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Subtotal *Versus* Total Gastrectomy for Gastric Cancer

Five-Year Survival Rates in a Multicenter Randomized Italian Trial

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Objective

To evaluate the impact of subtotal (SG) versus total (TG) gastrectomy on the oncologic outcome of patients with cancer of the distal stomach from 28 Italian institutions.

Summary Background Data

There is controversy over whether SG and TG have a different impact on the 5-year survival probability of patients with cancer of the distal half of the stomach.

Methods

The present analysis involved 618 patients randomized during surgery to SG (315) or TG (303), provided there was at least 6 cm from the proximal edge of the tumor to the cardia, there was no intraperitoneal or distant spread, and it was possible to remove the tumor entirely. Both surgical treatments included regional lymphadenectomy.

Results

Four patients died after SG and seven after TG. Median follow-up was 72 months after SG (range 2 to 125) and 75 months after TG (range 7 to 113). Five-year survival probability as computed by the Kaplan-Meier method was 65.3% for SG and 62.4% for TG. The test of equivalence led to the conclusion that the two procedures may be considered equivalent in terms of 5-year survival probability. The analysis of survival using a multivariate Cox regression model showed a statistically significant impact on survival of tumor site, tumor spread within the gastric wall, extent of resection to the spleen plus or minus neighboring organs or structures, and relative frequency of metastasis in resected lymph nodes.

Conclusions

Both procedures have a similar survival probability. The authors believe that SG, which has been reported to be associated with a better nutritional status and quality of life, should be the procedure of choice, provided that the proximal margin of the resection falls in healthy tissue.

Cancer of the stomach is the second most common cancer in the world. It has been estimated that more than 1 million new cases were diagnosed worldwide in 1997,[1] accounting for nearly 10% of all new cancers. In the same period, deaths attributable to stomach cancer were estimated at 835,000, or 11.8% of all cancer deaths.

Even though more than a century has elapsed since Billroth and Schlatter performed the first subtotal gastrectomy (SG) and total gastrectomy (TG) for cancer, respectively,[2,3] the best surgical procedure for cancer of the distal/middle stomach is still a matter of controversy.

An extensive survey of the surgical policies of 62 centers including 16,594 patients in several European countries[4] showed that 44% of surgeons would choose TG in cancer of the antrum, histologically defined as diffuse according to the Laurén classification.[5] A similar figure was reported in a multicenter survey in Italy for both Laurén histologic subtypes.[6] In the United States, according to the Register of the American College of Surgeons, approximately 19% of patients with cancer of the distal stomach were candidates for total or near-total gastrectomy.[7] Finally, a recent anal-

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ysis of the National Cancer Data Base of the United States[8] comprising 6400 patients showed that TG was used in 12.3% of patients with cancer of the antrum and pylorus. However, this percentage increased to 40% when other organs were included in the resection. The latter figure is slightly higher than that reported in a previous study.[9]

An *en principle* TG—that is, a total gastrectomy performed even when adequate clearance of margins can be obtained by subtotal distal resection—was initially proposed by McNeer et al in the United States[10] and subsequently in France by Lortat-Jacob et al.[11] However, it never gained worldwide acceptance because the oncologic results did not appear better than those achieved with SG in several nonrandomized series.[10–15] As far as we are aware, there has been only one randomized trial comparing TG and SG in cancer confined to the antrum, carried out by the French Association on Surgical Research.[16] This trial showed no statistical difference between the two procedures in terms of 5-year survival probability. However, the power of the study was weakened because fewer patients participated in it than was planned in the statistical design. Further, the two treatments were merely compared, without allowance being made in the analysis for the possible effect of important prognostic variables (*e.g.*, the number of metastatic lymph nodes and splenectomy).

The present study reports the results of a multicenter randomized Italian trial that investigated the effects of SG and TG in patients with cancer of the distal half of the stomach. It focused in particular on 5-year survival probability and the impact of certain prognostic factors on the oncologic outcome.

METHODS

Patients

Between April 1982 and December 1993, 1372 patients from 31 Italian institutions were screened for participation in a multicenter prospective controlled clinical trial to compare potentially curative SG and TG in patients with cancer of the distal half of the stomach. Details on eligibility criteria, surgical techniques, randomization, accrual, and follow-up modalities have been reported in a previous study.[17]

There were two levels of eligibility. Before surgery, patients were considered candidates if they had a cancer of the distal half of the stomach without apparent distant metastases, were no older than 75, were in relatively good condition, and had no history of previous cancer, gastric resection, or cytotoxic chemotherapy.[18] The second level of eligibility was determined during laparotomy by assessing the following eligibility criteria: a distance of at least 6 cm from the proximal edge of the tumor to the cardia; absence of hepatic or intraperitoneal spread of the tumor or metastatic deposits in the third nodal level, according to the Japanese classification[19]; and absence of unresectable infiltration of contiguous organs. Patients judged to be eligible at laparotomy were randomly allocated to SG or TG groups using an ordered set of sealed envelopes containing the indication of the treatment assigned according to a computer-generated random permuted blocks list. Before the patient was discharged, all information concerning eligibility criteria was sent to the coordinating center on a standard form.

Regardless of the type of operation performed (SG or TG), an effort was made to maintain a distance of at least 6 cm from the proximal edge of the tumor to the line of the anastomosis, thus minimizing the risk of leaving residual neoplastic deposits in the stomach or esophagus.[20–22] However, if patients had an involved margin of transection at the definitive histologic examination, they remained included in the evaluable set. This occurred in six patients from the SG group (four of them with a proximal clearance $<$6 cm) and one patient from the TG group (with a 10-cm margin of clearance). Finally, 13 patients (8 SG and 5 TG) had a distal margin infiltrated by the tumor. One patient from the SG group had both proximal and distal margins involved. Ten patients (four SG and six TG) received postoperative adjuvant chemotherapy.

A technique of D_2 gastrectomy, as described by Nakajima and Kajitani,[23] was recommended, as follows. The entire greater omentum, superior leaf of the mesocolon, pancreatic capsule, and lesser omentum were removed *en bloc* with the stomach. The left gastric artery was ligated at its origin. Lymphadenectomy included dissection of node levels 1 and 2. For all tumors, lymph nodes were removed along the lesser and greater curvature; suprapyloric and infrapyloric and right paracardial lymph nodes, and those along the left gastric artery, the common hepatic artery, and the celiac axis, were also removed. For tumors involving the middle third of the stomach, the resection was planned to include the left paracardial lymph nodes and those along the splenic artery and the hilum of the spleen (standard procedure). Splenectomy was an optional procedure left to the preference of the surgeon. The tumor was finally staged according to the recent TNM classification.[24]

Figure 1 shows the trial profile; 717 patients were found to be ineligible at the preoperative and intraoperative level, and 7 patients were excluded because the eligibility form had not been filled out. Twenty-six of the 648 randomized patients, accrued by three centers, were excluded by the monitoring committee because the information concerning baseline and follow-up visits was considered unreliable. Thus, the final evaluable set included 622 patients from 28 centers, 319 randomized to SG and 303 to TG.

The study was approved by the Ethical Committee of the Istituto Nazionale Tumori, Milan, and all the eligible patients gave their signed consent to it.

The present study focuses on the primary end point of the trial—death from all causes, including postoperative deaths, which accounted for four SG and seven TG patients.

To perform this analysis, the four SG patients lost to

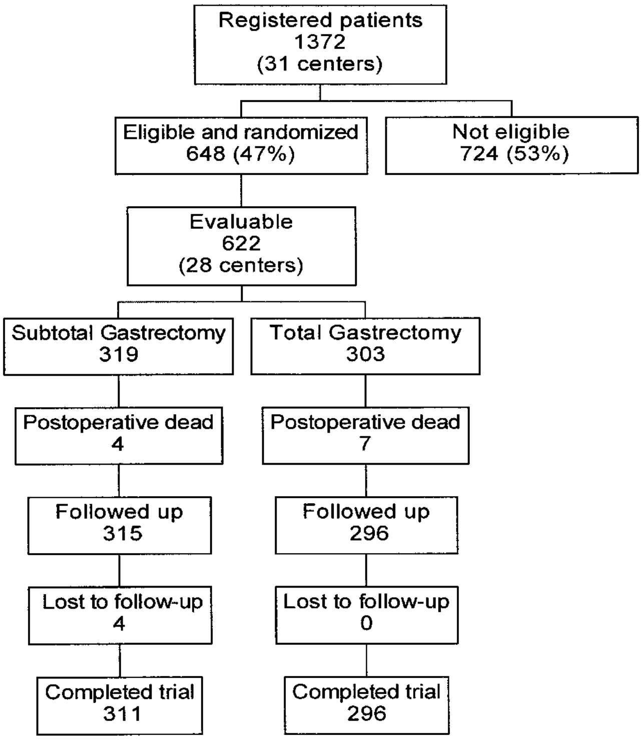


Figure 1. Profile of the subtotal/total gastrectomy trial. The evaluable set includes patients with reliable information on baseline and follow-up visits.

follow-up immediately after discharge were excluded, resulting in a set of 618 subjects. The TG group also included four patients who had originally been randomized to TG but subsequently underwent SG because of intraoperative complications. These patients had healthy proximal and distal margins of transection. The two surgical groups had similar demographic characteristics (Table 1).

Statistical Methods

Statistical analysis was carried out on the intention to treat the patient population, as defined by Gillings and Koch.[25]

The trial protocol aimed at testing the equivalence of the two surgical procedures, defined in terms of 5-year survival probability; the rejection of the null hypothesis enables the trialist to conclude in favor of equivalence.[26] Taking TG as the reference treatment with a 5-year survival probability equal to 50%, the null hypothesis stated that the SG group was expected to have a 5-year survival probability at least 10% lower. In terms of log hazard rate ratio β, this translated into $\beta \geq 0.28$ for the null hypothesis and $\beta < 0.28$ for the alternative hypothesis. Correspondingly, for a type I error probability of 5% (one-tailed test) and a type II error probability of 20%, a total sample size of some 600 patients was computed.[27]

Time to death was calculated from the date of surgery to the date of death from any cause, censoring the follow-up time at the most recent date for living patients. Survival curves were computed using the Kaplan-Meier method.[28]

A univariate Cox's proportional hazards regression model was used to obtain the estimate $\hat{\beta}$ of the log hazard rate ratio SG/TG; this statistic and its standard error allowed us to compute an asymptotically normal standardized deviate

$$z = \frac{\hat{\beta} - 0.28}{SE(\hat{\beta})}$$

to test the equivalence hypothesis. To avoid any bias that might result in estimating β as a result of covariate imbalances across the two surgery groups or of balanced covariates of prognostic relevance,[27] a multivariate Cox regression model was applied. The effect of surgery was adjusted for the following covariates: age at surgery, site of tumor (antrum, body, body and antrum or multiple lesions), degree of wall invasion (pT1, pT2, pT3-pT4), extension of surgery to neighboring organs or structures (none; to the spleen or to the spleen and neighboring organs or structures; to neighboring organs or structures but not the spleen), relative frequency of metastasis in resected lymph nodes (negative; $\leq$25% metastatic lymph nodes; $>$25% metastatic lymph nodes[29]), and involvement of transection margins (absent or present). Indicator variables were used to categorize all the covariates except for age, which was inserted into the model on a continuous scale. The relation of the log relative hazard of death *versus* age was investigated using the smoothed plot of martingale residuals[30] of the model excluding age; as a result, age was inserted into the model with the linear term only. The contribution of each covariate, adjusted for the effect of all the others, was tested with the likelihood ratio test.

Statistical analyses were performed using SAS[31] and S-Plus[32] software.

RESULTS

The series as a whole included mainly cancers of the antrum (72%). Half of the tumors had a maximum diameter between 2 and 5 cm, about 50% of the tumors had invaded the serosa or contiguous structures, and 55% of the patients had lymph node metastases. The surgery performed was defined as curative because no macroscopic tumor residual was left in the abdomen, but at the definitive histologic examination 15 patients in the SG group and 6 in the TG group were found to have a margin of transection infiltrated by the tumor (R1 resections).

The two surgery groups were similar for several baseline characteristics (see Table 1). However, splenectomy was performed more often in the TG group than in the SG group (chi square = 40.96, 3 *df*, p = 0.0010).

We report on follow-up data collected up to February 5, 1998. The distribution of follow-up time was similar in the

Table 1. CHARACTERISTICS OF THE 618 PATIENTS WHO COMPLETED THE TRIAL

	No. of Patients (%)	
	Subtotal Gastrectomy (n = 315)	Total Gastrectomy (n = 303)
Age (years)		
≤60	160 (51)	153 (51)
60 to 65	48 (15)	58 (19)
>65	107 (34)	92 (30)
Sex		
Female	132 (42)	129 (43)
Male	183 (58)	174 (57)
Site of tumor		
Single lesion		
Antrum	236 (75)	207 (68)
Body	37 (12)	52 (17)
Body and antrum	30 (10)	34 (11)
Multiple lesions	7 (2)	9 (3)
Undetermined	5 (1)	1 (0)
Size of tumor (cm) (maximum diameter)		
≤2	80 (25)	65 (21)
2 to 5	156 (50)	155 (51)
>5	64 (20)	75 (25)
Undetermined	15 (5)	8 (3)
Wall invasion (pathologic stage)		
Mucosa (pT1)	40 (13)	32 (11)
Submucosa (pT1)	56 (18)	42 (14)
Muscularis (pT2)	74 (23)	73 (24)
Serosa (pT3)	138 (44)	149 (49)
Serosa and other structures (pT4)	7 (2)	7 (2)
Histologic type		
Intestinal	156 (50)	151 (50)
Diffuse	115 (37)	122 (40)
Mixed	23 (7)	16 (5)
Undetermined	21 (6)	14 (5)
Extension of surgery		
None (standard procedure)	286 (91)	220 (73)
To spleen	15 (5)	56 (18)
To spleen and neighboring organs or structures	3 (1)	16 (5)
To neighboring organs or structures but not spleen	11 (3)	11 (4)
Nodal status		
Negative	155 (49)	126 (42)
Positive	160 (51)	177 (58)
Number of metastatic lymph nodes		
1–6 (N1)	96 (31)	112 (37)
7–15 (N2)	45 (14)	44 (14)
≥16 (N3)	19 (6)	19 (6)
Undetermined	0 (0)	2 (1)
Stage grouping		
IA	76 (24)	58 (19)
IB	58 (18)	46 (15)
II	65 (21)	68 (22)
IIIA	58 (18)	75 (25)
IIIB, IV	58 (18)	54 (18)
Undetermined	(0) (0)	2 (1)

two randomized groups; the median follow-up time was 72 months in the SG group (range 2 to 125 months) and 75 months in the TG group (range 7 to 113 months). Total deaths were 112 in the SG group and 118 in the TG group, and tumor spread accounted for 78.7% and 80.2% of the deaths, respectively. Of the few patients who received postoperative chemotherapy, two of the four in the SG group and three of the six in the TG group died within 2 years after surgery.

The overall survival curve is displayed in Figure 2. Figures 3 to 6 show the survival curves with regard to wall invasion categories, nodal status, TNM stage, and the two

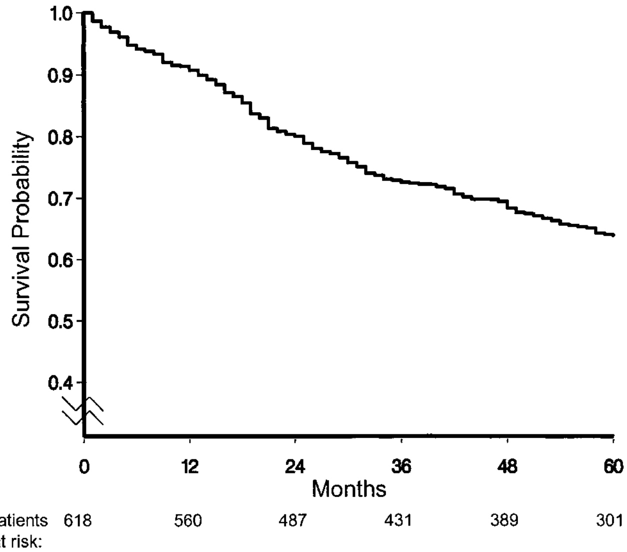


Figure 2. Survival curve for all causes of death (median follow-up: 73 months).

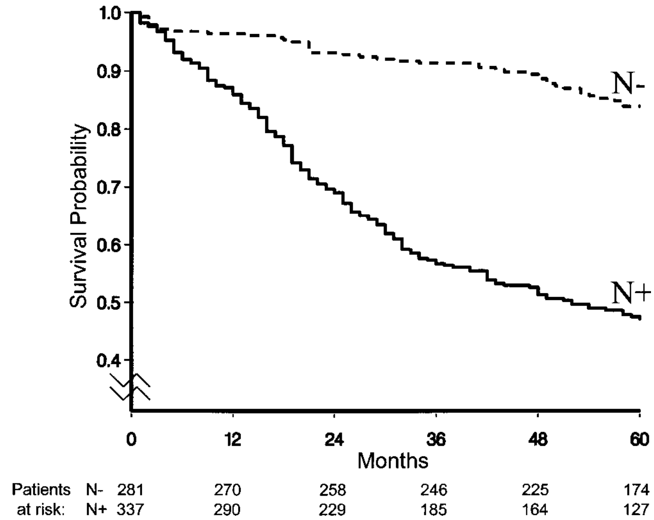


Figure 4. Survival curves with regard to nodal status.

surgery groups. For clarity, Table 2 reports the 5-year survival probability with regard to type of surgical treatment/tumor characteristics.

The test of equivalence (z = −2.89) led to the rejection of the null hypothesis and to the conclusion that the two surgical procedures could be considered equivalent in terms of 5-year survival probability. The hazard rate ratio SG/TG was 0.89; however, the two-sided 95% confidence interval was 0.68 to 1.17, indicating that the prognostic advantage of SG was not statistically significant.

The initial multivariate Cox model, in addition to the covariates mentioned in the statistics section, also included the first-order interaction terms surgery × site, with the goal of investigating whether the hazard rate ratio SG/TG changed in the three sites (antrum; body; and body and antrum or multiple lesions). Because this interaction was not found to be statistically significant, it was deleted from the model, leading to the results reported in Table 3. The adjusted surgery hazard rate ratio was 1.01 (two-sided 95% confidence interval 0.76 to 1.33), supporting the conclusion that the surgical procedures had similar effects on survival.

As expected, site of tumor, wall invasion, extension of surgery, and the relative frequency of metastatic lymph nodes were found to have a significant impact. In particular, the tumors localized in the antrum appeared to have an unfavorable prognosis compared with the others. Tumors staged pT3 or pT4 had a hazard rate significantly greater than those staged pT2. An extension of surgery to the spleen or to the spleen and neighboring organs or structures was associated with a statistically significantly worse prognosis with respect to a standard procedure. Patients with a relative frequency of positive lymph nodes ≤25% had a statistically significantly worse prognosis than patients with negative nodes. The prognosis became even worse when the relative

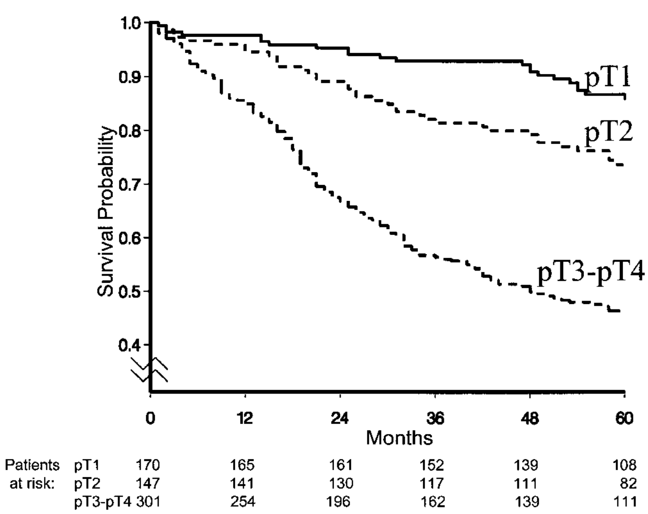


Figure 3. Survival curves with regard to wall invasion categories.

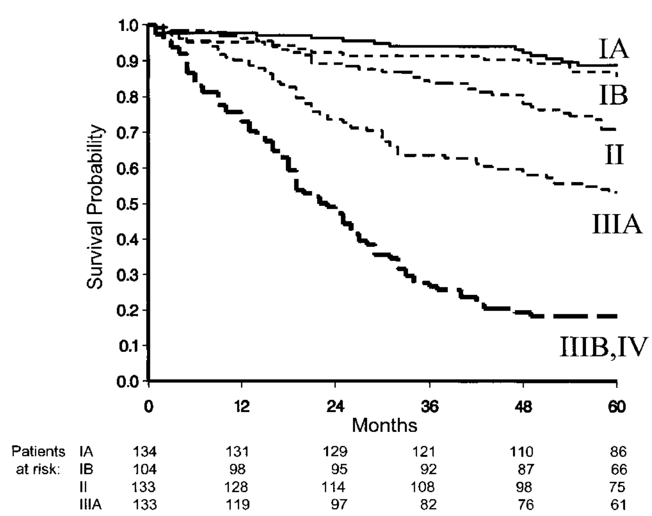
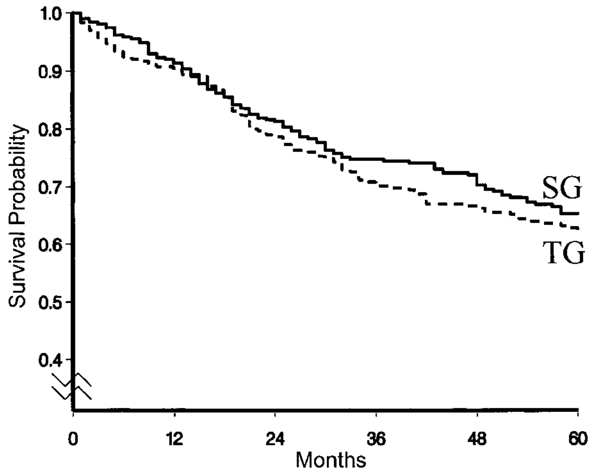


Figure 5. Survival curves with regard to TNM stage.



Patients at risk:	0	12	24	36	48	60
SG	315	286	252	227	204	149
TG	303	274	235	204	185	152

Figure 6. Survival curves with regard to surgical treatment.

frequency of involved nodes exceeded 25%. The aforementioned Cox model was extended to investigate the possible effect of the calendar period of surgery on overall survival, but no statistically significant contribution was found.

DISCUSSION

This study focuses on the impact that two different surgical procedures for gastric cancer have on 5-year survival probability. Both procedures included a D_2 lymphadenectomy (Japanese classification[19]) for two reasons. First, the D_2 dissection has had acceptable morbidity and perioperative mortality rates in the experience of Italian surgeons.[33,34] Second, the review of both large (a few thousand patients) retrospective series of Western and Japanese patients[7,33,35] and randomized clinical trials[36–39] have shown so far no benefit from extended lymphadenectomy.

A 64% 5-year survival probability after gastrectomy for cancer was found in the present study. This figure compares well with the 75% reported by the National Cancer Center in Tokyo[40] in a study comprising 2500 patients with a nodal status similar to our series; however, early gastric cancer accounted for 49% of the entire series in that study. Our results, which are better than those found in other Western surgical series, probably reflect the relatively high prevalence of pT1 cancer in this patient population, as well as the exclusion of patients with tumors of the upper third of the stomach, who are well known to have a worse prognosis.[41]

There was no difference in survival probability in patients assigned to SG or TG. This was true not only for patients with cancer of the antrum, a finding consistent with the conclusions of a previous randomized clinical trial on a limited number of patients,[16] but also for those with cancer of the middle third of the stomach. In conclusion, it would appear that there is no advantage in extending the resection to the stomach *in toto*, provided that the proximal margin of transection is in healthy tissue.

Following the data from the literature[20] and from this institution,[21] it was recommended in this protocol that at least 6 cm be maintained proximally from the tumor (or at least 3 cm if the cancer was confined to the muscular layer) to achieve an adequate proximal clearance of the tumor.

The multivariate analysis confirms the negative prognostic impact on survival of the extension of surgery to the spleen or to the spleen and neighboring organs and structures, of deep tumoral penetration through the gastric wall, and of metastatic involvement of the lymph nodes.

It is not surprising that the extension of surgery to the surrounding organs is associated with a worse prognosis: this procedure is usually performed when cancer is locally advanced (pT4) and has invaded the neighboring structures. More intriguing is the interpretation of the effect of splenectomy on the final outcome, because this procedure is usually performed as part of TG or when the spleen is inadvertently injured during removal of the stomach. However, the literature has already reported a lower 5-year survival probability for patients in whom gastrectomy is associated with splenectomy.[42–44] Nevertheless, this report

Table 2. FIVE-YEAR SURVIVAL PROBABILITY

	Survival Probability (%)
Whole series	64.0
Type of surgery	
Subtotal gastrectomy	65.3
Total gastrectomy	62.4
Site of tumor	
Antrum	61.8
Body	73.4
Body and antrum or multiple lesions	69.7
Wall invasion (pathologic stage)	
Mucosa or submucosa (pT1)	85.9
Muscularis (pT2)	73.6
Serosa (pT3) or serosa and other structures (pT4)	46.3
Extension of surgery	
None (standard procedure)	66.3
To spleen or spleen and neighboring organs or structures	57.0
To neighboring organs or structures but not spleen	36.4
Nodal status	
Negative	83.9
Positive	47.2
Relative frequency of metastatic lymph nodes	
≤25%	67.8
>25%	24.2
Stage grouping	
IA	88.8
IB	86.4
II	70.9
IIIA	53.2
IIIB, IV	18.3

Table 3. ANALYSIS OF TIME TO DEATH (ALL CAUSES) BY MULTIVARIATE COX REGRESSION MODEL

	LRT χ^2	*df*	p Value	HR	95% CI
Surgical treatment	0.003	1	0.9540		
SG/TG				1.01	0.76–1.33
Age	0.92	1	0.3367	—	—
Site of tumor	6.09	2	0.0477		
Body/antrum				0.61	0.39–0.96
Body and antrum or multiple lesions/antrum				0.77	0.51–1.16
Wall invasion	33.29	2	<0.0001		
pT2/pT1				1.25	0.74–2.14
pT3–pT4/pT2				2.23	1.56–3.20
Extent of surgery	6.21	2	0.0449		
To spleen or spleen and neighboring organs or structures/standard procedure				1.55	1.08–2.23
To neighboring organs or structures but not spleen/standard procedure				1.48	0.83–2.67
Relative frequency of metastatic lymph nodes	94.90	2	<0.0001		
≤25% metastatic lymph nodes/negative				1.82	1.21–2.73
>25% metastatic lymph nodes/≤25% metastatic lymph nodes				3.05	2.21–4.21
Involvement of transection margins	0.71	1	0.4000		
Present/absent				1.29	0.73–2.30

LRT χ^2, likelihood ratio test chi square; *df,* degrees of freedom; HR, hazard rate ratio; 95% CI, two-sided 95% confidence interval.

is the first to show an adverse prognostic impact of splenectomy on multivariate analysis on a large number of patients. This seems to suggest that splenectomy should not be performed as a routine adjunctive procedure to gastrectomy unless there are metastatic nodes at the splenic hilum that cannot be removed without splenectomy.

In terms of the prognostic role of lymph node metastases, the classification recently proposed by Yu et al[29] was adopted in our study. Because it is based on the ratio of invaded-to-removed nodes, it appears to be more simple, convenient, and reproducible than the UICC TNM staging system[45] or the Japanese staging system,[46,47] and it can pinpoint patients with different 5-year survival probability equally well.[29]

An unexpected finding was the better outcome of patients with cancer of the gastric body compared with those with cancer of the antrum. A possible explanation is the smaller distal clearance that can be achieved in antral tumors as a result of the anatomic boundaries with the pancreas. This finding is in keeping with a recent report of only 58% 5-year survival probability in nonobstructing cancer of the antrum.[48]

In conclusion, there are several advantages in performing a more conservative operation (SG) in patients with cancer of the lower or middle stomach. In fact, TG is technically a more demanding procedure than SG and is more often associated with splenectomy, which has an adverse effect on postoperative complications and on susceptibility to infections.[18,36,43,49,50] Further, TG involves a longer postoperative hospital stay (and consequently a higher cost), as previously shown.[18] Finally, patients who undergo TG have a lower calorie intake and require more meals per day to maintain an acceptable nutritional status, which nonetheless is always more depleted than that of patients who undergo SG.[51–53] This results in a poorer quality of life for these patients.[53–56]

We believe that a modern surgical strategy for cancer of the distal half of the stomach should involve conservative procedures that can achieve the same outcome as more radical surgery while producing a better quality of life for patients.

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