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Splenectomy Does Not Increase Early Morbidity in Patients Undergoing Total Gastrectomy: A Case-Control Study with Propensity Score Analysis

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Rezumat

Splenectomia nu crește morbiditatea precoce după gastrectomia totală: un studiu caz-martor cu analiza scorului de propenstitate

Scop: În cancerul gastric (CG), limfadenectomia de nivel D2 şi gastrectomia cu margini oncologice negative sunt de maximă importanță. Comunitățile ştiințifice din vest şi est sunt interesate de subiectul echilibrului dintre riscurile şi beneficiile splenectomiei în cazul pacienților cu CG. Datorita riscului de complicatii post-operatorii, tendința în țările vestice este să prezerve splina, în timp ce în ce țările estice (precum Japonia) este preferată splenectomia. Studiul nostru şi-a propus să determine dacă în cazul pacienților cu CG gastrectomia cu splenectomie a fost asociată cu o rată mai mare de morbiditate şi mortalitate precoce.

Metode: Am realizat un studiu retrospectiv de tip caz-martor în care am inclus pacienții cu CG (stadiile I-III) care au beneficiat de gastrectomie totală cu limfadenectomie D2 cu intenție curativă oncologica (într-un centru terțiar de mare volum în chirurgia CG). Am împărțit cazurile în două grupe: cu prezervare splenică (PS) şi cu sacrificare splenică (SS) şi am evaluat rata de complicații precoce după operație. Ulterior am realizat scorul de propensitate (PSM) şi analiza celor două grupe.

Rezultate: Am inclus 74 de pacienți, 29 în grupul SS şi 45 în grupul PS. Cinsprezece cazuri (20.2%) au avut complicatii precoce post-operator. Rata de complicații a fost de 53% (n=8) în grupul SS şi 46% (n=7) în grupul PS. Mortalitatea la 30 de zile a fost de 2.7%.

Concluzii: Splenectomia nu este asociată cu creşterea morbidității

precoce după gastrectomia totală cu limfadenectomie D2 dacă este realizata de către chirurgi experimentat.

Cuvinte cheie: cancer gastric, gastrectomie, splenectomie, limfadenectomie D2, morbiditate

Abstract

Aim: In gastric cancer (GC), D2 lymph node dissection is, alongside negative-margins gastrectomy, of paramount importance. There is a debate between Western and Eastern scientific communities concerning the risk-benefit balance with respect to splenectomy, as Western countries are inclined to perform spleen-preserving gastrectomy due to an increased risk for postoperative complications. In Eastern countries (such as Japan) this is not the case. Our study aimed to determine whether or not spleen-sacrificing total gastrectomy for GC was associated with a higher rate of early post-operative morbidity or mortality.

Method: We performed a retrospective case-control study in which we included patients who underwent total gastrectomy with D2 lymphadenectomy for GC (stages I-III) with curative intent, in a single high-volume tertiary oncologic centre. We divided the cases into two groups: spleen-preserving (SP) and spleen-sacrificing (SS) and evaluated the early complications rate following surgery. Afterwards, we performed propensity score matching (PSM) and analysis of the two groups.

Results: We included 74 patients, 29 in the SS group and 45 in the SP group. Fifteen cases (20.2%) developed early postoperative complications and the complication rate was 53% (n=8) in the SS group and 46% (n=7) in the SP group. The overall 30-day mortality rate was 2.7%.

Conclusions: Splenectomy is not associated with increased early morbidity following total gastrectomy with D2 lymphadenectomy if performed by an experienced surgeon.

Key words: gastric cancer, gastrectomy, splenectomy, D2 lymphadenectomy, morbidity

Introduction

With over one million annual new cases and just under eight hundred thousand annual new deaths per year (1), gastric cancer (GC) represents the fourth leading cause of cancer deaths worldwide (2). More so, recent years have brought a rise in the incidence of proximal, infiltrative gastric tumours, which are more frequent in young adults and tend to have a more aggressive course (3). Either initially or after neoadjuvant chemotherapy, surgery is the mainstay of treatment. R0 resection in the form of total gastrectomy with D2 lymphadenectomy offers the highest chance of cure for proximal non-metastatic gastric cancers (4).

To ensure proper D2 lymph node dissection and retrieval of No 10 and No 11 lymph node stations (5), many surgeons perform splenectomy in all cases, however, this practice is questioned by others considering the limited oncological benefit and increased morbidity associated with splenectomy. A randomised controlled trial performed by Sano et al (6) states that splenectomy offers no overall survival benefit in patients with proximal GC that does not invade the greater curvature. Moreover, the same authors state that splenectomy may increase postoperative morbidity through increased risk of pancreatic leaks and intra-abdominal collections. The sixth Japanese Gastric Cancer Association treatment guidelines published in 2021 (7)

suggest that splenectomy should be considered only for proximal tumours which invade the greater curvature, but with low strength of evidence, suggesting the need for more research in this area.

To bring new insights into this subject of research and enable better decision-making for patients with proximal gastric cancer undergoing gastrectomy, we aimed to perform a comparative study in our cohort of patients and compare morbidity between patients with splenectomy and patients without.

Material and Methods

Design and Setting

This is a single-centre, retrospective case-control study on patients diagnosed with gastric cancer who underwent total gastrectomy with curative indent. All patients were treated between October 2016 and February 2023 by three senior surgeons. Patient consent was waived by our Institution's Ethics Committee as the research did not pose any risks to the patients and the data were anonymized. The STROBE checklist v4 (3) for cohort studies was adhered to.

Inclusion and Exclusion Criteria

Only patients with gastric cancer who underwent curative surgery were included. Only patients who underwent total gastrectomy were included. Patients with subtotal, distal gastrectomies were excluded. Palliative procedures were excluded.

Data Extraction

Data were extracted from the electronic system of our hospital and the patient's medical files. Variables including patient details, demographics, clinical data, comorbidities, cancer staging, neoadjuvant treatment, preoperative blood tests, date of surgery, type of surgery, intraoperative complications, postoperative bloods, postoperative parameters, intensive care unit duration of stay, surgical complications, medical complications, date of discharge and data on outpatient follow-up were extracted and merged into an Excel database. One specialist surgeon (SM) verified the accuracy of extracted data and the attribution of complications.

Data Analysis

We synthesized the obtained data into qualitative and quantitative variables which were added in an Excel document. Dichotomous variables were compared using the t-test and continuous variables were compared using the Mann-Whitney U test, where $p<0.0.5$ was considered significant, confidence interval of 95%. To further reduce bias from confounding variables and selection bias, propensity score analysis (PSM) was performed using XLSTAT software. Matching control patients in the SS group were selected according to propensity scores, in a 1:1 ratio, determined by Mahalanobis distances, with patients in the SP group based on age, gender, and TNM staging.

Results

Patients' characteristics

A total of 74 patients were included in the study (*Fig. 1*), 29 in the SS group and 45 in the SP group, with 68.9% (n=51) male patients

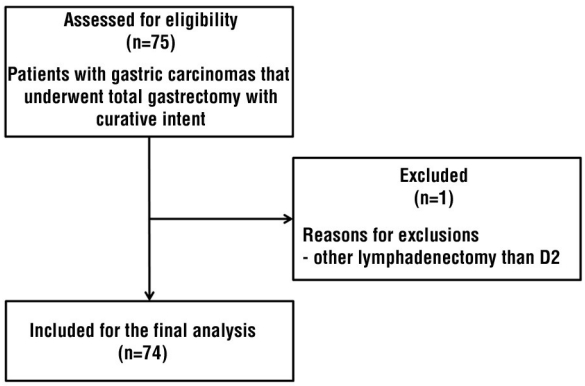

Figure 1. STROBE inclusion flowchart

and 31.1% (n=23) females. The mean age was 65.3 years. There was no significant difference in age between the two studied groups (p=0.72). With regards to preoperative comorbidities, 70.3% (n=52) had cardiovascular diseases, 10.8% (n=8) had metabolic comorbidities and 8.1% (n=6) had associated liver disease (*Table 1*). BMI under 18.5 was recorded in 29.7% (n=22) and 66.2% (n=49) were anaemic on diagnosis. A percentage of 22.9 (n=17) underwent neo-adjuvant chemotherapy with ECF or FLOT protocols. Cancer staging is depicted in *Table 2*. There was no significant difference in tumour staging between the two groups (*Table 2*). The mean preoperative albumin level was 4.2 g/dL in the SS group and 4.47 g/dL in the SP group. The mean preoperative haemoglobin level was higher in the SP group (12.2g/dL) than in the SS group (10.8g/dL) (*Table 2*).

Table 1. Distribution of preoperative comorbidities in the included cohort

Comorbidity	Total N(%)	SS group	SP group
Total	67 (90.5%)	28 (37.8%)	39 (52.7%)
Cardiovascular	52 (70.3%)	20 (27%)	32 (43.3%)
Diabetes	8 (10.8%)	7 (9.5%)	1 (1.4%)
Malnutrition	22 (29.7%)	9 (12.2%)	13 (17.6%)
Obesity	6 (8.1%)	2 (2.7%)	4 (5.4%)
Liver disease	6 (8.1%)	3 (4.05%)	3 (4.05%)
Preoperative anaemia	49 (66.2%)	23 (31.1%)	26 (35.1%)

SS: spleen sacrificing; SP: spleen preserving

Table 2. Distribution of mean values for albumin and haemoglobin and by stage in the included cohort

Patient characteristics	Total N(%)	SS group	SP group
Mean albumin (g/dL)		4.2	4.47
Mean Haemoglobin (g/dL)		10.8	12.2
Stage I	10 (13.5%)	2 (2.7%)	8 (10.8%)
Stage II	27 (36.5%)	8 (10.8%)	19 (25.7%)
Stage III	37 (50%)	19 (25.7%)	18 (24.3%)

Table 3. Distribution of early morbidity types in the included cohort

Morbidity	Total N(%)	SS group	SP group	p-value
Bleeding	4 (5.4%)	0 (0%)	4 (5.4%)	0.129
Duodenal stump leak	4 (5.4%)	3 (4%)	1 (1.4%)	0.163
Anastomotic leak	4 (5.4%)	2 (2.7%)	2 (2.7%)	0.512
Pancreatic leak and pancreatitis	2 (2.7%)	2 (2.7%)	0 (0%)	0.338
Sepsis	8 (10.8%)	5 (6.8%)	3 (4.1%)	0.147
Shock	4 (5.4%)	2 (2.7%)	2 (2.7%)	0.512
Need-to-reoperate	12 (16.2%)	5 (6.8%)	7 (9.5%)	0.545
Early mortality	2 (2.7%)	0 (0%)	2 (2.7%)	0.366

Morbidity Comparison

Overall early morbidity rate was 20.2% (n=15) and the 30-day mortality rate was 2.7% (n=2), both deaths were from the SP group. The morbidity rate was 53.3% (n=8) in the SS group, whereas patients in the SP group had a morbidity rate of 46.7% (n=7). There was no significant difference in both overall morbidity and individual complications between the two groups as presented in *Table 3*. Postoperative bleeding occurred only in the SP group (n=4). Gastrointestinal leak, either from the duodenal stump or the anastomosis, occurred with the same incidence (n=4 for each), more frequently in the SS group (n=3) for the first type of leak and with equal distribution between groups for the latter (n=2). Pancreatic leak or pancreatitis occurred only in the SS group (n=2). 10.8% of the cases (n=8) developed postoperative sepsis, more often after SS surgery (n=5), out of which 4 cases evolved into shock (n=2 for both groups). Twelve cases (16.2%) required reintervention for complications: 6.7% (n=5) in the SS group (2 anastomotic leaks, 2 duodenal stump leaks, one pancreatic leak with intraabdominal collections) and 9.4% (n=7) in the SP group (4 bleeding cases – from the spleen, the common hepatic artery, the mesentery and a hematoma with unknown source, and abdominal collections from 2 anastomotic leaks and acute complicated cholecystitis).

Patients' Characteristics after PSM

A total of 18 patients were selected after PSM (n=9 for each group), with 66.6% male patients (n=12) and 33.4% female patients (n=8). The mean age was 66.5 years. Three patients (16.6%) underwent neoadjuvant chemotherapy with ECF or FLOT protocols. With regards to coexisting comorbidities (overall value of 94.4%, n=17), 77.8% (n=14) had cardiovascular diseases, 27.7% (n=5) had

metabolic comorbidities and 11.1% (n=2) had associated liver disease (*Table 4*). A percentage of 22.2 (n=4) had a BMI less than 18.5 and 72.2% (n=13) were anaemic on diagnosis. Cancer staging is depicted in *Table 5*. There was no significant difference in tumour staging between the two groups (*Table 5*).

After PSM, the mean preoperative albumin level was 3.71 g/dL in the SS group and 4.43 g/dL in the SP group. The mean preoperative haemoglobin level was higher in the SP group (11.1g/dL) than in the SS group (9.1g/dL). The data are presented in *Table 5*.

Table 4. Distribution of comorbidities in the included cohort after PSM

Comorbidity	Total N(%)	SS group	SP group
Total	17 (94.4%)	9 (50%)	8 (44.4%)
Cardiovascular	14 (77.8%)	8 (44.44%)	6 (33.33%)
Diabetes	5 (27.7%)	5 (27.7%)	0
Malnutrition	4 (22.2%)	2 (11.1%)	2 (11.1%)
Obesity	3 (16.6%)	2 (11.1%)	1 (5.5%)
Liver disease	2 (11.1%)	0	2 (11.1%)
Preoperative anaemia	13 (72.2%)	8 (44.4%)	5 (27.8%)

Table 5. Distribution of mean values for albumin and haemoglobin and by stage in the included cohort after PSM

Patient characteristics	Total N(%)	SS group	SP group
Mean albumin (g/dL)		3.71	4.43
Mean Haemoglobin (g/dL)		9.1	11.1
Stage I	1 (5.5%)	1 (5.5%)	0
Stage II	8 (44.4%)	2 (11.1%)	6 (33.3%)
Stage III	9 (50%)	6 (33.33%)	3 (16.67%)

Morbidity Comparison after PSM

Overall early morbidity rate was 16.7% (n=3) and the 30-day mortality rate was 0%. The morbidity rate was 11.1% (n=2) in the SS group, whereas patients in the SP group had a morbidity rate of 5.5% (n=1). All complications are described in *Table 6*. Postoperative bleeding occurred only in the SP group (n=1). The gastrointestinal leak occurred only in the SS group (n=2), either from the duodenal stump (n=1) or the anastomosis (n=1). 11.1% of the cases (n=2) developed postoperative sepsis, only after SS surgery (n=2), out of which one case went into shock (from the SS group). One patient from each group required additional surgery for complications.

Table 6. Distribution of early morbidity types in the included cohort after PSM

Morbidity	Total N(%)	SS group	SP group	p-value
Bleeding	1 (5.5%)	0	1 (5.5%)	1
Duodenal stump leak	1 (5.5%)	1 (5.5%)	0	1
Anastomotic leak	1 (5.5%)	1 (5.5%)	0	1
Pancreatic leak and pancreatitis	0	0	0	1
Sepsis	2 (11.1%)	2 (11.1%)	0	0.470
Shock	1 (5.5%)	1 (5.5%)	0	1
Need-to-reoperate	2 (11.1%)	1 (5.5%)	1 (5.5%)	1
Early mortality	0	0	0	1

Discussion

Our analysis showed that, in our cohort, splenectomy does not increase overall morbidity and mortality in patients undergoing total gastrectomy and D2 Lymphadenectomy for proximal gastric cancer, although, as expected, the risk of pancreatic leak and pancreatitis is higher in SS patients. Likely the difference in pancreatic complications is statistically insignificant due to the lower number of included patients, but the low operability rate of GC should be taken into account (8). However, when the spleen is preserved there is a higher risk of intraoperative and postoperative bleeding (9), which balances the rate of overall morbidity. The oncological value of splenectomy is questioned by a meta-analysis of RCTs published in 2018 (10). For oncological reasons, even the updated Japanese guidelines (7) revised their splenectomy recommendations only for T2-T4 tumours invading the greater curvature. The same study noted a two-time fold increase in postoperative complications in patients with splenectomy. But for experienced upper GI surgeons (11), the difference in morbidity might be lower, if not, insignificant, as suggested by our results. The three surgeons achieved surgical-technique consistency as members of the same surgical team, an important differentiating element to consider when conducting multi-centric investigations.

Both European and Japanese groups are in agreement that proximal tumours invading

the greater curvature have an indication for splenectomy for oncological clearance of splenic hilum nodes (12) and this should be performed safely without significant morbidity in expert hands as suggested herein. An interesting phase II Japanese trial (13) is underway to assess whether dissection in the splenic hilum with spleen preservation is oncologically safe in proximal advanced cancers with greater curvature involvement. So far 52 patients have been enrolled and we should expect results from them in 2024.

This study did not evaluate the oncological outcomes between SS and SP groups and should be done in further research. Also, the question remains whether splenectomy does add to long-term morbidity through the absence of the spleen and its immune regulator effects (14). Post-splenectomy sepsis is a known short- and long-term complication (15) and could be another reason to preserve the spleen if not directly threatened by greater curvature cancer invasion. Another limitation of this study is the low number of patients and its retrospective nature, although we would argue that by including patients retrospectively, their management reflected real clinical practice, without the risk of performance bias as found in clinical trials, especially in surgical ones, where surgeons deviate their practice under the governance of a clinical study.

Conclusion

If splenectomy is indicated for oncological clearance in proximal gastric cancers with greater curvature involvement, it should be performed safely without increased morbidity by experienced upper GI surgeons.

Conflict of Interest Statement

No funding or financial assistance was received by the authors. The authors have no conflicts of interest to disclose.

Author's Contributions

All authors contributed to the study conception and design. SI collected the data and wrote the manuscript; SM, SL, MGD reviewed the article and offered feedback; RB, WLO, BB collected the data and designed the tables and figures; AMM performed statistical analysis; CER and NV designed the study and interpreted the data; SM performed the subgroup analysis and propensity score matching. All authors critically revised the manuscript, commented on the drafts of the manuscript and approved the final version.

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