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ORIGINAL

# Preservation vs Resection of the Spleen for Gastric Cancer

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**ABSTRACT**

**Background:** Resection of the spleen en-block 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. We tested the hypothesis that the spleen in the critical early postsurgical period suppress tumor growth from minimal residual disease and reduces the risk of recurrent disease.

**Methods:** Patients were included if they underwent gastrectomy, with or without splenectomy, for a gastric adenocarcinoma. Standardized, strongly-defined criteria were used to accurately stratify patients, who had an extended (D2) lymph node dissection, into the curative and noncurative 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 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). On 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 a significant 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. Because at baseline there was a significant imbalance of tumor stage in favor of spleen-preservation group we conducted a stage-stratified subgroup analysis.

This treatment effect remained consistent in subgroup analyses according to nodal and serosal status and 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.

**Conclusions:** 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. Large randomized trial is needed to confirm this finding. Indications for splenectomy are few, limited to those patients with advanced proximal cancers.

## INTRODUCTION

Adenocarcinoma of the stomach remains a major health problem despite declining incidence worldwide. There is little progress in reducing mortality of this disease in the Western world. In the U.S.A, overall survival rate is only 22%.[1] Surgery remains the treatment of choice and when it results in a complete tumor removal, namely R0 resection, according to the International Union Against Cancer (UICC),[2] can be associated with long-term survival or even cure.[3] Unfortunately, even after curative surgery recurrence is developed that is the cause of death in most patients. To a better control of surgical failures great efforts over the past decades have been made to develop effective adjuvant treatment including various chemotherapy regimens and radiotherapy. However, the effectiveness of adjuvant chemotherapy to improve survival remains controversial, since no single randomized controlled trial (RCT) has showed significant survival advantage but meta-analysis indicate a small absolute survival benefit with adjuvant chemotherapy.[3-5]

Given this inability of adjuvant treatment, extensive surgery consisted of total gastrectomy, splenectomy and extended (D2) lymph node dissection has been

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previously proposed for a better tumor control from Japan[7] and the West.[8] Unitl now there is not RCT and the findinngs of nonrandomized studies comparing spleen preservation and splenectomy during total gastrectomy are conflicting. Several observational studies found no significant advantage in survival in favor of splenectomy[9-11] and moreover, others report an adverse effect of splenectomy on postoperative short-term and/or long-term outcome,[12-17] but the data are still inconclusive. Two of these studies are RCTs[16,17] but they designed to assess differences between D1 and D2 resections and therefore the assesments for the adverse effects of splenectomy should also be evaluated with caution.[18] 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, that in a recent report accounts for 48.7% of resected cases.[19]

The uncertainty about resection-over-preservation of the spleen, prompted us to conduct this prospective study. Emphasis was given on 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 propability to detect a significant effect of spleen preservation on patient's outcome. The low incidence of metastasis to the splenic-hilum nodes which we observed in an our own previous study was also another reason to to perform the present study.[20] Because it is likely that there is an association between splenectomy, surgical stress-induced immunosuppression and early recurrence special consideration was given in the incidence of early recurrence between the study groups.

## METHODS

Patients and eligibility criteria

Patients were eligible if they had a histologically confirmed gastric carcinoma and had undergone a 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[21]: 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 an 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.[2]

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, 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 D2 R0 subgroup. The 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 is responsible for reported results.

After surgery we screened the patients using clinical examination, laboratory tests, chest radiography and abdominal ultrasound every 3 months, and 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 1999.We recorded first recurrence and deaths from any cause.

*Statistical Analysis*

The 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 R0 D2 subgroup. Because it was expected that splenectomy would be performed more often in advanced tumor stages, leading in a significant imbalance, we planned a predefined adjustment and subgroup analysis according to these well-known prognostic baseline variables (nodal/serosal status).

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

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

## RESULTS

Overall survival for all resected patients

202 of the 210 resected patients were followed-up on; 95 had gastrectomy with preservation of the spleen and 107 had 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 independently 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, reveals that the presence of the spleen improved survival only among patients (n=151) who had an R0 resection in innadjustment (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; mean survival time 10 months (95% CI, 5 to 14) for spleen preservation patients and 13 months (95% CI, 9 to 18) for 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). Table 1 lists the baseline characteristics. There was a significant imbalance in stratification factors related to prognosis; 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 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 in one patient and cardiac complications in the other patient.

*Recurrences*

Of 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 of 56 (27%) spleen-preservation patients compared with 45 of 67 (67%) splenectomized patients (Table 1). 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 2]. 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 prognostic important subgroups at baseline (node, serosa negative/positive cancers) (Table 2). 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 (Fig. 2A, 2B).

**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 3).

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 2]. The reduction in the relative risks of death from any cause among the 4 predefined subgroups [node, serosa (negative/positive) cancers) were statistically marginal significant or insignificant (Table 2).

Prospectively-defined subgroup analyses for several baseline variables listed in Table 1, 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) and 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-hazards analysis reveals that preservation over resection of the

**TABLE 1.** BASE-LINE CHARACTERISTICS OF 126 PATIENTS RECEIVED A CURATIVE (R0) D2 RESECTION FOR GASTRIC CANCER

| CHARACTERISTIC | 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 |
| Dead | 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.[12] The abbreviation pT, pN denote pathologically confirmed tumor-nodes.
Because of rounding, not all percentages total 100.

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 3).

**Risks resulting from preservation of the spleen**

Presence of metastases in the splenic hilum lymph nodes was evident in only 4 of 67 R0 D2 splenectomized patients (6%), whereas no metastasis into the spleen or tumor invasion through 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 four 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 also 3 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

**TABLE 2: ANALYSIS OF THE RISKS OF RECURRENCE AND DEATH FROM ANY CAUSE IN THE STUDY GROUPS BY UNIVARIATE ANALUSIS.**

| VARIABLE | PRESERVATION OF THE SPLEEN | RESECTION OF THE SPLEEN† | RELATIVE RISK OF RECURRENCE OR DEATH (95% CI) ‡ | P VALUE§ |
|---|---|---|---|---|
| | No. of patients who recurred or died / Total No. | | | |
| **Recurrence-free survival*** | | | | |
| **Early recurrence** | 9/56 | 36/67 | 0.24 (0.12-0.50) | <0.001 |
| Inadjustment analysis | | | 0.33 (0.16-0.69) | 0.003 |
| Adjustment analysis for nodal status | | | | |
| | 15/56 | 45/67 | 0.28 (0.16-0.52) | <0.001 |
| **Overall recurrence** | | | 0.38 (0.21-0.69) | 0.002 |
| Inadjustment analysis | 11/21 | 36/41 | 0.43 (0.21-0.85) | 0.01 |
| Adjustment for nodal status | 4/35 | 9/26 | 0.27 (0.08-0.89) | 0.03 |
| Node-positive cancer | | | | |
| Node-negative cancer | | | 0.40 (0.21-0.73) | .003 |
| | 10/20 | 36/45 | 0.48 (0.24-0.98) | .04 |
| Adjustment for serosal status | 5/36 | 9/22 | 0.26 (0.09-0.79) | .01 |

**TABLE 3.** 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.

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[7,8] could not be confirmed in several subsequent studies.[9-11] Moreover, in several clinical reports, splenectomy was associated with a higher rate of post-surgical complications and mortality[9-12,14,16,17] without an increase in survival.[9-11] Furthermore, other studies found better or equal survival in patients with preservation of the spleen.[12-15] Similarly, subgroup analysis of two RCTs showed better recurrence-free survival among patients with preservation rather than resection of the spleen,[16,17] but this comparison was out of the scope (D1 vs D2 resections) of these trials.

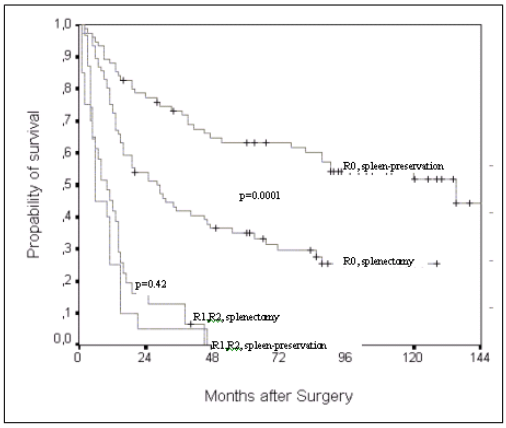
Despite all these unfavorable results, splenectomy rate continuous to be high, ranging from 26% to 48.7%.[15-17,19] The explanations for this surgical judgment include the reliance of surgeons on more radical surgery in an effort to control recurrences and the lack of convincing data which indicate that preservation of the spleen improves long-term survival. Indeed, to drawn conclusions about the effect of splenectomy on survival is a very difficult challenge because of the heterogeneity of data in 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 for a decision making.

Attempting to explain how and why the present study, in contrast to other reports, shows lower recurrence and increased survival rates after spleen preservation we should emphasize the following:

First, we could precisely stratified the resected patients into the subgroups with curative (R0) and non-curative (R1,R2) subgroups. This stratification facilitates an accurate assessment of the spleen effect on recurrence risk and survival. Appropriate discrimination of patients into 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%[22] at surgery has positive the level 2 nodes which require D2 resection for accurate histological diagnosis.

Second, of the reports available, in our knowledge, this is the first study focused on the evaluation of spleen effect on early recurrence. This is clinically important because if there is an association between surgical stress-induced immunsuppresion enhanced by splenectomy and recurrence, the estimation of early-recurrence incidence increases the probability to detect a

FIGURE 1




| NO. AT RISK | | | | | | | |
|---|---|---|---|---|---|---|---|
| *R0, spleen-preservation | 75 | 58 | 46 | 42 | 30 | 22 | 1 |
| R0, splenectomy | 76 | 40 | 27 | 16 | 8 | 4 | 0 |
| *R1,R2 spleen-preservation | 20 | 1 | 0 | | | | |
| R1,R2 splenectomy | 31 | 5 | 0 | | | | |

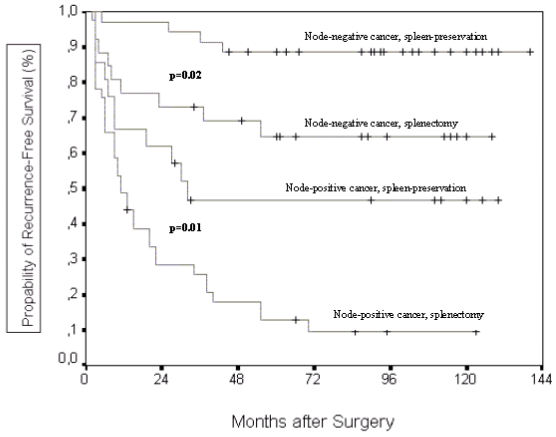



FIGURE 2A

| NO. AT RISK | | | | | | |
|---|---|---|---|---|---|---|
| Node-negative cancer, spleen-preservation | 35 | 34 | 30 | 26 | 20 | 13 |
| Node-negative cancer, splenectomy | 26 | 19 | 17 | 10 | 6 | 3 |
| Node-positive cancer, spleen-preservation | 21 | 13 | 8 | 8 | 7 | 5 |
| Node-positive cancer, splenectomy | 41 | 11 | 7 | 3 | 1 | 1 |

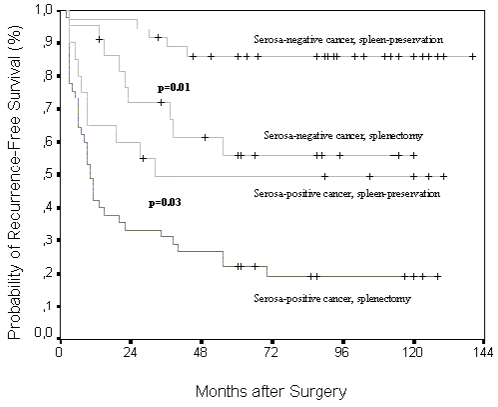



FIGURE 2B

| NO. AT RISK | | | | | | | |
|---|---|---|---|---|---|---|---|
| Serosa-negative cancer, spleen-preservation | 36 | 35 | 29 | 25 | 19 | 11 | |
| Serosa -negative cancer, Splenectomy | 22 | 15 | 12 | 7 | 3 | 1 | |
| Serosa -positive cancer, spleen-preservation | 20 | 12 | 9 | 9 | 8 | 7 | |
| Serosa -positive cancer, Splenectomy | 45 | 15 | 12 | 6 | 4 | 3 | |

**LEGENDS**

**Figure 1.** Kaplan-Meier Estimates of Overall Survival for all Patients Studied (n=202, intent-to-treat) with gastric cancer who had a Curative (R0) and Noncurative (R1,R2) resection, according to the presence (spleen-preservation group) or absence (splenectomy group) of the spleen. Treatment with preservation of the spleen was associated with a significantly higher rate of overall survival (p=0.0001 by the log-rank test) only among R0 patients (n=151). There was no difference among patients who had a noncurative resection (n=51), with a mean survival time of 10 months (95% CI, 5 to 14) for spleen-preservation and 13 months (95% CI, 9 to 18) for splenectomy groups (p=0.42). .

**FIGURE 2.** Kaplan-Meier Estimates of Recurrence-Free Survival in D2 R0 group of patients (n=123) according to the prospectively defined nodal and serosal status.

**Fifure 2A.** The presence of the spleen was associated with an absolute survival benefit of recurrence-free survival at ten years of 23.5 % (88.5 % vs. 65%; p=0.02 by the log-rank test) for node-negative cancer and of 36.3% (46.5% vs. 10.2%; p=0.01) for node-positive cancer. There was no significant difference between spleen-preservation patients with node-positive cancer and splenectomized patients with node-negative cancer (p=0.19).

**Fifure 2B.** The presence of the spleen was associated with an absolute survival benefit of recurrence-free survival at ten years of 29.3 % (85.8 % vs. 56.5%; p=0.01 by the log-rank test) for serosa-negative cancer and of 30% (49.6% vs. 19.6%; p=0.03) for serosa-positive cancer. There was no significant difference between spleen-preservation patients with serosa-positive cancer and splenectomized patients with serosa-negative cancer (p=0.39).

significant difference between preservation and resection of the spleen. Over 75% of recurrences occur within 2 years after R0 surgery.[23,24] In this study we 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 absolutely necessary because in our study there was a significant imbalance of these factors (nodal/serosal status) between 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.[25] However, the findings of our study are consistent with that of the largest study available, which included 3477 USA patients.[15] Wanebo et al. based on obtained significant survival differences in favor of spleen preservation in tumor stages II and III, propose preservation of the spleen in patients with these stages at diagnosis.[15] In this study as well as in our study, a trend toward 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 emphasize the significance of spleen-preservation in our study is that recurrence-free survival and overall survival was 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 own 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 was found in only 4 of 67 D2 R0 patients. All 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 Japanese experience,[26] indicating that in practice, at risk of having positive nodes in the splenic hilus are only patients with proximal advanced-stage cancers. This incidence was 15%. In a recent study from Europe metastastasis in the splenic hilus nodes was found only among patients with proximal advanced-stages cancers and even this incidence was low (9.8%).[27] Similarly, in our study such a lymphatic spread was also found 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 toward spleen preservation has already been started even among cases with tumors in the upper third of the stomach at an early tumor stage.[28]

How can be explained the decrease in early recurrence and mortality observed among spleen-preservation patients in this study? A hypothesis is that it 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 subsequent formation of secondary tumors (recurrence) after curative surgery.[29] 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).[30] Under a surgical stress-induced immunosuppression,[31] changes in minimal residual tumor cell kinetics after curative surgery with rapid tumor growth have been experimentally demonstrated on critical early postoperative time.[32] 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)[33-36] 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 few only cases. The status of these nodes determines the surgical judgment for splenectomy. However, despite advances in imaging technology (endoscopic ultrasonography, computer tomography, magnetic resonance imaging, positron emission tomography) the preoperative or even intraoperative diagnostic accuracy is not so high to allow decision-making. Thus, at the present time tumor site and stage are used to be predicted nodal status. Since lymphatic spread to the splenic hilus area is occurred only in advanced-stages 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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