Prognostic Impact of Prophylactic Splenectomy for Upper-third Gastric Cancer: A Cohort Study

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Abstract. *Aim: The aim of this study was to investigate the effect of splenectomy on survival outcomes and recurrence in patients who underwent curative surgery for gastric cancer. Patients and Methods: This is a retrospective study of 129 patients who underwent upper-third gastric cancer curative resection with lymphadenectomy. Forty-two patients (32%) also underwent splenectomy. Results: The median follow-up period was 33 months. Approximately 40% of the patients had lymph node metastases; four of them had nodal involvement along the splenic artery and 5 had nodal involvement at the splenic hilum. No patients in the pT1-2 group with nodal metastases had involvement of the splenic hilar lymph nodes. There was no significant association between splenectomy and either overall or disease-free survival in the patients. Conclusion: Splenectomy should not be performed in patients with pT1-2 tumors for prophylactic lymphadenectomy.*

Gastric cancer is the second most frequent cause of cancer-related death. The most effective treatment for gastric cancer is surgery with lymphadenectomy.

Upper-third gastric cancer can metastasize to the lymph nodes at the splenic hilum (1-3); these are classified as regional lymph nodes under the TNM classification system (4). In patients with advanced gastric cancer who underwent splenectomy, nodal metastases at the splenic hilum were present in 9.8-18.3% (3, 5-7). Splenectomy is often performed for advanced gastric cancer to achieve complete dissection of lymph nodes at the splenic hilum (8-10). However, there are reports about adverse effects of splenectomy for gastric cancer (11-13), and reports of no survival benefit of splenectomy for gastric cancer treatment (14, 15). There are also long-term side-effects associated with splenectomy, including immunosuppression and increased susceptibility to overwhelming bacterial infection by encapsulated organisms such as pneumococcus (16, 17).

It is therefore important to evaluate the indications for splenectomy in gastric cancer, while assessing the potential benefit and harm associated with the procedure, and determining the factors, which can help identify patients who will derive the most benefit from prophylactic splenectomy.

The aim of this retrospective study was to investigate the effect of splenectomy on survival and recurrence in patients who underwent curative surgery for upper-third gastric cancer.

Patients and Methods

Study design. We retrospectively studied the patients who underwent curative surgery including lymph node dissection for upper-third gastric cancer at the Digestive Disease Center, Showa University Northern Yokohama Hospital between October 2001 and December 2010. Although the extent of gastrectomy was decided by preoperative diagnosis of disease spread (primary tumor and enlarged lymph nodes) using endoscopy and computed tomography (CT), each surgeon decided intraoperatively to achieve complete disease resection. Splenectomy was performed for disease with detectable enlarged lymph nodes at the splenic hilum by preoperative diagnosis or intraoperative inspection. Intraoperative pathological examination was not generally obtained. Clinical and histological data and prognosis were determined based on medical records. All diseases were pathologically staged using the seventh edition of the TNM classification, published in affiliation with the International Union Against Cancer (UICC) (4). Lymph nodes were described according to the third English edition of the Japanese Classification of Gastric Carcinoma (18).

Patients. Inclusion criteria were: (i) Presence of histologically-proven adenocarcinoma of the upper-third of the stomach; (ii) presence of histologically solitary tumors; (iii) no prior treatment with endoscopic resection, chemotherapy, or radiotherapy; and (iv) patient age 20-80 years. The exclusion criteria were: (i) presence of synchronous or metachronous malignancy; and (ii) presence of severe organ dysfunction.

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Key Words: Gastric cancer, splenectomy, lymph node metastasis.

Table I. *Clinicopathological findings of patients included in this study.*

Variable	N=129
Age (year), mean±SD	66.9±10.6
Gender	
Male	100 (77.5%)
Female	29 (22.5%)
Tumor location*	
U	79 (61.2%)
UE	18 (14.0%)
UM	23 (17.8%)
UME	9 (7.0%)
Main tumor site of cross section*	
Less	71 (55.0%)
Gre	16 (12.4%)
Ant	9 (7.0%)
Post	30 (23.3%)
Circ	3 (2.3%)
Macroscopic type*	
0	55 (42.6%)
1	6 (4.7%)
2	24 (18.6%)
3	36 (27.9%)
4	4 (3.1%)
5	4 (3.1%)
Pathological tumor size (mm), mean±SD	52.3±31.0
Main histological type†	
Differentiated	73 (56.6%)
Undifferentiated	56 (43.4%)
Lymphatic invasion	
L0	55 (42.6%)
L1	74 (57.4%)
Venous invasion	
V0	57 (44.2%)
V1	72 (55.8%)
V2	0 (0)
Pathological depth of tumor invasion	
pT1	46 (35.7%)
pT2	22 (17.1%)
pT3	41 (31.8%)
pT4	20 (15.5%)
Lymph node metastasis	
pN0	78 (60.5%)
pN1	15 (11.6%)
pN2	19 (14.7%)
pN3	17 (13.2%)
Distant metastasis	
M0	125 (96.9%)
M1	4 (3.1%)
TNM stage	
I	58 (45.0%)
II	36 (27.9%)
III	31 (24.0%)
IV	4 (3.1%)
Extent of gastrectomy	
Proximal	45 (34.9%)
Total	84 (65.1%)
Surgical approach	
Laparoscopic surgery	77 (59.7%)
Open surgery	52 (40.3%)
Splenectomy	
No	88 (68.2%)
Yes	41 (31.8%)
Partial pancreatectomy	
No	128 (99.2%)
Yes	1 (0.8%)
Adjuvant chemotherapy	
No	73 (56.6%)
Yes	56 (43.4%)

*According to the third English edition of the Japanese Classification of Gastric Carcinoma (18). †Differentiated: papillary adenocarcinoma and tubular adenocarcinoma; undifferentiated: mucinous adenocarcinoma, poorly differentiated adenocarcinoma and signet-ring cell carcinoma. U: upper part; UE: upper part with esophageal invasion; UM: upper and middle parts; UME: upper and middle parts with esophageal invasion; Less: lesser curvature; Gre: greater curvature; Ant: anterior wall; Post: posterior wall; Circ: circumferential involvement.

All patient data were approved for use by the Institutional Review Board of Showa University Northern Yokohama Hospital (no. 1203-02), and this study was registered with the University Hospital Medical Information Network in Japan (no. UMIN000007425, http://apps.who.int/trialsearch/trial.aspx?trialid=JPRN-UMIN000 007425).

Statistical analysis. Statistical analysis was performed using JMP 9.0.2 (SAS Institute, Cary, NC, USA). Fisher's exact test was used to compare patients' characteristics (sex, extent of gastrectomy, surgical approach, tumor location, esophageal invasion, and distant metastasis). We used the χ^2 test to compare depth of tumor invasion, lymph node metastasis, and TNM stage between patient subgroups. The non-parametric Mann-Whitney test was used to assess differences in age and tumor size. Kaplan-Meier curves of estimated overall and disease-free survival were generated and compared between the groups using a two-sided log-rank test. A value of $p<0.05$ was considered statistically significant.

Results

Clinicopathological characteristics. A total of 129 patients were eligible and included in this study. The median follow-up period for the surviving patients was 33 months.

Clinicopathological characteristics of the patients are summarized in Table I. Approximately 80% of the patients were men, and the average age was 66.9 years. About 21% of the patients had tumors with esophageal invasion. Seventy-four (57.4%) and 51 (39.5%) out of 129 patients had lymphatic invasion (L1) and lymph node metastasis (pN1-3), respectively. Forty-five patients (34.9%) underwent proximal gastrectomy and the remaining 84 (65.1%) underwent total gastrectomy. Forty-one patients (31.8%) also underwent splenectomy.

Table II. *Incidence of nodal metastases along the splenic artery and splenic hilum.*

Depth of tumor invasion	Number of patients with metastasis /dissection (%)		Number of patients with distant lymphatic metastasis [M1 (LYM)]
	LNs along splenic artery (n=78)	LNs at splenic hilum (n=45)	
Overall	4/78 (5.1%)	5/45 (10.9%)	3
pT1	0/15 (0)	0/4 (0)	0
pT1a (m)	0/6 (0)	0/1 (0)	0
pT1b (sm)	0/9 (0)	0/3 (0)	0
pT2 (mp)	1/16 (6.3%)	0/7 (0)	0
pT3 (ss)	1/29 (3.4%)	3/21 (14.3%)	2
pT4	2/18 (11.1%)	2/13 (15.4%)	1
pT4a (se)	2/16 (12.5%)	1/11 (9.0%)	1
pT4b (si)	0/2 (0)	1/2 (50.0%)	0

LNs: Lymph nodes; m: invade lamina propria or muscularis mucosa; sm: invade submucosa; mp: invade muscularis propria; ss: invade subserosa; se: perforate serosa; si: invade adjacent structures.

The relationship between the pathological depth of tumor invasion and metastases to the lymph nodes along the splenic artery or at the splenic hilum is summarized in Table II. Seventy-eight and 45 patients underwent dissection of the lymph nodes along the splenic artery and at the splenic hilum, respectively. There were four patients with nodal metastases along the splenic artery, and five had nodal metastases at the splenic hilum. No patient had nodal metastasis both along the splenic artery and at the splenic hilum. Nodal metastases along the splenic artery were seen in patients with pT2 or deeper tumors, and metastases at the splenic hilum were seen in pT3 or deeper tumors.

Outcomes by patients with nodal metastases at the splenic hilum. The details of the five patients who had synchronous nodal metastases and one patient who had a metachronous recurrence at the splenic hilar lymph nodes are summarized in Table III. Three patients had disease recurrence and died from cancer. Only one patient had a metachronous nodal recurrence at the splenic hilum 17 months after surgery (Figure 1), and then had cancer-related death. In these six patients, all tumors were >3 cm and they had had multiple lymph nodes metastases; four had esophageal invasion, and four had a histologically-undifferentiated component. All six patients were pathologically diagnosed with advanced disease, higher than stage III. Notably, all six patients with synchronous or metachronous nodal metastases at the splenic hilum had been preoperatively diagnosed as splenic hilar node-negative by CT.

Survival rates of patients according to splenectomy. Overall survival rates were compared between the patients with and those without splenectomy. In patients with pT1-4 tumors, patients who did not undergo splenectomy demonstrated higher overall survival compared with those who did (Figure 2A). Patients were grouped by the pathological depth of tumor invasion into pT1-2 or pT3-4, which correlated with the probability of node metastasis at the splenic hilum. Within the pT1-2 group, there was no significant difference in overall survival between those who had undergone splenectomy and those who had not (Figure 2B). We compared the clinicopathological characteristics of the patients with pT3-4 tumors with potential nodal metastases at the splenic hilum according to splenectomy. Patients with more advanced disease were more likely to have undergone splenectomy (presence of esophageal invasion, $p=0.003$; N category, pN0 and pN1-3, $p=0.034$; stage II and stage III-IV, $p=0.009$) (Table IV). Within the pT3-4 group, patients who did not undergo splenectomy also had a trend towards better overall survival, although the comparison did not reach statistical significance (Figure 2C).

Discussion

The aims of this study were to assess the impact of splenectomy on survival and recurrence in patients with upper-third gastric cancer, and to determine which patients might benefit from splenectomy in terms of survival and recurrence.

For advanced gastric cancer, radical surgery including gastrectomy, lymphadenectomy, and resection of the other organs, for example, spleen and pancreas, is often performed to achieve complete tumor resection (9, 10). Although pancreatectomy is mainly performed for tumor with direct pancreatic invasion (T4 tumor), splenectomy is generally performed for prophylactic resection of the lymph nodes at the splenic hilum. In particular, upper-third gastric cancer can metastasize to the lymph nodes at the splenic hilum; thus, combined splenectomy has been often performed as curative surgery. Immunosuppression occurs after splenectomy (16), and the survival benefit of splenectomy in gastric cancer is

Table III. *Clinicopathological findings of patients with synchronous and metachronous nodal recurrence at the splenic hilum.*

Case	Sp	No. of node metastases at splenic hilum	Age (years)	Gender	Tumor site†	Macroscopic type†	pT	Size (mm)	Histological type	L	V	pN	pM	pStage	Follow-up period (months)	Status
1	Yes	4	46	M	UM	0-IIc	3	35	Poor	1	1	2	0	IIIA	65	Alive without relapse
2	Yes	3	55	M	UME	3	3	70	Poor>tub2	2	1	3b	1‡	IV	8	Deceased by cancer
3	Yes	2	74	M	UE	3	3	80	Tub1	1	3	3a	0	IIIB	37	Deceased by cancer
4	Yes	1	53	F	UE	3	4a	60	Poor	1	1	1	0	IIIA	36	Deceased by cancer
5	Yes	1	61	M	U	2	4b§	65	Tub2>tub1	0	1	2	0	IIIC	52	Alive without relapse
6	No	–	59	F	UME	3	4a	75	Sig>poor	3	3	3a	0	IIIC	39	Deceased by cancer

†According to the third English edition of the Japanese Classification of Gastric Carcinoma (18). ‡Peritoneum. §Directly invaded pancreas and spleen. Sp, Splenectomy; Poor, poorly differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; tub1, well differentiated adenocarcinoma; sig, signet-ring cell carcinoma; M: Male; F: Female; U: upper part; UE: upper part with esophageal invasion; UM: upper and middle parts; UME: upper and middle parts with esophageal invasion.

controversial (12, 15, 19). If we cannot precisely detect positive nodes, unnecessary splenectomy must be avoided. Unfortunately, all six patients in the present study with nodal metastases at the splenic hilum were diagnosed as node-negative.

None of our patients with pT1-2 tumor had nodal metastasis at the splenic hilum, and splenectomy had no significant survival benefit for patients with pT1-2 tumors. All six patients with nodal metastases at the splenic hilum had pT3 or deeper tumors. Five of these patients had synchronous nodal metastases, and three and two patients had pT3 and pT4 tumors, respectively. There were 61 cases of pT3-4 disease, and cases with nodal metastases at the splenic hilum represented 4.6% of all upper-third gastric carcinomas and 9.8% of pT3-4 tumors. Our study included patients with early-stage cancer and showed a lower incidence of nodal metastases at the splenic hilum than in previous studies (3, 5-7).

None of our patients had synchronous nodal metastasis to lymph nodes, both along the splenic artery and at the splenic hilum. This suggests that the lymph nodes along the splenic artery are not a relay point to the nodes at the splenic hilum. Nevertheless, it is notable that nodal recurrence at the splenic hilum occurred in one case, and it is possible that this recurrence might have been prevented by splenectomy. Based on our findings, approximately 5% of patients with upper-third gastric carcinomas and 10% of those with pT3-4 tumors in the upper-third of the stomach had synchronous nodal metastases at the splenic hilum. Consequently, the survival benefit of splenectomy for the purpose of lymph node dissection may be limited.

The survival rate was relatively lower in the splenectomized group compared with the non-splenectomized group in patients with pT3-4 tumors. We offer several possible explanations for this. One is that there were more patients with

Table IV. *Clinicopathological characteristics of the patients with pT3-4 tumor.*

Variable	Without splenectomy (n=28)	With splenectomy (n=33)	*p*-Value
Mean age, year (range)	70.1 (49-86)	65.3 (41-84)	0.129
Gender, n (%)			0.538
Male	21 (75.0%)	24 (72.7%)	
Female	7 (25.0%)	9 (27.3%)	
Extent of gastrectomy, n (%)			0.021
Proximal	8 (28.6%)	2 (6.1%)	
Total	20 (71.4%)	31 (93.9%)	
Surgical approach, n (%)			0.096
Laparoscopic surgery	10 (35.7%)	14 (50.0%)	
Open surgery	23 (82.1%)	14 (50.0%)	
Tumor location†, n (%)			0.037
U or UE	20 (71.4%)	15 (45.5%)	
UM or UME	8 (28.6%)	18 (54.5%)	
Esophageal invasion, n (%)			0.003
No	23 (82.1%)	15 (45.5%)	
Yes	5 (17.9%)	18 (54.5%)	
Tumor size, mm (range)	58.7 (12-120)	75.8 (33-175)	0.090
Depth of tumor invasion, n (%)			0.356
pT3	20 (71.4%)	21 (63.6%)	
pT4	8 (28.6%)	12 (36.4%)	
Lymph node metastasis, n (%)			0.034
pN0	14 (50.0%)	8 (24.2%)	
pN1-3	14 (50.0%)	25 (75.8%)	
Distant metastasis, n (%)			0.078
M0	0	4 (90.2%)	
M1	28 (100%)	29 (9.8%)	
TNM stage, n (%)			0.009
II	17 (60.7%)	9 (27.3%)	
III-IV	11 (39.3%)	24 (72.7%)	

†According to the third English edition of the Japanese Classification of Gastric Carcinoma (18). U: upper part; UE: upper part with esophageal invasion; UM: Upper and middle parts; UME: upper and middle parts with esophageal invasion.

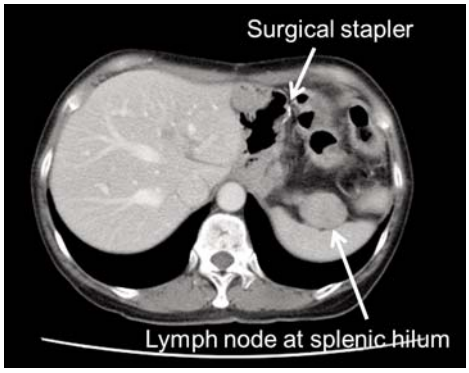

Figure 1. *Computed tomography of a patient with metachronous recurrence at the splenic hilar node, 17 months after curative surgery.*

advanced disease in the splenectomized than the non-splenectomized group. Next, the incidence of nodal metastases at the splenic hilum was low; therefore, the survival benefit of splenectomy was limited. Finally, lymphadenectomy does not affect other possible routes of spread, such as hematogenous and peritoneal dissemination. The majority of patients with recurrence in our cohort study, in fact, showed evidence of hematogenous and peritoneal dissemination.

There is no significant survival benefit for splenectomy as prophylactic lymphadenectomy; therefore, adequate application of splenectomy is important. It is reported that the incidence of disease in splenic hilar lymph nodes is low for tumors arising on the lesser curvature of the stomach (1, 3, 5). In this study, tumor in two out of six patients with synchronous or metachronous nodal metastases at the splenic hilum originated from the lesser curvature, demonstrating the potential for such primary tumors to metastasize to the lymph nodes at the splenic hilum. These data suggest that cross-sectional localization of the tumor is inadequate to determine whether splenectomy is indicated. In contrast, there is a report that a pT4 tumor is a risk factor for nodal metastasis at the splenic hilum (20). In our study, pT3 or deeper tumors, larger than 3 cm, and multiple positive perigastric nodes were relatively typical characteristics of the presence of nodal metastases at the splenic hilum. pT4 tumor is generally large; therefore, it might have been excluded from our study, which limited tumor location to the upper third of the stomach. We had no cases with nodal metastasis only at the splenic hilum, as reported previously (15).

Preoperative assessment of lymph node metastases can be achieved by CT (21), magnetic resonance imaging (22), ultrasound (23), or positron emission tomography (24), although the sensitivity varies between these modalities. In our study, preoperative imaging failed to detect all six cases with splenic hilar lymph node metastases, underscoring the difficulty in pre-treatment detection of nodal metastases at the splenic hilum.

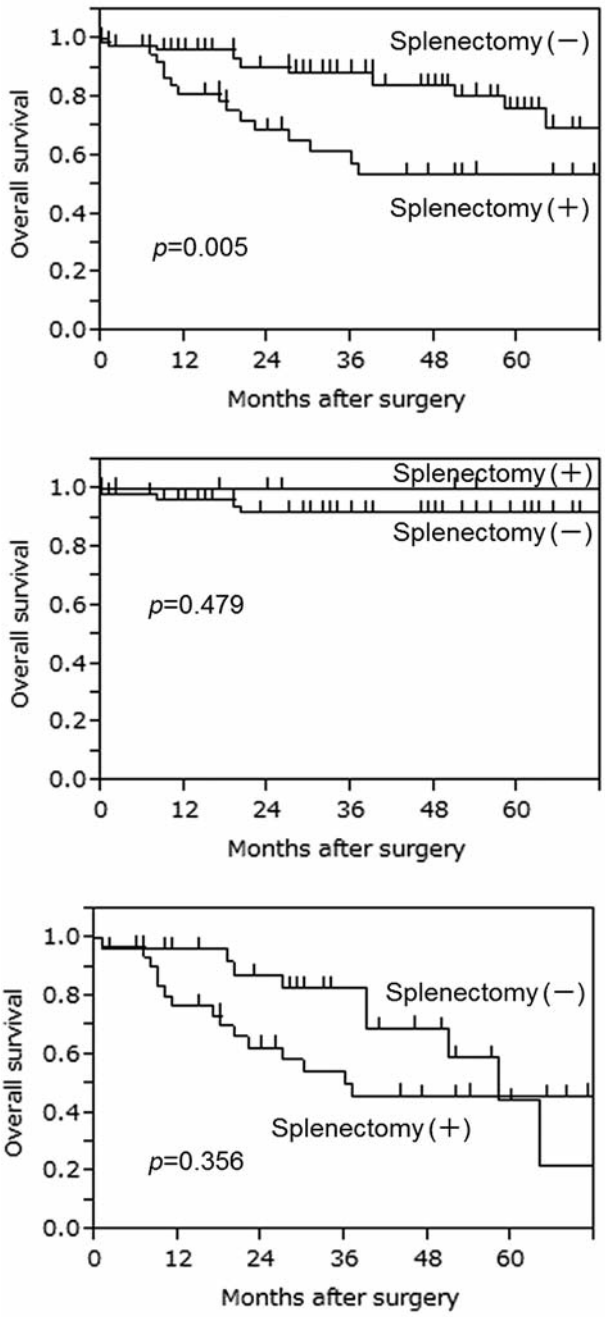

Figure 2. *Overall survival of patients according to splenectomy. A: Overall survival of patients with pT1-4 tumors who did (n=41) and did not (n=88) undergo splenectomy. B: Overall survival of patients with pT1-2 tumors who did (n=8) and did not (n=60) undergo splenectomy. C: Overall survival of patients with pT3-4 tumors who did (n=33) and did not (n=28) undergo splenectomy.*

Conclusion

We conclude that splenectomy should not be performed for prophylactic lymphadenectomy in patients with pT1-2 tumors. In patients with pT3–4 tumors, prophylactic

splenectomy has no significant survival benefit. Therefore, splenectomy should be performed only for advanced gastric cancer (pT3-4) with clinical or intraoperative macroscopic lymph node metastases at the splenic hilum.

Competing Interests

The Authors declare that they have no competing interests.

Authors' Contributions

HI (Hiroaki Ito) conceived and designed the study, collected clinical data, and performed the statistical analysis and data interpretation. HI (Haruhiro Inoue) participated in the study design and performed data interpretation. NO, HS, SM, TO and YT collected clinical data. SK participated in the study design and coordination. All authors read and approved the final manuscript.

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