

## Long-term results following potentially curative gastrectomy for gastric cancer

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### Summary

**Purpose:** The purpose of this study was to report the results of gastric cancer surgery in patients who had undergone potentially curative gastrectomy.

**Methods:** The hospital mortality, morbidity, survival, recurrences and the sites of failure were retrospectively analyzed in D<sub>1</sub> group (conventional gastrectomy), and in D<sub>2</sub> group (extended lymph node resection).

**Results:** D<sub>1</sub> and D<sub>2</sub> groups were comparable for age, gender, American Society of Anesthesiologists (ASA) class, type of surgery, and histopathologic characteristics ( $p > 0.05$ ). D<sub>2</sub> group patients were in better physical status ( $p = 0.008$ ). The recurrence rate was higher in D<sub>1</sub> group ( $p = 0.019$ ). Independent prognostic indicators of morbidity

were male gender ( $p = 0.012$ ), and poor ASA class ( $p < 0.001$ ). Poor ASA class was the single independent prognostic indicator of hospital mortality ( $p = 0.001$ ). Ten-year survival for D<sub>1</sub> and D<sub>2</sub> was 44.1 and 64.8%, respectively ( $p = 0.0433$ ). D<sub>2</sub> gastrectomy improved survival in stage IIIA. The independent prognostic indicators of survival were total gastrectomy ( $p = 0.003$ ), lymph node involvement ( $p < 0.0001$ ), and extended lymphadenectomy ( $p = 0.003$ ). The independent prognostic variables of recurrence were stage ( $p = 0.001$ ), and extended lymph node resection ( $p = 0.006$ ).

**Conclusion:** D<sub>2</sub> gastrectomy improves survival in gastric cancer, particularly in stage IIIA.

**Key words:** gastric cancer, morbidity, mortality, survival

### Introduction

Gastric carcinoma is one of the leading causes of death worldwide, although its incidence has generally declined. The most effective therapy of gastric cancer is potentially curative resection of the tumor. Adjuvant intravenous (i.v.) chemotherapy [1], and radiotherapy [2] have failed to improve survival. Chemoradiotherapy has shown to improve survival in the adjuvant setting, but further studies are required to document these findings [3].

Lymph nodes represent the most important prognostic factor in gastric cancer [4]. However, the extent of lymph node resection remains an issue of controversy. The Japanese results have shown that patients undergoing D<sub>2</sub> gastrectomy show a significant survival benefit, although no prospective study has been performed in Japan [5]. Several Western studies have reproduced the Japanese results [6,7]. Nevertheless,

other studies have strongly questioned the value of D<sub>2</sub> gastrectomy [8,9], either because the survival did not improve or because the morbidity and mortality rates were significantly increased.

The purpose of this study was to report the results of gastric cancer surgery in patients who had undergone potentially curative gastrectomy by comparing D<sub>1</sub> and D<sub>2</sub> gastrectomy carried out at a single institution.

### Methods

The patient records having had potentially curative gastrectomy (R<sub>0</sub>) from 1990-2005 were retrospectively analyzed. Gastric carcinoma was diagnosed with gastroscopy and biopsy. All of the patients were routinely staged preoperatively with physical examination, chest-x-ray, abdominal CT scan, bone scan, hematological-biochemical tests, and tumor markers estima-

tion (CEA, CA 19-9, CA-125). Patients with resectable tumor with no distant metastases or peritoneal spread ( $M_0$ ) were included in the analysis. Patients were assigned to undergo D<sub>1</sub> or D<sub>2</sub> gastrectomy according to surgeon's decision and skill.

Age, gender, ASA class, Karnofsky performance status, tumor distribution, surgical procedure, pathological (p), T, N stage (pTN), Lauren classification, degree of differentiation, morbidity, hospital mortality, recurrences and the anatomic sites of failure were analyzed.

The endpoints of the study were: 1) the identification of differences in morbidity and hospital mortality between D<sub>1</sub> and D<sub>2</sub> gastrectomy; 2) the determination of survival in both groups; 3) the identification of the independent prognostic variables of survival; and 4) the identification of the number of patients that developed recurrence as well as the independent prognostic variables of recurrence.

### *Surgery*

Subtotal gastrectomy was performed for tumors located at the lower third. Total gastrectomy was performed for tumors of the middle and upper third and for those of the gastric remnant. Reconstruction of the alimentary tract was made using hand-sewn Roux-en-Y gastro-jejunostomy and hand-sewn or stapled Roux-en-Y esophago-jejunostomy. In D<sub>2</sub> gastrectomy the resection included the nodal groups 1-12. Lymph node station 10 was left intact unless splenectomy was performed. Splenectomy was carried out for tumors located at the greater curvature of the stomach with preservation of the pancreatic tail if the latter was not invaded. The lymph node stations were removed *en bloc* with the specimen and classified immediately afterwards according to the criteria established by the Japanese Research Society for Gastric Cancer [10].

### *Pathologic examination and classifications*

Histopathologic type and TNM stage were assigned using the criteria provided by the Fourth Edition of the International Union Against Cancer classification [1]. All of the patients with pathologic stages I-III were included in the final analysis.

### *Follow-up*

No patient was lost during follow-up. Patients were assessed in 3-6 months intervals with physical examination, hematological and biochemical tests, tumor markers estimation (CEA, CA 19-9, CA-125), abdominal CT scan, upper gastrointestinal tract endoscopy,

and chest x-ray. Whole body bone scan and/or skeletal x-rays were performed in those cases in which osseous metastases were suspected. Recurrences and the sites of failure were recorded.

### *Statistical analysis*

Statistical analysis was possible using SPSS statistical software (Statistical Package for Social Sciences). The Pearson's chi-square test was used to compare parametric data. Univariate survival analysis was made using the Kaplan-Meier method and the comparison of survival curves was carried out using the log-rank test. Multivariate analysis was made using the Cox proportional hazards model for the identification of the prognostic variables of survival. Logistic regression analysis was used to identify the prognostic factors of morbidity, mortality, and recurrence. A two-tailed p-value <0.05 was considered statistically significant.

## **Results**

From 1990-2005, 127 patients with gastric adenocarcinoma underwent resection with curative intent. D<sub>1</sub> gastrectomy was performed in 65 patients and D<sub>2</sub> gastrectomy in 62 patients. The mean patient age in D<sub>1</sub> group was 68.6±10.5 years (range 33-85), and in D<sub>2</sub> group 65.8±9.5 years (range 35-80) (p>0.05). The groups were similar for male/female ratio, tumor distribution, ASA class, type of operation (total/subtotal gastrectomy), Lauren classification, degree of differentiation, T, pTNM stage, sites of failure, hospital mortality and morbidity (p>0.05). The groups differed in performance status, lymph node involvement, and number of patients with recurrence (Table 1). Concomitant surgery included 1 distal pancreatectomy, 19 splenectomies, 1 transverse colectomy, and 9 cholecystectomies in D<sub>1</sub> group, and 6 distal pancreatectomies, 15 splenectomies, 2 transverse colectomies, and 9 cholecystectomies in D<sub>2</sub> group.

The mean number of resected lymph nodes in D<sub>2</sub> group was 36±9 (range 27-69) and in D<sub>1</sub> group 22±10 (range 9-32; p=0.002).

The overall hospital mortality and morbidity rate was 11% and 34.6%, respectively. The hospital mortality in D<sub>1</sub> group was 13.8% (9 patients), and in D<sub>2</sub> group 8.1% (5 patients; p>0.05). The majority of hospital deaths (4 cases) in D<sub>2</sub> group happened during the first 3 years of the study (1990-1993). The complications in the immediate postoperative period are demonstrated in Table 2. Multivariate analysis showed that ASA class was the single independent prognostic

**Table 1.** Patient and disease characteristics

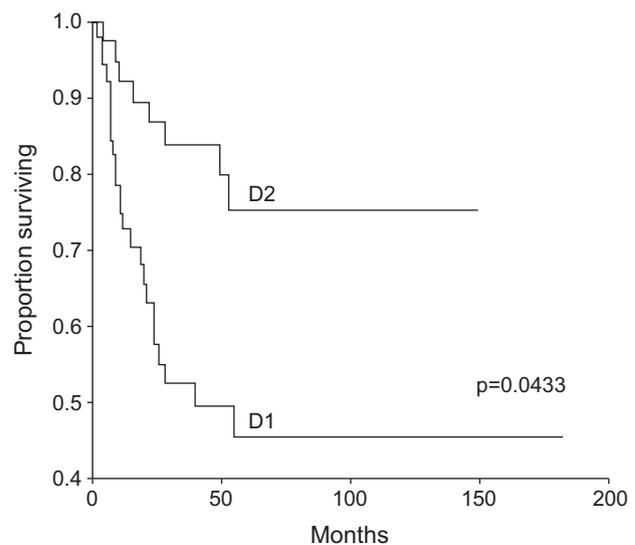
Characteristics	D <sub>1</sub> group	D <sub>2</sub> group	p-value
Male/female ratio	46/19	41/21	>0.05
Tumor localization			>0.05
Fundus	6	7	
Body	23	23	
Antrum	30	30	
Gastric remnant	6	2	
ASA class			>0.05
I	32	38	
II	21	21	
III	12	3	
Karnofsky performance status			0.012
90-100	50	59	
70-80	13	3	
50-60	2	0	
Type of gastrectomy			>0.05
Subtotal	32	28	
Total	33	34	
Concomitant surgery	30	32	>0.05
T			>0.05
T <sub>1</sub>	4	5	
T <sub>2</sub>	15	6	
T <sub>3</sub>	39	46	
T <sub>4</sub>	7	5	
N			0.012
N <sub>0</sub>	26	24	
N <sub>1</sub>	35	23	
N <sub>2</sub>	4	15	
pTNM stage			>0.05
IA	4	5	
IB	8	4	
II	17	16	
IIIA	27	20	
IIIB	9	17	
Lauren classification			>0.05
Intestinal	20	33	
Diffuse	18	4	
Mixed	3		
Differentiation grade			>0.05
G <sub>1</sub>	7	5	
G <sub>2</sub>	9	6	
G <sub>3</sub>	42	36	
Hospital mortality	9	5	>0.05
Hospital morbidity	26	18	>0.05
Age (years)			>0.05
<65	23	26	
>65	42	36	
Recurrence	30	16	0.019
Pattern of recurrence			>0.05
Distant	14	5	
Locoregional	15	11	
Adjuvant chemotherapy	16	20	>0.05

stic variable for mortality ( $p=0.001$ , hazard ratio/HR=0.256, 95% CI=0.115-0.568). The independent prognostic variables for morbidity were ASA class ( $p<0.001$ , HR=3.607, 95% CI=1.921-6.771) and gen-

**Table 2.** Postoperative complications

Complication	D <sub>1</sub> group	D <sub>2</sub> group
Respiratory	5	5
Cardiac	3	3
Postoperative bleeding	1	0
Anastomotic failure	5	2
Prolonged ileus	1	0
Trauma-related	7	4
Intraabdominal abscess	2	3
Cerebrovascular accident	2	1

All p-values are non significant

**Figure 1.** 10-year survival rate for D1 and D2 gastrectomy.

der ( $p=0.012$ , HR=0.285, 95% CI=0.107-0.76), because the rate of complications was higher in male patients. Neither pancreatectomy nor splenectomy were related to morbidity and mortality.

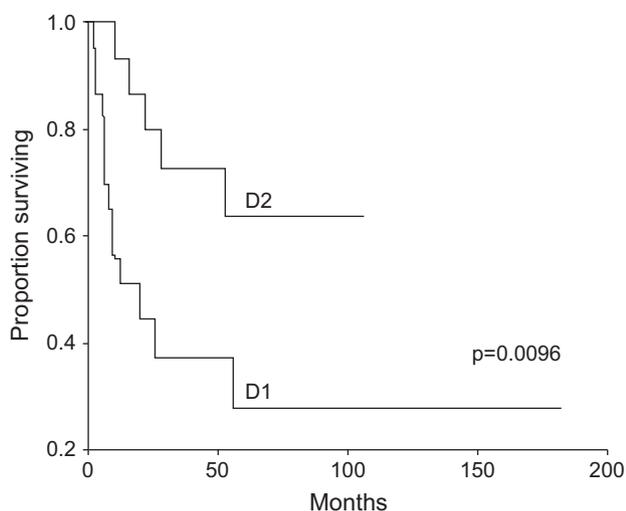
### Survival

The mean survival for D<sub>1</sub> and D<sub>2</sub> group was 84 (95% CI=62-106), and 104 (95% CI=86-122) months, respectively. Ten-year survival rate for D<sub>1</sub> and D<sub>2</sub> group was 44.1% and 64.8%, respectively ( $p=0.0433$ ; Figure 1). The mean survival for D<sub>1</sub> and D<sub>2</sub> group in stage IIIA was  $58\pm 17$  (95% CI=25-92), and  $79\pm 10$  (95% CI=60-99) months, respectively ( $p=0.0096$ ; Figure 2).

Univariate analysis demonstrated that ASA class, performance status, pT, pN, TNM stage, radical lymph node resection, and total gastrectomy were closely related to survival (Table 3). Nodal status ( $p<0.001$ , HR=0.371, 95% CI=0.192-0.716), radical lymph node resection ( $p=0.003$ , HR=2.52, 95% CI=1.584-4.011),

**Table 3.** Univariate analysis of prognostic variables

Variable	p-value
Gender	>0.05
Tumor distribution	>0.05
ASA class	0.0284
Performance status	<0.0001
Type of gastrectomy	0.0112
T	0.0317
N	0.0025
TNM stage	0.0003
Lauren classification	>0.05
Grade	>0.05
Adjuvant chemotherapy	>0.05
Radical lymph node resection	0.0433

**Figure 2.** 10-year survival rate in stage IIIA for D1 and D2 gastrectomy.

and total gastrectomy ( $p=0.003$ ,  $HR=2.787$ , 95%  $CI=1.425-5.45$ ) were identified as independent prognostic indicators of survival by multivariate analysis.

### Follow-up

The mean follow-up time was 43.5 months (range 12-167) and was not different between the groups. Recurrence was recorded in 45 (35.4%) patients. There were 14 patients with distant and 15 patients with locoregional metastases in D<sub>1</sub> group. In D<sub>2</sub> group 5 patients developed distant and 11 locoregional metastases. In total 29 (44.6%) patients in the D<sub>1</sub> group and 16 (25.8%) patients in the D<sub>2</sub> group recurred ( $p=0.019$ ). The extent of lymph node resection ( $p=0.006$ ,  $HR=3.186$ , 95%  $CI=1.388-7.311$ ), and the stage ( $p=0.001$ ,  $HR=0.403$ , 95%  $CI=0.238-0.68$ ) were identified as prognostic variables of recurrence by multivariate analysis.

## Discussion

Although the patients in this study were assigned in D<sub>1</sub> and D<sub>2</sub> group without the use of standard criteria, the groups were different only for performance status.

Several studies have shown that radical lymphadenectomy is associated with high morbidity and mortality rates, implying that the method may be harmful [8,9,12,13].

Other studies have shown that morbidity and mortality are the same following D<sub>1</sub> and D<sub>2</sub> gastrectomy [14], or even increased following D<sub>1</sub> gastrectomy [15]. The relatively high mortality rate (8.1%) in D<sub>2</sub> group is the result of the learning curve of D<sub>2</sub> gastrectomy.

Numerous retrospective studies have shown the value of D<sub>2</sub> gastrectomy in gastric cancer [5,6,7,16]. Large prospective multi-institutional randomized Western trials have not reproduced similar results [8,9]. Totally different results have been reported in other studies. These studies were either prospective randomized [17] or retrospective with large numbers of patients [15] from one institution. The studies consistently demonstrate that the lymph node status and the extent of lymph node resection are prognostic indicators of survival.

The evaluation of the total number of resected lymph nodes in addition to the groups of resected lymph nodes has served as the objective control of D<sub>2</sub> gastrectomy [18]. Data analysis of the present study has shown that D<sub>2</sub> gastrectomy offers significant survival benefit in patients with gastric cancer (64.8% 10-year survival rate vs. 44.1% for D<sub>1</sub> gastrectomy). In addition, the lymph node status and extensive lymphadenectomy have been identified as independent prognostic variables of survival [4,6,15,19-21]. The increased survival may be partly the result of the high proportion of patients with early gastric cancer (12 patients in D<sub>1</sub> group and 9 in D<sub>2</sub> group). All of the patients with early gastric cancer had 100% 10-year survival rate regardless of the extent of lymph node resection. A stage-by-stage analysis has demonstrated that only stage IIIA patients have significantly better survival because they have been offered extended lymph node resection. Stage II and IIIA patients have been shown to have significant survival benefit by D<sub>2</sub> gastrectomy [18]. In contrast, the effect of extended lymph node resection has been strongly questioned in early gastric cancer [18,22].

The hospital mortality, morbidity [23,24] and overall survival [24,25] have not been different for tumors of the antrum following either total or subtotal gastrectomy. In the present study the tumors of the gastric antrum have not been analyzed in particular but total gastrectomy has been identified as a favorable prognostic variable of survival. Other studies have

confirmed the same results [7], probably because the extent of lymphadenectomy is even more radical in total gastrectomy.

The extent of surgery has been found to play a significant role in the development of recurrences. In D<sub>2</sub> group the total number of recurrences has been found to be significantly lower than the number of recurrences in D<sub>1</sub> group (16 vs. 30 patients,  $p=0.019$ ). In addition, it has been shown by multivariate analysis that radical lymphadenectomy is a prognostic indicator for the development of recurrence. Similar results have been demonstrated by other studies in which the interest has been focused in the reduction of locoregional failures [9,26]. In this study the difference in sites of failure has been the same for D<sub>1</sub> and D<sub>2</sub> gastrectomy. Despite the improved results that undoubtedly affect the long-term survival, the total number of recurrences still remain high.

## Conclusions

Radical lymph node resection in gastric cancer offers significant survival benefit by decreasing the total number of recurrences. The morbidity and hospital mortality in radical lymphadenectomy is the same as in conventional surgery. Total gastrectomy seems to offer a benefit in survival when combined with radical lymph node resection.

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