A Prospective Randomized Trial Comparing R_1 Subtotal Gastrectomy with R_3 Total Gastrectomy for Antral Cancer

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Objective

The authors determined if more radical surgery with extended lymphadenectomy improves the results of gastrectomy in patients with adenocarcinoma of the gastric antrum.

Summary Background Data

The overall survival in patients with gastric cancer is disappointing. Improved survival has been reported by Japanese authors. Whether this is because of a higher number of early gastric cancers in the Japanese series, different biologic behavior in Asians, or the adoption of radical surgery with lymphadenectomy remains unclear.

Methods

R_1 subtotal gastrectomy with omentectomy and R_3 total gastrectomy (omentectomy, splenectomy, distal pancreatectomy, lymphatic clearance of the celiac axis, and skeletonization of vessels in the porta hepatis) were evaluated in a prospective, randomized comparison.

Results

Fifty-five patients were randomized—25 to the R_1 group and 30 to the R_3 group. The two groups were comparable for age, sex, tumor size, TNM stage, and length of follow-up. The R_3 group had a longer operating time (140 vs. 260 min; $p < 0.05$), a greater transfusion requirement (0 vs. 2 units, $p < 0.05$) and a longer hospital stay (8 vs. 16 days; $p < 0.05$) (medians; Mann-Whitney U test). The only postoperative death was in the R_3 group and was caused by intra-abdominal sepsis. Fourteen patients in the R_3 group developed left subphrenic abscesses. There were no major complications in the R_1 group. Overall survival was significantly better in the R_1 group (median survival estimated by Kaplan-Meier method, 1511 vs. 922 days, $p < 0.05$, log-rank test).

Conclusions

R_3 total gastrectomy can be performed with a low mortality, but it has a high morbidity because of intra-abdominal sepsis. The data do not support the routine use of R_3 total gastrectomy for treatment of patients with antral cancer.

Debate continues regarding the value of radical surgery for apparently localized gastric cancer.[1] Survival rates in Japan, where extended lymph node dissection is practiced routinely, are better than those reported in the western literature.[2] Whether this is because of more radical surgery or other unidentified factors remains unclear because no randomized study comparing conservative surgery with the most radical surgery for antral cancer has been reported. This prospective, randomized trial compares two different extremes in the surgical management of adenocarcinoma of the gastric antrum. Patients were randomized either to the standard procedure of R₁ subtotal gastrectomy or the most radical resection of R₃ total gastrectomy. The study determined whether radical surgery improved survival and documented the attendant mortality and morbidity.

PATIENTS AND METHODS

Patient Selection

A patient undergoing a laparotomy for adenocarcinoma of the gastric antrum were eligible to enter the trial if all macriscopic tumor could be excised and if a 6-cm proximal resection margin could be obtained to allow a safe margin for a radical subtotal gastrectomy to be performed. Intraoperative cytologic or histologic proof of lymph node involvement was not performed. The absence of liver metastases was determined preoperatively by ultrasonography and confirmed at operation by palpation. Patients were excluded if, at laparotomy, they had peritoneal or liver metastases. Patients older than 75 years of age or with serious concomitant disease considered unfit for total gastrectomy also were excluded.

Ethics

The study was approved by the ethics committee of the Chinese University of Hong Kong, and patients gave informed consent before entry.

Randomization

Randomization was carried out after laparotomy. If the inclusion criteria for the study were satisfied, patients were allocated to R₁ or R₃ procedure by opening a numbered, sealed envelope containing the treatment option. The treatment options were determined by random numbers generated on a personal computer.

Operative Procedures

R₃ total gastrectomy included total excision of the greater and lesser omenta, splenectomy, distal pancreatectomy, lymphatic clearance of the celiac axis and its trifurcation, and skeletonization of the vessels in the porta hepatis. Intestinal continuity was restored by an end-to-side esophagojejunostomy, using a circular stapler, with a 40-cm jejunal Roux limb. R₁ subtotal gastrectomy included a 6-cm proximal resection margin. The left and right gastric arteries were divided at their origins and the greater and lesser omenta were resected en bloc. No further lymph node dissection was performed. Reconstruction was by a 40-cm jejunal Roux limb with a sutured two-layered gastrojejunal anastomosis. The distal resection margin in both procedures was through the first part of duodenum. The duodenal stump was closed with a linear stapler, and the staple line was inverted by sutures. A tube drain was placed near to the duodenal stump in both procedures and close to the esophagojejunal anastomosis and pancreatic stump after R₃ total gastrectomy. All surgeons involved in the trial were trained initially and supervised in the procedures.

Processing of Specimens

The gastrectomy specimens were sent for histologic examination either fresh or in 10%-buffered formalin. The lymph nodes were dissected first and separated into anatomic groups including cardiac, lesser curve, pyloric, greater curve, omental, and perisplenic nodes. Then the stomach was pinned onto a corkboard and fixed in formalin for 24 hours before sectioning. After fixation, the margins were marked with india ink, and sections were taken from the proximal and distal margins. Sections of the tumor were taken from the tumor margin, through the full thickness of the tumor to assess serosal involvement and from adjacent mucosa. Non-neoplastic mucosa away from the tumor also was sampled. The tissue then was processed through dehydration and embedded into paraffin blocks for sectioning in the standard fashion. Routine 5 μm-sections were obtained, and hematoxylin and eosin staining were performed. Then the tumor could be staged accurately by the TNM system, allowing the operation to be categorized as curative or noncurative.

Postoperative Management

All patients received 48 hours prophylactic broad spectrum antibiotics that were continued if indicated clinically. No adjuvant treatment was given to either group postoperatively.

Table 1. PATIENT DETAILS

	R₁	R₃
No. of patients	25	29
M:F	20:5	22:7
Median age (yrs)	60	58
(range)	(32–75)	(31–75)
Number >65 yrs	8	9
Median follow-up (days)	856	756
(range)	(149–1611)	(85–1464)

Follow-Up and Documentation of Recurrence and Death

All patients were reviewed at 3 monthly intervals in the outpatient clinic. At each visit, the patients weight and symptoms were recorded. If recurrence was suspected clinically, upper gastrointestinal endoscopy and appropriate imaging were arranged. In addition, patients were given dietary advice, 3 monthly vitamin B_{12} injections, and supplements of iron, calcium, and vitamins, as required. Those patients who failed to attend the clinic were traced and, if alive, asked to return for review. If the patient had died, the date of death was recorded.

Statistical Methods

The chi square test and Mann-Whitney test were used to examine whether the distribution of the prognostic variables and consequences of the operations were sig-

Table 2. STAGE OF DISEASE

	R₁	R₃
T_1		
N_0	8	8
N_1	2	1
N_2	—	—
T_2		
N_0	5	3
N_1	2	4
N_2	—	1
T_3		
N_0	1	2
N_1	6	5
N_2	1	3
T_4		
N_0	—	1
N_1	—	—
N_2	—	1
Median size (cm)	2	2.9
range	(0.5–6.0)	(0.5–6.0)
Intestinal	14	16
Diffuse	11	13

Table 3. OPERATIVE DETAILS

	R₁	R₃	
Median operation time (min)*	140	260	$p < 0.05$
(range)	(100–300)	(140–375)	
Median blood loss (mL)*	300	600	$p < 0.05$
(range)	(150–1070)	(250–2300)	
No. of patients transfused*	7	23	$p < 0.05$
Median no. of units transfused*	0	2	$p < 0.05$
(range)	(0–6)	(0–6)	
Median postoperative stay (days)	8	16	$p < 0.05$
(range)	(6–17)	(7–97)	

Mann-Whitney U-test
* Relates to primary procedure only.

nificantly different. Univariate life table methods (Kaplan-Meier method and log-rank tests) were used to examine survival. Two versions of the log-rank test—the Mantel-Cox and the Breslow method—were used. The Breslow test was preferred when there were small numbers of subjects remaining at the end of the study. Subsequently, multivariate Cox regression analysis was done to identify any independently significant prognostic variables.

RESULTS

Fifty-five patients were recruited into the trial between October 1987 and December 1991. Twenty-five patients were randomized to R_1 subtotal gastrectomy, and 30 patients were randomized to R_3 total gastrectomy. However, one patient in the R_3 group was excluded postoperatively because there was histologic involvement of the duodenal resection line and was, therefore, deemed to

Table 4. MAJOR MORBIDITY

| No. of Patients	Complications	Comments
14	Left subphrenic abscess	5 patients had 6 open drainage operations
		4 patients had 7 percutaneous aspirations
		4 patients managed conservatively
		1 died of sepsis
7	Relaparotomies	5 patients had 6 open drainage operations for L subphrenic abscess
		2 patients had 3 secondary haemorrhages (all related to L subphrenic abscess)
3	Oesophagojejunal anastomotic leak	
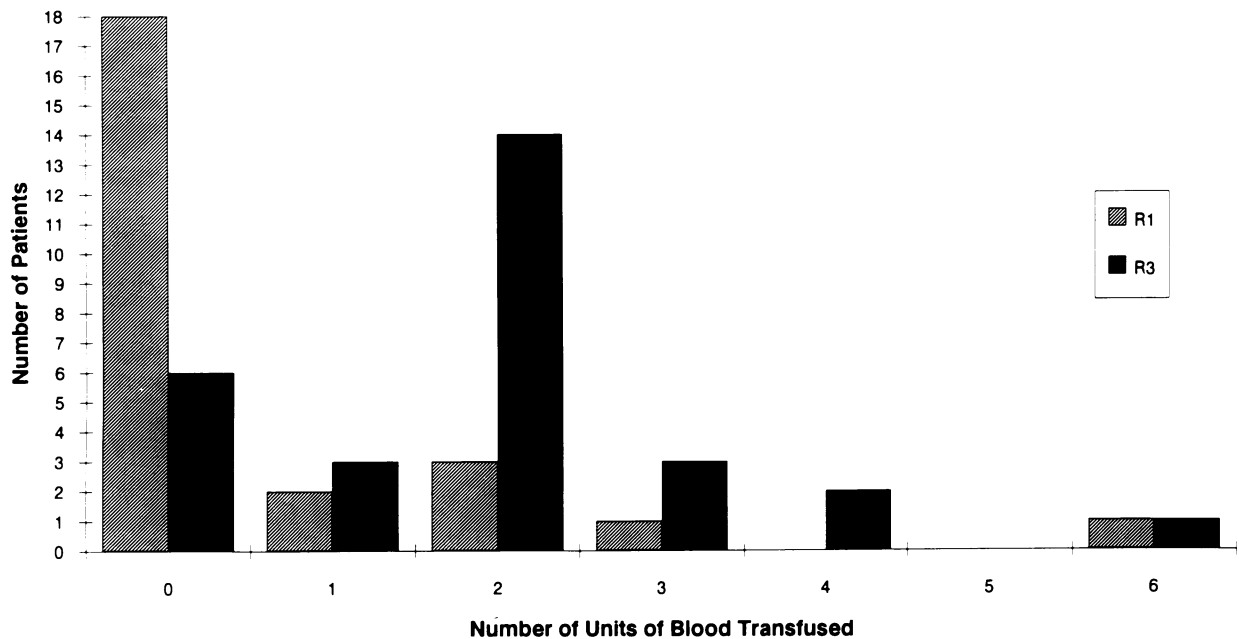
Figure 1. The distribution of number of units of blood transfused per patient in the R_1 and R_3 groups.

have had only a palliative resection.[3] This left 54 patients for analysis of survival. The characteristics of the two patient groups were comparable for age, sex, and length of follow up (Table 1). The groups also were comparable for distribution and stage of disease (Table 2).

Mortality and Morbidity

The only perioperative death was a 70-year-old man in the R_3 group who died 17 days after operation because of fulminant intra-abdominal sepsis; autopsy was refused. In comparison with the R_1 group, the R_3 patients had a significantly longer operating time and greater operative blood loss (Table 3) and blood transfusion requirements (Fig 1). They also had a significantly longer hospital stay because of a greater number of postoperative complications. Fourteen patients in the R_3 group developed left subphrenic abscesses (Table 4). In addition, nine laparotomies were performed again (seven patients) in the R_3 group—six for open drainage of a left subphrenic abscess and three to control secondary hemorrhage related to left subphrenic abscesses. There were three anastomotic leaks in the R_3 group (10%), and all were managed conservatively with total parenteral nutrition and healed without further surgery. There were no major complications or reoperations in the R_1 group of patients. There were no duodenal stump leaks in either group and no incidental splenectomy in the R_1 group. No patient had a clinically significant deep vein thrombosis or pulmonary embolism.

Survival Analysis

Five years after starting the trial, seven patients from the R_1 group and 14 patients from the R_3 group have died (Table 5). Sites of documented recurrent disease in patients who have died are shown in Table 6.

On univariate analysis, overall survival, as estimated by the Kaplan-Meier method, was significantly better in the R_1 group (median survival: R_1, 1511 *vs.* R_3, 922 days, Breslow log-rank test, $p = 0.04$ and Mantel-Cox log-rank test, $p = 0.07$; Fig 2). Significant adverse prognostic factors on univariate analysis included male gender, increasing T stage, increasing N stage, and increasing tumor size. Of the 19 early gastric cancers (T_1) in the study (10 R_1 *vs.* 9 R_3; Table 2) 3 have died, but only 2— one from each group—from recurrent disease. The patient in the R_1 group was a 69-year-old man with a T_1N_1 lesion who had a relatively curative procedure; the patient in the R_3 group was a 59-year-old man with a T_1N_0

Table 5. SURVIVAL

Outcome	R_1	R_3
30-day mortality	—	1
Died from disease	4	10
Died from proven other cause	1 (lymphoma)	—
Died cause unknown	2	3
Alive with proven recurrence	—	—
Alive with no recurrence	15	15
Lost to follow-up	3	—

Table 6. SITE OF PROVEN RECURRENCE IN 14 PATIENTS (ALL PATIENTS DEAD)

	R_1	R_3
Gastric bed	1	1
Liver metastases proven on ultrasound	3	5
Ascites	1	3
Pelvic recurrence	—	2
Portal nodes	1	—
CNS metastases	—	1
Lung metastases	—	1
Neck lymph nodes	—	1

Some patients had mulitple sites of recurrence.

Figure 3. The survival curves for the R_1 and R_3 groups stratified by T stage.

lesion who had an absolutely curative procedure, but died of metastatic lung disease that was presumed but not proven to be from the gastric cancer. The T_1 group had a significantly longer survival rate than the T_2, T_3, or T_4 groups. Furthermore, stage T_2, T_3, and T_4 groups all had a better survival after R_1 resection (Fig. 3). Node-negative tumors had a significantly longer survival rate than node-positive disease, but survival was significantly better in node-negative disease treated by R_1 subtotal gastrectomy. Tumors larger than 1.5 cm in diameter had a significantly worse prognosis.

Operation-related characteristics, such as no blood transfusion requirement and operative outcome (e.g., absolutely curative procedures), also were significant on univariate analysis for better survival. In contrast, operative blood loss, operative time, tumor type (intestinal vs. diffuse), complications, and hospital stay were not significant.

Multivariate analysis of variance by the Cox proportional hazards model was performed to identify any in-
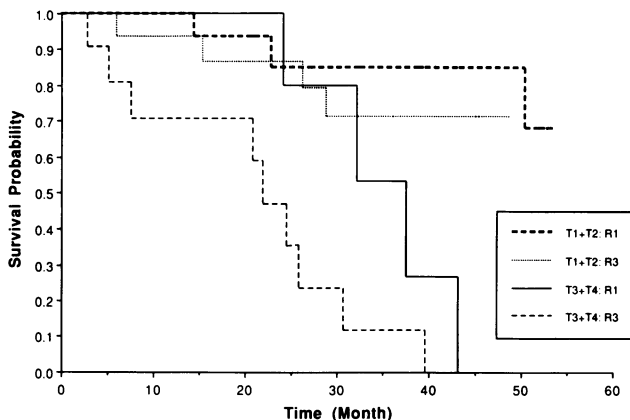
dividually significant prognostic variables for survival. Of 14 variables studied, 3 had a significant unfavorable association with survival. They were a relatively noncurative procedure, blood transfusion, and male gender.

If the effect of a blood transfusion is removed statistically by multivariate analysis, then the survival of the R_1 group was no better than the R_3 group. (p value for the R_1 vs. R_3 variance changed from 0.04 to 0.37). This suggests that a blood transfusion is an intermediate variable between R_1 and R_3 survival, with the better survival in the R_1 group on univariate analysis explained by the lower blood transfusion requirement for the R_1 resection.

DISCUSSION

In the west, the overall survival of patients with gastric cancer has not changed during the last 30 years and remains a disappointing 5% to 10%.[4] In contrast, during the same period, the Japanese Research Society for Gastric Cancer has reported improved survival figures, with an overall survival, after resection, of approximately 50%.[5] During this time, the operative mortality in most Japanese series has fallen to less than 5%,[2] and an increasing number of early gastric cancers have been detected by population screening programs.[6] However, these improvements together do not explain the improved Japanese survival data as stage for stage, Japanese patients survive longer.[7] It has been suggested that the biologic behavior of the tumor may be different in Asians.[8] Generally, the improved survival in Japan has been attributed to the adoption of radical surgery with lymphadenectomy. The rationale for this policy is that gastric bed recurrence should be reduced by effective locoregional control of the cancer. This policy seems attractive because it is known that in the west, approximately half of all patients treated by curative gastrec-
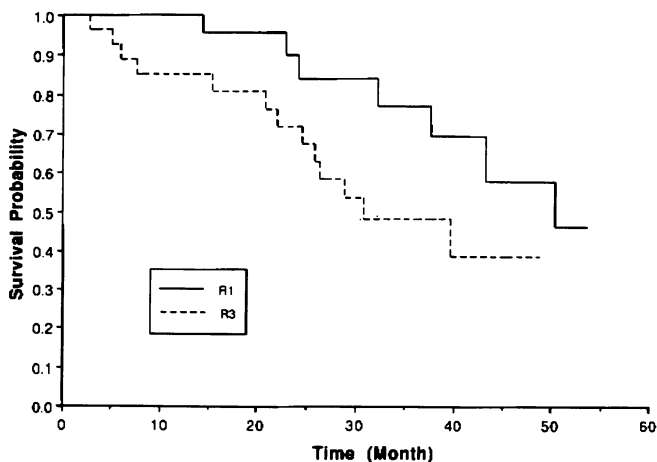

Figure 2. The overall survival curves for the R_1 and R_3 groups.

tomy will die of residual or recurrent local disease.[9] Despite the improved results of large Japanese series, only one randomized study comparing conservative with more radical surgery has been published to date.[1] In that trial, R_2 resection was compared with a conservative gastrectomy without omentectomy and only limited survival data were available. This is the first prospective, randomized trial comparing the "gold standard"—R_1 subtotal resection with the most radical resection for cancer of the antrum.

In this study, overall survival after R_3 resection was significantly worse than after R_1 resection. This was despite the low operative mortality of R_3 resection. On multivariate analysis, blood transfusion was a prognostic factor associated with a significantly worse survival, and this was independent of the type of procedure performed. The possibility that blood transfusion has an adverse effect on survival in cancer patients has been studied, but to date, there is no clear evidence of a causal association between blood transfusion and tumor growth.[10] In particular, of four studies specifically examining the relationship between transfusion and stomach cancer, two found a significant adverse effect[11,12]; the other two showed no effect.[13,14]

Immunologic abnormalities after splenectomy may have contributed to the worse survival in the R_3 group. Controversy remains regarding the effect of splenectomy on tumor immunology in cancer patients in general and the role of splenectomy with gastrectomy for cancer, specifically.[15] However, no deaths in this study were attributable to postsplenectomy sepsis, despite the fact that none of the R_3 patients received any prophylaxis. It also is possible that the extensive lymphatic dissection in R_3 resection itself may have an adverse effect on prognosis because of local tumor spillage from the many divided lymphatic vessels. Previous data from Japan questions the benefit of R_3 resection.[16,17] Within a group of patients with the same stage of disease, the prognosis decreased when the more extensive resection was performed. Unfortunately, no follow-up randomized trial was carried out.

The overall operative mortality of 1.8% (1/54) and, in particular, the operative mortality in the R_3 total gastrectomy group of 3.4% (1/29) compares very favorably with the best results in the Japanese literature[18] and is better than most western series.[19] However, the R_3 procedure carried a high morbidity that is reflected in the increased hospital stay, greater number of blood transfusions, and the need for reoperations. A similarly high morbidity has been reported by Dent et al. for R_2 resection.[1] Left subphrenic abscess was the most common major postoperative complication in this study, despite the use of prophylactic drains and antibiotics. The only postoperative death and all nine laparotomies that had to be redone were related to this complication. A similar experience

has been reported previously by Lundell et al.[20] The high incidence of subphrenic abscess in the R_3 group is likely to be related to the distal pancreatectomy. However, the mechanisms of pancreatic damage leading to sepsis are unclear. We took great care to identify and ligate the main pancreatic duct before oversewing the remaining pancreatic tissue. Duct leakage, direct pancreatic injury, or ischemia are all possible factors. Hyperamylasemia has been reported in association with gastrectomy with lymphadenectomy, although clinical acute pancreatitis was not seen in the study of Korenaga et al.[21] or in this study. If pancreatic duct leakage is the major cause of left subphrenic abscess, it may be beneficial to drain the transected end of the pancreas into the small bowel. However, the result of this and other studies[1,20] make the routine adoption of distal pancreatectomy unattractive.

The 10% (3/29) esophagojejunal anastomotic leak rate in the R_3 group is higher than that reported by recent large series[22,23] with leak rates of less than 5%. In this study, all esophagojejunal anastomoses were made with a circular stapler, which made the fashioning of a reliable esophagojejunal anastomosis technically less demanding. In contrast, a high subtotal gastrectomy also can be technically demanding, but there were no gastrojejunal leaks in the R_1 group, presumably reflecting the richer blood supply of the stomach. Although eight surgeons were involved in the trial, three of the surgeons performed 75% of the procedures. Complications did not appear to be operator related or caused by a learning curve because they occurred throughout all the surgeons' experiences.

Unlike others,[19] we have not adopted a policy of elective postoperative ventilation because significant respiratory complications (other than a sympathetic left pleural effusion in association with subphrenic abscess) were not encountered.

Total gastrectomy "de principe" has been advocated for all gastric cancers because of the high local recurrence rate after subtotal gastrectomy[24] and because multicentric foci of cancer have been reported in approximately 20% of cases of advanced disease.[25] However, this philosophy has been opposed because of the higher morbidity and mortality of total gastrectomy and the longer-term functional and nutritional sequelae.[26] The results of this study are in accord with a recent large, randomized trial[27] in confirming that total gastrectomy can be performed with a low mortality. To date, during follow-up, no stump cancers have been detected in the subtotal group and no multifocal disease was found in any of the resected specimens. The choice of a 6-cm proximal resection margin in the R_1 subtotal group appears justified because no proximal resection line disease was found. However, one duodenal margin was positive for cancer on histology in the R_3 group, and this was seen with a

diffuse type tumor, which has a propensity for submucosal spread.

Future efforts to improve survival with gastric cancer must concentrate on early diagnosis to detect a greater number of early gastric cancers because this policy has been shown by both the Japanese[6] and others in the west[28] to significantly improve survival.

In view of the high early postoperative morbidity, longer-term functional and nutritional sequelae associated with total gastrectomy and the lack of survival advantage, this study does not support the routine use of R_3 total gastrectomy for treatment of patients with antral cancer.

Acknowledgments

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