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Impact of Spleen Preservation in Patients with Gastric Cancer

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Abstract. *Background: Resection of the spleen en bloc with the stomach for gastric cancer is still widely performed for a curative resection (R0), but the presence of the spleen may have a favorable effect on recurrence control and survival. The hypothesis that the spleen suppresses tumor growth from minimal residual disease in the critical early postsurgical period and reduces the risk of recurrent disease was tested. Patients and Methods: Patients were included who underwent gastrectomy, with or without splenectomy, for gastric adenocarcinoma. Standardized, strongly-defined criteria were used to accurately stratify patients, who had an extended (D2) lymph node dissection, into the curative and non-curative resection groups. Limited, D1 resection confounds appropriate R-stratification and thus D1 patients were excluded. Prospectively-defined primary endpoints were early (within two years) and overall recurrence and death from any cause and secondary endpoints were postsurgical risks (morbidity, mortality) and metastases to the splenic hilum nodes. Results: Overall survival for the total population studied (n=202) was better for preservation-versus-resection of the spleen among R0 patients (p=0.0001), but not for those with non-curative resection (p=0.42). For the R0 D2 group of patients, preservation (n=59) over resection (n=67) of the spleen, there was no significant difference in in-hospital postoperative morbidity or mortality (3.4% vs. 0%). At a median follow-up of 112 months, significantly the preservation of the spleen, lowered the risks of early recurrence (HR, 0.33; 95% CI, 0.16 to 0.69; p=0.003) and death from any cause (p=0.009) after adjustment analysis. Since at baseline there was a significant imbalance of tumor stage in favor of the spleen-preservation group, we conducted a stage-stratified subgroup analysis. This treatment effect remained consistent in the subgroup analyses according to nodal and serosal status, while in multivariate analysis preservation of the spleen was an independent predictor of outcome. An overestimation of the risk for residual disease in the splenic hilum nodes in the case of spleen preservation was obtained in 94% of splenectomized patients. Conclusion: Our findings indicate that preservation of the spleen may be associated with a reduced risk of early and overall recurrence translated into a better survival in patients receiving curative surgery for gastric cancer. A large randomized trial is needed to confirm this finding. Indications for splenectomy are few, being limited to those patients with advanced proximal cancers.*

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Adenocarcinoma of the stomach remains a major health problem despite declining incidence worldwide. Reviewing the most recently published data, Roukos *et al.* (1) assessed that there has been little progress in reducing the mortality of this disease in the Western world. In the U.S.A, the overall survival rate is only 22% (2). Surgery remains the treatment of choice and, according to the International Union Against Cancer (UICC [3]), when it results in complete tumor removal, namely R0 resection, can be associated with long-term survival or even cure (1). Unfortunately, even after curative surgery, recurrence develops and mortality rates are high (1, 4). Over the past decades efforts have been made to improve tumor control through better surgical treatment and development of effective adjuvant treatment including chemotherapy and radiotherapy. However, the effectiveness of adjuvant chemotherapy in improving survival remains controversial, since no single randomized controlled trial (RCT) has shown significant survival advantage and meta-analysis indicates a small absolute survival benefit with adjuvant chemotherapy (1, 4-7).

Given the moderate efficacy of chemoradiation (8-10), extensive surgery has been suggested, mainly by Japanese surgeons (11, 12) and Western authors (13). This radical surgery consists of total gastrectomy (14), splenectomy and extended (D2) lymph node dissection (15) and it can be

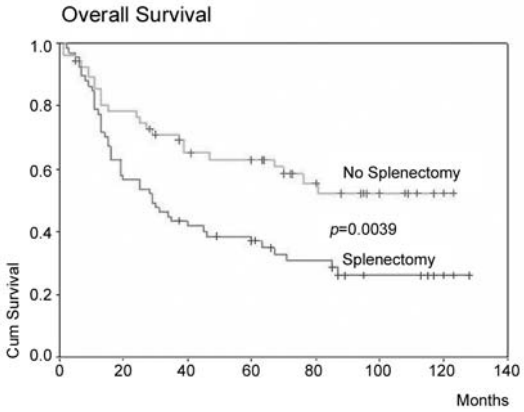

Figure 1. *Kaplan-Meier estimates of overall survival in the R0, D2 group of patients (n=125). Overall survival was significantly better in the spleen-preservation group.*

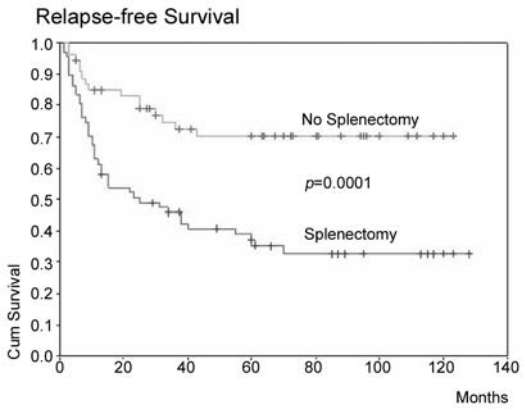

Figure 2. *The presence of the spleen among D2 RO patients was associated with a relative benefit of recurrence-free survival at ten years by 37.2% (p=0.001, log-rank test).*

safely perfomed by experienced surgeons (1, 12, 16, 17). The role of the preservation or resection of the spleen during total gastrectomy has not yet been clarified. Several observational studies found no significant advantage in survival in favor of splenectomy (18-20) and, moreover, others report an adverse effect of splenectomy on postoperative short-term and/or long-term outcome (21-26), but the data are still inconclusive. Two of these studies were RCTs (25, 26), but were designed to assess differences between D1 and D2 resections and therefore the assessments for the adverse effects of splenectomy should also be evaluated with caution (27). This controversy and the reliance of surgeons worldwide on the necessity of splenectomy to achieve an R0 resection are likely explanations for the high rate of splenectomy, which in a recent report accounted for 48.7% of resected cases (28).

The uncertainty regarding resection-over-preservation of the spleen prompted us to conduct this prospective study. Emphasis was placed on the precise definition of curative (R0) resection after an extensive, D2 dissection and the discrimination between early and late recurrence, because accurate stratification into these subgroups may increase the probability of detecting a significant effect of spleen preservation on patient's outcome. The low incidence of metastasis to the splenic-hilum nodes observed in our previous study also provided an incentive to perform the present study (29). Since it is likely that there is an association between splenectomy, surgical stress-induced immunosuppression and early recurrence, special consideration was given to the incidence of early recurrence in the study groups.

Patients and Methods

Patients and eligibility criteria. Patients were eligible if they had a histologically confirmed gastric carcinoma and had undergone surgical resection. From January 1986 to December 1992, all patients who underwent gastrectomy alone (spleen-preservation group) or combined with resection of the spleen (splenectomy group) in the Department of Abdominal and General Surgery at Johann-Wolfgang-Goethe University Hospital in Frankfurt, Germany, were included in this prospective study.

Surgery. Resection of the spleen during gastrectomy was optional. Total gastrectomy with extended lymph node dissection was the treatment of choice. Extended (D2) lymph node dissection was performed with a systematic and standardized pancreas-preserving technique, according to the slightly modified guidelines of the Japanese Research Society for Gastric Carcinoma (JRSGC; 22): D2 node dissection entailed the removal of perigastric compartment I nodes (stations 1 to 6: D1 dissection) and the extraperigastric compartment II nodes including those around the celiac axis (stations 7 to 9), along the splenic artery (station 11), to the splenic hilum (10) and in ligamentum hepatoduodenal (station 12).

Pathology and quality control for appropriate patient stratification. All diagnostic, surgical and histopathological data prospectively documented in a standardized protocol were used for the accurate stratification of patients according to curability of resection (R-stratification: R0 or R1/R2), extent of lymph node dissection (D1 or D2), tumor site (proximal *vs.* distal half of the stomach), type of gastrectomy (total *vs.* subtotal), histological type of Lauren classification (intestinal *vs.* diffuse), as well as nodal status (negative *vs.* positive), serosal status (serosa-negative *vs.* positive) and tumor-node-metastasis (TNM) staging system (3).

Surgery was defined as curative if, at laparotomy, there was no macroscopic evidence for distant metastasis or suspected enlarged lymph nodes beyond the compartment II and the resection resulted in complete tumor removal with histologically proven tumor-free status in all resection margins in the final histological examination. A resection which did not fulfill all of these criteria was defined as non-curative (R1, R2 resection).

Because D1 dissection is associated with residual D2-positive nodes and thus is inaccurate for R-stratification, estimates of recurrence and survival were focused on the D2 R0 subgroup. The

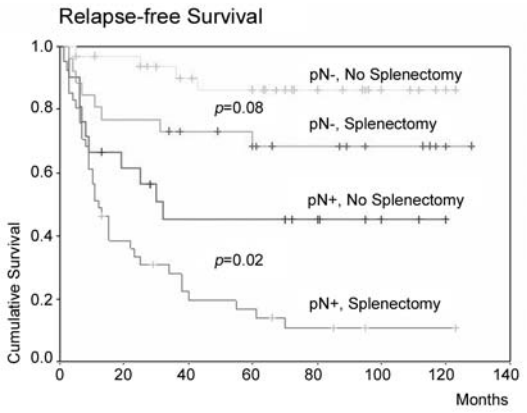

Figure 3. *The presence of the spleen among D2 RO patients was associated with a relative benefit of recurrence-free survival at ten years by 23.5% (p=0.08, log-rank test) for node-negative cancer and by 36.3% (p=0.02, log-rank test) for node-positive cancer.*

pathology report of lymph node examination was used to control the surgical report for a complete D2 resection.

None of the patients treated curatively underwent adjuvant chemotherapy or radiotherapy and thus surgery alone was responsible for the reported results.

After surgery, patients were screened by clinical examination, laboratory tests, chest radiography and abdominal ultrasound every 3 months, and by endoscopic examination and computed tomography every 6 months. After the third year, follow-up was done at 1-year intervals. The follow-up was completed at the end of 1999. First recurrence and deaths from any cause were recorded.

Statistical analysis. Primary endpoints were recurrence-free survival (recurrence), gastric cancer-specific survival (death from recurrence) and overall survival (death from any cause); the secondary endpoints, short-term postoperative outcome (morbidity, mortality) and frequency of metastasis to the splenic hilum lymph nodes. Recurrence or death from the disease, whichever occurred first, was separated into early recurrence (tumor appearance during the first 2 years) and overall recurrence (tumor at any time). All time periods up to the event (recurrence, death, last follow-up visit) were calculated from the date of surgery. The time-to-event endpoints were estimated using the Kaplan and Meier method, and differences between the groups were compared with the log-rank test. The relative risks of recurrence and death were calculated with the Cox proportional hazard model (univariate analysis).

Data were analyzed according to a prospectively defined plan. Primary analysis included all resected patients (intent-to-treat principle). All further estimates of recurrence and survival were focused on the R0 D2 subgroup. Because it was expected that splenectomy would be performed more often in advanced tumor stages, leading to a significant imbalance, a predefined adjustment and subgroup analysis was planned according to these well-known prognostic baseline variables (nodal/serosal status).

A multivariate analysis including all stratified factors at baseline (tumor site, stage, type and spleen-preservation) was prospectively planned in Cox's model, which would prove significant by univariate analysis (log-rank test) to estimate the independent effect of these variables on outcomes.

Table I. *Base-line characteristics of 126 patients who received a curative (R0) D2 resection for gastric cancer.*

Characteristics	Preservation of the spleen (N=59)	Resection of the spleen (N=67)
Median age (yr)	66	65
Sex (M/F)	36/23	42/25
		no. (%)
Tumor site		
Proximal half of the stomach	19 (32)	30 (45)
Distal half	39 (66)	30 (45)
Infiltration of both	1 (2)	7 (10)
Depth of invasion (UICC/AJCC)*		
Serosa-negative cancers	37 (63)	22 (33)
pT1	20 (34)	5 (8)
pT2	17 (29)	17 (25)
Serosa-positive cancer (pT3)	22 (37)	45 (67)
Lymph node status (JRSGC)†		
Node-negative cancers (pN0)	36 (61)	26 (39)
Node-positive cancers	23 (39)	41 (61)
PN1	13 (23)	20 (30)
PN2	10 (17)	21 (31)
Lauren classification		
Intestinal type carcinoma	25 (42)	23 (34)
Diffuse or mixed type carcinoma	34 (58)	44 (66)
Type of gastrectomy		
Total	48 (81)	67 (100)
Subtotal	11 (19)	0
Resection of tail of pancreas	2 (3)	4 (6)
Status at last follow-up		
Alive		
Without recurrence	34 (58)	19 (28)
With recurrence	0	0
Deceased	24 (40)	48 (72)
In-hospital postoperatively	2 (3)	0
Recurrence	15 (25)	45 (67)
Cause other than gastric cancer	7 (12)	3 (5)
Lost to follow-up	1 (2)	0

*The tumor-node-metastasis classification of the Union International Contre le Cancer (UICC) and the American Joint Committee on Cancer, 4th edition was used (1).
†The nodal stage of the Japanese Research Society for Gastric Cancer, 1st English ed. was used.
[1,2]The abbreviation pT, pN denote pathologically confirmed tumor-nodes.
Because of rounding, not all percentages total 100.

For statistical analyses, the SPSS software for Windows (version 10.0) was used.

Results

Overall survival for all resected patients. Two hundred and two of the 210 resected patients received followed-up; 95 had gastrectomy with preservation of the spleen and 107 had

Table II. *Univariate analysis of the risks of recurrence and death from any cause in the study groups.*

Variable	Preservation of the spleen	Resection of the spleen†	Relative risk of recurrence or death (95% CI)††	*p*-values
	No. of patients who recurred or died / Total No.			
Recurrence-free survival*				
Early recurrence				
All patients	9/56	36/67	0.24 (0.12-0.50)	<0.001
Adjustment analysis for nodal status			0.33 (0.16-0.69)	0.003
Overall recurrence				
All patients	15/56	45/67	0.28 (0.16-0.52)	<0.001
Adjustment for nodal status			0.38 (0.21-0.69)	0.002
Node-positive cancer	11/21	36/41	0.43 (0.21-0.85)	0.01
Node-negative cancer	4/35	9/26	0.27 (0.08-0.89)	0.03
Adjustment for serosal status			0.40 (0.21-0.73)	.003
Serosa-positive cancer	10/20	36/45	0.48 (0.24-0.98)	.04
Serosa-negative cancer	5/36	9/22	0.26 (0.09-0.79)	.01
Overall survival‡				
All patients	24/58	48/67	0.49 (0.30-0.80)	0.001
Adjustment for nodal status			0.50 (0.30-0.84)	.009
Node-positive cancer	15/22	37/41	0.53 (0.29-0.99)	.05
Node-negative cancer	9/36	11/26	0.78 (0.18-1.09)	.08
Adjustment for serosal status			0.51 (0.30-0.87)	.01
Serosa-positive cancer	13/21	37/45	0.56 (0.29-1.07)	.08
Serosa-negative cancer	11/37	11/22	0.44 (0.19-1.03)	.06

*At risk for evaluation of recurrence were 123 out of 126 patients who received a curative D2 resection and left the hospital; 2 patients died postoperatively in hospital and one was lost to follow-up.
†Splenectomy group served as the reference group. CI denotes confidence interval.
††The Cox proportional hazard model was applied. Relative risk less than 1.00 represents a decreased risk of recurrence or death, whereas greater than 1.00 represents an increased risk of recurrence or death.
§Hazard ratio was used to calculate *p*-values
‡This analysis included 125 patients; one was lost to follow-up. All deaths irrespective of cause, including postoperative in-hospital deaths, were included.

Table III. *Results of multivariate Cox regression analyses.*

Variable	Recurrence-free survival		Gastric cancer-specific survival		Overall survival	
	Hazard ratio (95% CI)*	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Spleen (presence *vs.* absence)	0.42 (0.23-.76)	0.005	0.42 (0.23-0.77)	0.005	0.53 (0.32-0.89)	0.01
Lymph-node status (positive *vs.* negative)	3.66 (1.88-7.11)	<0.001	3.66 (1.87-7.14)	<0.001	3.23 (1.82-5.73)	<0.001
Serosal-status (positive *vs.* negative)	2.27 (1.19-4.33)	0.01	2.22 (1.15-4.26)	0.01	1.75 (1.00-3.05)	0.05

*Hazard ratios less than 1.00 represent a decreased risk, whereas greater than 1.00 represent an increased risk. CI denotes confidence interval.

gastrectomy combined with splenectomy. Overall, the presence over absence of the spleen was associated with better overall survival ($p=0.0003$ by the log-rank test) and was associated with a decreased risk of death from any cause [HR, 0.66 (95% CI 0.46-0.95; $p=0.02$)] in a multivariate Cox regression analysis independent of the standard prognostic factors, including pathological, node stage (pN), tumor depth (pT), curability of resection (R) and extent of lymph node dissection (D). A subgroup analysis, however, revealed that the presence of the spleen improved survival only among patients (n=151) who had an R0 resection in inadjustment ($p=0.0001$) and adjustment for tumor stage ($p=0.008$) analysis, whereas there was no such effect on patients (n=51) with noncurative surgery (Figure 1). Despite resection, survival for these patients with residual disease after resection was poor, with a mean survival time of 10 months (95% CI, 5 to 14) for spleen preservation patients and 13 months (95% CI, 9 to 18) for the splenectomized patients ($p=0.42$).

Curative gastrectomy with extended (D2) lymph node dissection. Of the 146 patients who fulfilled our criteria for a D2 resection, 126 met the criteria for stratification into the R0 group; 59 had gastrectomy alone (spleen-preservation group) and 67 underwent gastrectomy combined with resection of the spleen (splenectomy group). Baseline characteristics for this group are provided in Table I. There was a significant imbalance in stratification factors related to prognosis, with a higher distribution of less advanced nodal stage (pN, $p=0.02$) and tumor depth (pT, $p=0.001$) in the spleen-preservation group.

Short-term postoperative outcome. There was no difference between preservation *versus* resection of the spleen in postoperative septic complications [anastomotic leakage, intra-abdominal infection, wound infection; 6 (10%) and 8 (12%)] or overall significant complications [11 (18.6%) and 13 (19.4%)] or frequency of re-operations [5 (8.5% and 5 (7.5%)]. There was also no difference in hospital mortality between the spleen-preservation group [2 (3.4%)] and the splenectomy group (0%). The cause of death of the 2 patients in the spleen-preservation group who died postoperatively in the hospital was sepsis as a result of anastomotic leak age in one patient and cardiac complications in the other.

Recurrences. Of the 126 patients, 2 died postoperatively in hospital and one was lost to follow-up. We estimated recurrence risk among 123 R0, D2 patients. The median length of follow-up was 55 months for all 123 patients and 112 months for survivors. Gastric cancer recurred in 15 out of 56 (27%) spleen-preservation patients compared with 45 out of 67 (67%) splenectomized patients (Table I). This difference in the rate of recurrence was significant in the early follow-up period (early recurrence; $p<0.001$ in inadjustment and $p=0.003$ in adjustment analysis for nodal status) or at any time after surgery (overall recurrence) (Table II). This favorable effect of the spleen was also consistently observed in the prospectively defined subgroup analyses, with a reduction in the relative risks of overall recurrence ranging from 52% to 74% among the prognostically important subgroups at baseline (node, serosa-negative/positive cancers) (Table II). Kaplan-Meier analyses of recurrence-free survival yielded similar results in inadjustment analysis ($p<0.0001$), adjustment analyses for nodal status ($p=0.0008$) and serosa status ($p=0.001$), and subgroups analyses (Figures 2, 3).

Survival. In all, 72 patients died, 24 in the spleen-preservation group and 48 in the splenectomy group. The causes of death were recurrent gastric cancer in 60 patients (83%), other diseases with no evidence of recurrence in 10 (14%) and postoperative complications in 2 (3%). All 60 patients who recurred died shortly after recurrence manifested (median survival time only 5 months). Thus, the reduction in the risk of death from gastric cancer was similar to that of recurrence (Table III).

Compared with splenectomy, preservation of the spleen significantly lowered the risk of death from any cause and improved overall survival in inadjustment ($p==0.001$) and adjustment analysis ($p=0.009$ for nodal status and $p=0.01$ for serosa status) (Table II). The reduction in the relative risks of death from any cause among the 4 predefined subgroups [node, serosa (negative/positive) cancers) was statistically marginally significant or insignificant (Table II).

Prospectively-defined subgroup analyses for several baseline variables, listed in Table I, confirmed the prognostic significance of pathological nodal status ($p<0.0001$) and serosal status ($p<0.0001$), but did not show any significant difference with respect to the site of the primary tumor (upper *vs.* middle *vs.* distal third of the stomach; $p=0.67$) or the histological type according to Lauren classification (intestinal *vs.* diffuse-type, $p=0.14$). In a Cox's model which included the prognostic significant factors, the proportional hazard analysis revealed that preservation over resection of the spleen was associated with significantly reduced risks of recurrence or death from gastric cancer by 58 % (95% CI, 0.23 to 0.76; $p=0.005$) and death from any cause by 47% (95% CI, 0.32 to 0.89; $p=0.01$), independently of pathological nodal status and serosal status (Table III).

Risks resulting from preservation of the spleen. The presence of metastases in the splenic hilum lymph nodes was evident in only 4 out of 67 R0 D2 splenectomized patients (6%), whereas no metastasis into the spleen or tumor invasion through the serosa to the spleen was found. Of the 117 lymph nodes retrieved from the hilum of the spleen [mean nodal yield per specimen 1.7 nodes (range 0-4)], 6 were positive.

Analysis of variables thought to be associated with increased risk of metastasis to the splenic hilum nodes

revealed: a) all 4 patients with positive splenic hilum nodes had a tumor located in the proximal half of the stomach (4/30, 13%) which had penetrated the serosa (pT3-cancer, 4/ 45, 9%) and b) 3 of these 4 patients had a tumor in the greater curvature (3/30, 10%) and 3 also had positive several of the other compartment II nodes (3/21, 14%). All 4 had an early recurrence (3, 11, 12 and 13 months after surgery) and died within 2 years.

Discussion

In this study, preservation of the spleen, as compared with splenectomy, during curative gastrectomy for cancer substantially reduced the risks of recurrence and death from any cause. There was no significant difference in in-hospital postoperative morbidity and mortality between the two groups. A survival benefit was evident throughout the 10-year follow-up period in favor of the preservation of the spleen, irrespective of nodal status and serosal status.

The addition of splenectomy to total gastrectomy in the surgical treatment of gastric cancer aiming at increasing local control and survival (11, 31) could not be confirmed in several subsequent studies (18-20). Moreover, in several clinical reports, splenectomy was associated with a higher rate of postsurgical complications and mortality (18-21, 23, 25, 26) without an increase in survival (18-20). Furthermore, other studies found better or equal survival in patients with preservation of the spleen (21-24). Similarly, subgroup analysis of two RCTs showed better recurrence-free survival among patients with preservation rather than resection of the spleen (25, 26), but this comparison was out of the scope (D1 *vs.* D2 resections) of these trials.

Despite all these unfavorable results, the splenectomy rate continues to be high, ranging from 26% to 48.7% (24-26, 28). The explanations for this surgical judgement include the reliance of surgeons on more radical surgery in an effort to control recurrences and the lack of convincing data which indicate that preservation of the spleen improves long-term survival. Indeed, drawing conclusions about the effect of splenectomy on survival is a very difficult challenge because of the heterogeneity of data in the observational studies available. Most of these include small numbers of patients. Since there is lack of RCTs, which could solve this problem, the data of the present study seems to be useful in decision-making.

In an attempt to explain how and why the present study, in contrast to other reports, showed lower recurrence and increased survival rates after spleen preservation the following should be emphasized. First, the resected patients were stratified into curative (R0) and non-curative (R1, R2) subgroups. This stratification facilitated an accurate assessment of the spleen effect on recurrence risk and survival. Appropriate discrimination of patients into the R0 and R1/R2 subgroups was made by inclusion in this prospective analysis of patients who had undergone a true D2 dissection on the basis of standardized criteria. Inclusion of D1 patients confounds R-stratification because a substantial proportion of patients, about 30% (32, 33) at surgery, had positive level 2 nodes, which require D2 resection for accurate histological diagnosis.

Second, to our knowledge, this is the first study focused on the evaluation of the spleen effect on early recurrence. This is clinically important because, if there is an association between surgical stress-induced immunosuppresion enhanced by splenectomy and recurrence, the estimation of early-recurrence incidence increases the probability of detecting a significant difference between preservation and resection of the spleen. Over 75% of recurrences occur within 2 years after R0 surgery (34-36). In this study it was observed that, by an early recurrence rate of 75% (45/60), the presence of the spleen decreased the risks of early recurrences in adjustment for nodal status analysis by 67% (95% CI, 0.16 to 0.69; $p=0.003$).

Third, a consistent effect of spleen-preservation was seen in all four prospectively predefined subgroups (node negative/positive, serosa negative/positive cancers). Nodal status and serosal status have been established as the most important prognostic factors in gastric cancer. This subgroup evaluation is essential because, in our study, there was a significant imbalance of these factors (nodal/serosal status) between the spleen-preservation and splenectomy groups. This imbalance at baseline is the limitation of this study, which remains even after subgroup analysis because of the small numbers of patients in each subgroup compared. Small subgroups and few events (recurrence/death) confound statistical comparisons (37). However, the findings of our study are consistent with that of the largest study available, which included 3477 USA patients (24). Wanebo *et al.*, based on obtained significant survival differences in favor of spleen preservation in tumor stages II and III, proposed preservation of the spleen in patients with these stages at diagnosis (24). In this study, as well as in our study, a trend towards better survival was found in patients with stage I disease, but the difference was not statistically significant. It is likely that a very large study is needed to have statistical power for stage I patients because, at this tumor stage, events are rare. However, even if the spleen has no effect on recurrence and survival, there is no reason for splenectomy at this tumor stage since lymph nodes at the splenic hilus are tumor-free.

A finding that holds great clinical importance and emphasizes the significance of spleen-preservation in our study is that recurrence-free survival and overall survival were similar among patients with node-positive cancers and spleen-preservation and those with node-negative cancers and splenectomy. The treatment effect was also consistent with multivariate analysis in which spleen-preservation was an independent predictor of outcome.

Fourth, our study reflects an overestimation of the residual-tumor risk with preservation of the spleen. Splenectomy, performed in 53% of patients with total gastrectomy, was actually needed for an R0 resection in only 6%, since metastases in the splenic hilum nodes were found in only 4 of 67 D2 R0 patients. These four patients had a tumor in the proximal third of the stomach with serosa invasion (T3 tumor). This lymphatic spread finding is consistent with a Japanese study (38), indicating that, in practice, only those patients with proximal advanced-stage cancers are at risk of having positive nodes in the splenic hilus. This incidence was 15%. In a recent study from Europe, metastasis in the splenic hilus nodes was found only among patients with proximal advanced-stages cancers and even this incidence was low (9.8%) (39). Similarly, such a lymphatic spread was also found in the present study only among proximal T3 cancers with an incidence of 18.2%.

Based on favorable findings with spleen preservation and a low incidence of metastasis in the splenic hilus, a trend towards spleen preservation has already been started even among cases with tumors in the upper third of the stomach at an early tumor stage (40).

How can the decrease in early recurrence and mortality observed among spleen-preservation patients in this study be explained? It could be hypothesized that such a decrease is attributable to the suppressive role of the spleen on the growth of minimal residual disease. Minimal residual disease should be the major source of the subsequent formation of secondary tumors (recurrence) after curative surgery (41, 42). Minimal residual disease is defined as micrometastasis (greater than 0.2 mm and less than 2 mm) or isolated tumor cells (ITC; not greater than 0.2 mm) in lymph nodes, distant organs and in blood circulation. The identification of ITC is usually based on immunohistochemical or molecular methods (RT-PCR) (43). Under a surgical stress-induced immunosuppression (44), changes in minimal residual tumor cell kinetics after curative surgery with rapid tumor growth have been experimentally demonstrated on critical early postoperative time (45). Though the role of the spleen in tumor immunology is still unclear, some molecular research findings (T-cells and NK cell activity, immunosuppressive acidic protein (IAP), specific antitumor reactivity by stimulation of spleen cells with MAGE peptide) (46-49) support the hypothesis that the presence of the spleen enhances an antitumor immune response of the host, resulting in suppression of recurrence-development from minimal residual disease.

The data of our study suggest a favorable effect of the spleen on recurrence control and survival. Although this treatment effect should be confirmed by randomized trials (the JCOG 0110-MF Japanese trial is ongoing), considering the low incidence of metastasis to the splenic hilus lymph nodes, splenectomy to avoid residual disease is required in only a few cases. The status of these nodes determines the surgical judgement for splenectomy. However, despite advances in imaging technology (endoscopic ultrasonography, computer tomography, magnetic resonance imaging, positron emission tomography) the pre-operative or even intra-operative diagnostic accuracy is not high enough to allow decision-making. Thus, at the present time tumor site and stage are used to predict nodal status. Since lymphatic spread to the splenic hilus area occurs only in advanced stage cancers of the proximal third of the stomach, decision for resection or preservation of the spleen should be individualized only among patients with an advanced tumor in the upper third of the stomach.

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