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

HIROAKI ITO, HARUHIRO INOUE, NORIKO ODAKA, HITOSHI SATODATE, SHUMPEI MUKAI, TOMOKATSU OMOTO, YUSUKE TAKEHARA and SHIN-EI KUDO

Digestive Disease Center, Showa University Northern Yokohama Hospital, Tsuzuki-ku, Yokohama, Japan

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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Correspondence to: Hiroaki Ito, Digestive Disease Center, Showa University Northern Yokohama Hospital, 3-5-1 Chigasakicho, Tsuzuki-ku, Yokohama 224-8503, Japan. E-mail: h.ito@med.showa-u.ac.jp

Key Words: Gastric cancer, splenectomy, lymph node metastasis.
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-UMIN000007425).

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 χ2 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.
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.

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

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 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
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>
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<tr>
<th>Case</th>
<th>Sp</th>
<th>No. of node metastases at splenic hilum</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Tumor site†</th>
<th>Macroscopic type†</th>
<th>Size (mm)</th>
<th>Histological type</th>
<th>L</th>
<th>V</th>
<th>pN</th>
<th>pM</th>
<th>pStage</th>
<th>Follow-up period (months)</th>
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<tr>
<td>1</td>
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<td>4</td>
<td>46</td>
<td>M</td>
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<td>35</td>
<td>Poor</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>IIIA</td>
<td>65</td>
<td>Alive without relapse</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>3</td>
<td>55</td>
<td>M</td>
<td>UME</td>
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<td>70</td>
<td>Poor_tub2</td>
<td>2</td>
<td>1</td>
<td>3b</td>
<td>1‡</td>
<td>IV</td>
<td>8</td>
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</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>2</td>
<td>74</td>
<td>M</td>
<td>U</td>
<td>3</td>
<td>80</td>
<td>Tub1</td>
<td>1</td>
<td>1</td>
<td>3a</td>
<td>0</td>
<td>IIIB</td>
<td>37</td>
<td>Deceased by cancer</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>1</td>
<td>53</td>
<td>F</td>
<td>UE</td>
<td>3</td>
<td>4a</td>
<td>Poor</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>36</td>
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<tr>
<td>5</td>
<td>Yes</td>
<td>1</td>
<td>61</td>
<td>M</td>
<td>U</td>
<td>2</td>
<td>4b§</td>
<td>Tub2_tub1</td>
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<td>1</td>
<td>2</td>
<td>0</td>
<td>IIIC</td>
<td>52</td>
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<td>–</td>
<td>59</td>
<td>F</td>
<td>UME</td>
<td>3</td>
<td>4a</td>
<td>Sig&gt;poor</td>
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<td>3a</td>
<td>0</td>
<td>IIIC</td>
<td>39</td>
<td>Deceased by cancer</td>
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</tbody>
</table>

†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.
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 pretreatment detection of nodal metastases at the splenic hilum.

**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
spleenectomy has no significant survival benefit. Therefore, spleenectomy 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. 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.

Acknowledgements
We are extremely grateful to all the patients and to the clinical staff who cared for these patients. We also are thankful to Dr. Shigebaru Hamatani for his reliable pathological diagnoses.

References


