (0.86–1.28)

[a] Adjustments were made for age (continuous), sex, year of the surgery (continuous), Charlson Comorbidity Index (0, 1, or ≥2 [excluding gastric cancer under treatment]), tumor location (proximal, middle, or distal), pathologic stage (stage 0-I, II, III, or IV), and neoadjuvant therapy (yes/no).

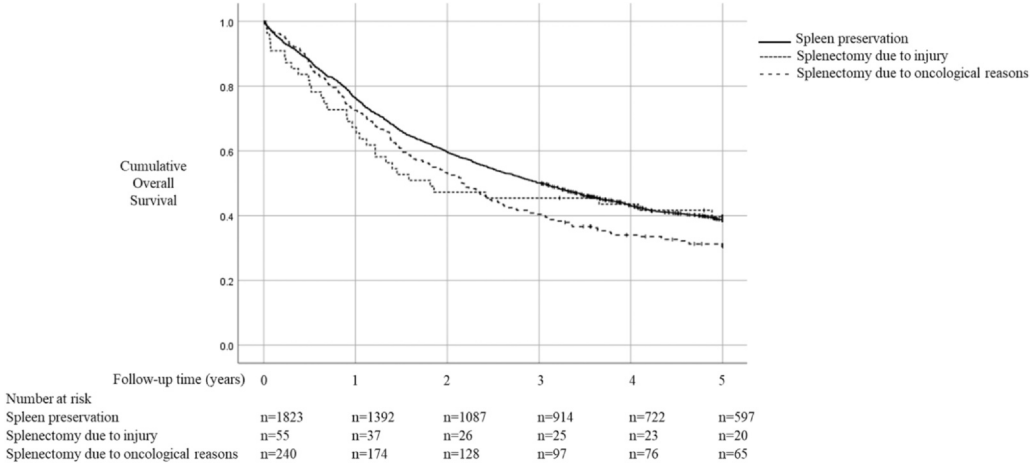

Figure 2. The observed 5-year overall survival curves between patients who underwent gastrectomy with splenectomy due to oncologic reasons or injury and those who underwent spleen-preserving gastrectomy.

survival among patients with gastric cancer is controversial, and thus far, studies have mostly been limited by small sample size [8]. Splenectomy is often performed to complete the dissection of splenic hilar lymph nodes, although splenectomy is justified when tumor invasion to the spleen exists [2,5,11]. Of note, 2 recent meta-analyses of 14 retrospective studies and 4 randomized controlled trials showed that splenic hilar lymphadenectomy with spleen-preserving technique had comparable oncologic outcomes compared with gastrectomy with splenectomy [8,18]. However, the incidence of metastatic splenic hilar lymph nodes is higher with proximal and middle tumors, especially those located in the greater curvature [5,19,20]. There are studies showing that metastasis in splenic hilar nodes predicts the presence of distant metastasis and worse prognosis, even though curative resection could be performed. Therefore, the addition of splenectomy would be ineffective [21–23]. In sensitivity analysis, including only R0 resections, splenectomy was

Table 3
Risk of 5-year overall mortality after total or partial gastrectomy for gastric adenocarcinoma between the whole cohort and subgroups stratified by type of splenic injury and splenectomy and expressed as hazard ratios with 95% CIs.

Variable	No. of patients	Gastrectomy and spleen preservation	Gastrectomy with splenectomy due to injury	Gastrectomy with splenectomy due to oncologic reasons
All patients (crude)	2118	1.00 (reference)	1.10 (0.78–1.56)	1.24 (1.05–1.46)
All patients (adjusted)[a]	2072	1.00 (reference)	1.26 (0.87–1.81)	1.10 (0.92–1.31)
Siewert III tumors				
All patients (crude)	196	1.00 (reference)	2.08 (0.66–6.59)	1.42 (0.95–2.10)
All patients (adjusted)[a]	193	1.00 (reference)	1.02 (0.31–3.39)	1.12 (0.73–1.73)
R0 resections				
All patients (crude)	1531	1.00 (reference)	1.26 (0.82–1.92)	1.46 (1.18–1.77)
All patients (adjusted)[a]	1507	1.00 (reference)	1.31 (0.84–2.04)	1.26 (1.01–1.56)
Patients with stage III-IV diseases				
All patients (crude)	956	1.00 (reference)	1.51 (0.94–2.45)	0.90 (0.73–1.11)
All patients (adjusted)[a]	955	1.00 (reference)	1.57 (0.97–2.56)	1.00 (0.81–1.23)

[a] Adjustments were made for age (continuous), sex, year of the surgery (continuous), Charlson Comorbidity Index (0, 1, or ≥2 [excluding the gastric cancer under treatment]), tumor location (proximal, middle, or distal), pathologic stage (stage 0-I, II, III, or IV), and neoadjuvant therapy (yes/no).

Table 4
Risk of 90-day overall mortality after total or partial gastrectomy for gastric adenocarcinoma between the whole cohort and subgroups expressed as hazard ratios with 95% CIs.

Variable	No. of patients	Gastrectomy and spleen preservation	Gastrectomy with splenectomy
All patients (crude)	2118	1.00 (reference)	0.99 (0.63–1.57)
All patients (adjusted)[a]	2072	1.00 (reference)	1.07 (0.65–1.78)
Siewert III tumors			
All patients (crude)	196	1.00 (reference)	0.98 (0.31–3.07)
All patients (adjusted)[a]	193	1.00 (reference)	0.94 (0.24–3.78)
R0 resections			
All patients (crude)	1531	1.00 (reference)	1.04 (0.51–2.10)
All patients (adjusted)[a]	1507	1.00 (reference)	1.18 (0.54–2.57)
Patients with stage III-IV diseases			
All patients (crude)	956	1.00 (reference)	0.87 (0.49–1.53)
All patients (adjusted)[a]	955	1.00 (reference)	1.07 (0.59–1.95)

[a] Adjustments were made for age (continuous), sex, year of the surgery (continuous), Charlson Comorbidity Index (0, 1, or ≥2 [excluding the gastric cancer under treatment]), tumor location (proximal, middle, or distal), pathologic stage (stage 0-I, II, III, or IV), and neoadjuvant therapy (yes/no).

Table 5
Risk of 90-day overall mortality after total or partial gastrectomy for gastric adenocarcinoma between the whole cohort and subgroups stratified by type of splenic injury and splenectomy and expressed as hazard ratios with 95% CIs.

Variable	No. of patients	Gastrectomy and spleen preservation	Gastrectomy with splenectomy due to injury	Gastrectomy with splenectomy due to oncologic reasons
All patients (crude)	2118	1.00 (reference)	1.83 (0.86–3.92)	0.81 (0.47–1.40)
All patients (adjusted)[a]	2072	1.00 (reference)	1.86 (0.81–4.23)	0.89 (0.49–1.61)
Siewert III tumors				
All patients (crude)	196	1.00 (reference)	N/A[b]	1.04 (0.33–3.26)
All patients (adjusted)[a]	193	1.00 (reference)	N/A[b]	1.01 (0.25–4.04)
R0 resections				
All patients (crude)	1531	1.00 (reference)	2.49 (0.90–6.87)	0.71 (0.28–1.77)
All patients (adjusted)[a]	1507	1.00 (reference)	1.85 (0.57–5.98)	0.95 (0.36–2.49)
Patients with stage III-IV diseases				
All patients (crude)	956	1.00 (reference)	2.82 (1.14–6.96)	0.63 (0.32–1.25)
All patients (adjusted)[a]	955	1.00 (reference)	2.63 (1.04–6.61)	0.80 (0.39–1.64)

N/A, not available.
[a] Adjustments were made for age (continuous), sex, year of the surgery (continuous), Charlson Comorbidity Index (0, 1, or ≥2 [excluding the gastric cancer under treatment]), tumor location (proximal, middle, or distal), pathologic stage (stage 0-I, II, III, or IV), and neoadjuvant therapy (yes/no).
[b] Not calculated due to 0 events in the group.

associated a with higher 5-year mortality risk. Based on these findings and because of possible residual confounding factors, it is possible that patients who underwent splenectomy had more advanced disease. In addition, as a lymphoid organ, the major function of the spleen is immune response, and there is growing evidence that splenectomy could lead to a negative effect on host defense, increasing the risk of developing cancer and promoting residual disease growth [11,24–26].

When comparing survival rates according to the cause of splenectomy, the 5-year OS rates were 39.7% in patients who underwent splenectomy due to injury and 30.8% in patients who underwent splenectomy due to oncologic reasons in our series. This finding highlights and supports the earlier finding that poor prognosis of patients is associated with advanced and high-stage gastric cancer with spread to adjunct organs or splenic hilar lymph nodes. However, the rate of splenectomy was 13.9% in our series, which is somewhat lower than that of earlier studies in which the splenectomy rates have been higher, ranging from 26.0% to 48.7% [27–30].

It is noteworthy that splenectomy is associated with a high morbidity rate and an increased risk of postoperative complications [5,7,8,18,31], which are known to worsen long-term outcomes [32]. In previous studies, the 90-day mortality rates after gastric cancer surgery have varied from 7.1% to 10.1% [33–35]. Here, there was no remarkable difference in the 90-day mortality rate between patients who underwent splenectomy (7.1%) and those who underwent spleen-preserving gastrectomy (7.2%). In turn, the 90-day mortality rates were 12.7% after gastrectomy with splenectomy due to injury

and 5.8% after gastrectomy with splenectomy due to oncologic reasons. According to our study findings, splenic injury may worsen short-term survival. However, no difference was observed in long-term outcomes. Complete resection of splenic hilar nodes is technically demanding and often requires splenectomy or leads to splenectomy due to splenic injury [18,36]. Excessive intraoperative blood loss and blood transfusion have adverse effects on the prognosis because of immunosuppression, unfavorable postoperative conditions and complications, and tumor cell spillage into the abdomen [36,37]. The incidence of infections is the highest in the first 2 years after splenectomy but persists throughout life, and the risk of thromboembolic complications is significantly increased in the immediate postoperative period but in the long term [38]. Overall, the negative short-term outcomes may decrease long-term survival in patients undergoing gastrectomy with splenectomy.

Conclusion

The observed 5-year overall survival was higher in patients who underwent gastrectomy and spleen preservation than in those who underwent gastrectomy with splenectomy. The worst prognosis was observed in patients who underwent gastrectomy with splenectomy due to oncologic reasons, highlighting the poor prognosis in patients with advanced gastric cancer. However, splenectomy due to injury does not compromise long-term prognosis.

Ethics approval

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

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Author contributions

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

Declaration of competing interest

The authors declare no competing interests.

Data availability

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

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