

Gastrectomy with D2 lymphadenectomy for gastric cancer: Morbidity, mortality and survival

Mohamed I Kassem, MD; Abdel Hamid Ghazal, MD; Magdy A Sorour, MD; Aymen Azzam, MD; Mohamed El-Riwini, MD; Hassan El-Bahrawy, MD

GIT Surgical Unit, Department of General Surgery, University of Alexandria, Egypt.

Abstract

Background: Gastric cancer is the second leading cause of cancer death worldwide. Ninety percent of gastric cancers are adenocarcinomas. Overall, there is a decline in the incidence of gastric cancer in most countries over the past 50 years. Surgical resection is the most effective treatment for curable gastric cancer. Controversy still surrounds the value of extensive lymph node dissection in the curative treatment of gastric carcinoma. The overall 5-year survival rate among patients with resectable gastric cancer ranges from 10% to 30% in the western world. In contrast, Japanese publications report a marked improvement in survival (between 50% and 62%), largely attributed to lymph node resection known as "D2 lymphadenectomy".

Methods: The study was a prospective follow-up study on 50 consecutive patients with gastric cancer (without distant metastasis) between March 2007 and February 2010 in the Upper Gastrointestinal Surgery Unit, Faculty of Medicine, Alexandria University, Egypt. Patients less than 65 years with histologically proven and potentially curable gastric cancer were eligible for the study. Preoperatively, all patients underwent upper gastrointestinal endoscopy with biopsies and histopathologic examination. Computed tomography (CT) scans were done to look for metastases.

Results: Fifty patients (36 men, 14 women) underwent gastric resection with D2-lymphadenectomy for gastric adenocarcinoma in a three-year period. Mean age was 46.6 years with a range of 23-65 years. Almost 44% of patients had preoperative co-morbid disease. Weight loss with epigastric pain and dyspepsia was the most common presenting symptom (80%). Fifty patients underwent D2 resection, fifteen patients with radical total gastrectomy and intra-abdominal oesophagojejunostomy, and thirty five patients with a subtotal distal gastrectomy and gastrojejunostomy. The hospital mortality rate was 4% (2/50). Morbidity rate was 44% (22/50), some of them presented with more than one complication. The median time of hospital stay was 22 days (mean 22.3, range 13-40). Follow-up included clinical, laboratory and CT examinations of all patients after surgery. In addition, when relapse was suspected, endoscopy with biopsy, and CT scan were performed. During the first 2 years follow-up, locoregional relapses were observed in 2 patients (local lymph nodes relapse). One patient presented with peritoneal recurrence, and 2 patients showed distant spread. The overall actuarial one-year survival in D2 patients was 92% and 76% at two years.

Conclusion: The results obtained in our series of patients submitted to gastrectomy with D2 lymphadenectomy suggest that this technique offers low morbidity, mortality and acceptable 2-year survival rates. The survival benefit with D2 is obtained when a tumor invades muscularis propria or penetrates serosa without invasion of adjacent structures.

Introduction:

Gastric cancer is the second leading cause of cancer death worldwide, although its incidence is decreasing.¹ Ninety per cent of gastric cancers are adenocarcinomas. Overall,

there is a decline in the incidence of gastric cancer in most countries over the past 50 years.²⁻⁶ The reason for this decline remains unknown, but there is speculation that the eradication of *Helicobacter pylori* and a change

in diet may be contributing factors.²

Gastric cancer mortality is largely attributable to relapse of the disease, manifested in different ways in more than one location simultaneously.⁷ Gastric cancer relapse and patient survival depend on both the stage of the disease at the time of diagnosis and on the extent of surgery.⁸

The overall 5-year survival rate among patients with resectable gastric cancer ranges from 10% to 30% in the western world.⁹ In contrast, Japanese publications report a marked improvement in survival (between 50% and 62%), largely attributed to lymph node resection known as “D2 lymphadenectomy”.¹⁰ Some studies suggest that surgeon expertise not only plays an important role in reducing surgical morbidity and mortality but also contributes substantially to improving survival.¹¹

Surgical resection is the most effective treatment for curable gastric cancer. Controversy still surrounds the value of extensive lymph node dissection in the curative treatment of gastric carcinoma. Reports from the Gastric Cancer Registry and other retrospective studies¹²⁻¹⁵ have made radical gastrectomy with extended D2 removal of regional lymph nodes the standard for the treatment of curable gastric cancer in Eastern Asia and the United States.¹⁶⁻²¹

The aim of gastrectomy is to achieve an R0 resection. A curative resection was defined as R0, and patients with positive microscopic margins (R1) and evidence of gross residual disease (R2) were considered to have palliative resections. The Japanese Research Society for Gastric Cancer (JRSGC) has assigned the lymph nodes draining the stomach into 16 different lymphatic stations and this is divided into four echelons (N1-N4).²² The extent of lymphadenectomy is defined as D1-D4 depending on the lymph node stations dissected. In the Western World, removal of the perigastric lymph nodes along the lesser curvature and the greater curvature is a D1 resection. D2 gastrectomy, involves D1 resection plus removal of the omental bursa and the front leaf of the transverse mesocolon and the nodes along the left gastric artery, the

common hepatic artery, the coeliac artery, the splenic artery and splenic hilum (N2 nodes). D3 involves D2 plus removal of nodes in the hepatoduodenal ligament, in the retropancreatic space and along the vessels of the transverse mesocolon. D4 resection involves a D3 resection and removal of the nodes around the abdominal aorta. In reality, D3 and D4 resections are rarely practiced where D2 resections are the gold standard lymphadenectomy.²²

Once the gastric tumor invades the subserosa (stage T2b), the serosa (stage T3), or the adjacent structures (stage T4), metastases can spread to the para-aortic lymph nodes, which are termed N3 nodes according to the Japanese Classification of Gastric Carcinoma,²³ and M1 nodes according to the International Union Against Cancer (UICC) tumor–node–metastasis (TNM) classification.²⁴

Why should D2 lymphadenectomy be considered? Firstly; the principle, it is known that second echelon N2 nodes will be involved in a high proportion of gastric cancer cases, and most patients have node-positive disease. The excision of this echelon of nodes will increase the likelihood of an R0 resection, and this may benefit a subset of patients. Secondly, the experience of centers in Japan and the West reported low operative risks and excellent outcomes.²⁵⁻²⁷ Complete locoregional tumor removal with adequate margins of clearance has been repeatedly identified and widely accepted as a major factor in reducing locoregional tumor recurrences and improving survival in patients with gastric cancer. Safe margins, by this definition, entail no residual tumor at resection margins and gastric bed, and no lymph node with tumor in the area of lymphatic drainage.^{28,29}

The aim of this study was to evaluate the morbidity, mortality, and survival in the surgical treatment of curable gastric cancer with radical gastrectomy and D2 lymphadenectomy and the factors that could influence them, and to evaluate whether extending the lymph node dissection to N2 level can improve the survival rate and reduce the incidence of locoregional relapse.

Patients and methods:

The study was a prospective follow-up study on 50 consecutive patients with gastric cancer (without distant metastasis) between March 2007 and February 2010 in the Upper Gastrointestinal Surgery Unit, Faculty of Medicine, Alexandria University, Egypt. Patients less than 65 years with histologically proven and potentially curable gastric cancer were eligible for the study.

Patients with severe cardiorespiratory, renal or metabolic disease precluding extended resections were excluded, as were those with distant metastases at preoperative staging.

Preoperatively; all patients underwent upper gastrointestinal endoscopy with biopsies for histopathologic examination, and computed

tomography (CT) for staging of gastric cancer and look for metastases **Figure(1,2)**.

A total of 50 patients with gastric cancer were operated on. Patients who underwent an en bloc resection of the stomach with extended D2-lymphadenectomy were selected for this study. The lymph node dissection included compartments I (No. 1-6) and II (No. 7-15).

The records: Age, gender, co-morbidity, type of gastrectomy, additional organ resection (splenectomy) and pathologic TNM stage were reviewed in the 50 D2 gastrectomies prospectively. Operative mortality and morbidity were defined as death or complications occurred within 30 days after the operation.

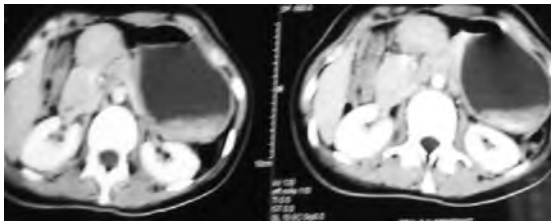


Figure (1)

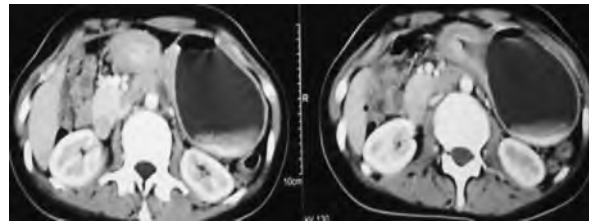


Figure (2)

Figure (1,2): CT evidence of cancer stomach (distal third).

Results:

Fifty patients (36 men, 14 women) underwent gastric resection with D2-lymphadenectomy for gastric adenocarcinoma in a three-year period. Mean age was 46.6 years with a range of 23-65 years. Patients with a histopathological diagnosis other than adenocarcinoma were excluded, as were those with synchronous neoplasm, and those with tumors located at the oesophagogastric junction. There were no exclusions due to co-morbidity or age, except for those patients for whom surgery did not intend to be radical due to the extent of illness, or patients for whom surgery was exclusively palliative.

Almost 44% of patients had preoperative co-morbid disease (some of patients presented with more than one co-morbidity). The factors of co-morbidity (n=29) in the 22 patients were diabetes mellitus (n=9), ischemic heart disease (n=8), hypertension (n=7), chronic obstructive pulmonary disease (n=4) and chronic cardiac failure (n=1). Weight loss with epigastric pain

and dyspepsia was the most common presenting symptom (80%), anorexia and dysphagia (10%), upper abdominal discomfort (6%), and haematemesis (4%).

Fifty patients underwent D2 resection, fifteen patients with radical total gastrectomy and intra-abdominal oesophagojejunal anastomosis **Figures(3,4)**, and thirty five patients with a subtotal distal gastrectomy and gastrojejunostomy **Figures(5-15)**. Six patients underwent splenectomy, one patient underwent distal pancreatectomy, and one patient underwent transverse colectomy in an attempt to achieve R0 resections in the locally advanced tumors. Distal subtotal gastrectomy was reserved for those patients with tumors located in the distal third of the stomach, corresponding to the Lauren intestinal type, and which, on macroscopic examination, appeared not to invade the gastric serosa. The remaining patients underwent total gastrectomy.

Resection was extended to the neighboring organs when tumor invasion was suspected.

Splenectomy was performed in patients with advanced proximal tumors with suspected splenic infiltration, or with apparently invaded splenic hilar lymph nodes. In the 6 patients in whom a splenectomy was carried out, 2 were for tumors at the upper part of the stomach, 3 for the tumors of the middle part, and one for the tumors diffusely affect the stomach (3 patients had T4 tumors and 3 patients had localized tumors near the splenic hilum with

suspicion of lymphatic invasion). A distal pancreatectomy was performed in patients with suspected tumor infiltration or metastatic disease in the lymph nodes of the splenic artery chain. Distal pancreatectomy was done in one patient with T3/T4 tumors and the tumor invasion was confirmed. Transverse colectomy with primary anastomosis was done in one patient with T4 tumor invasion of the transverse mesocolon.

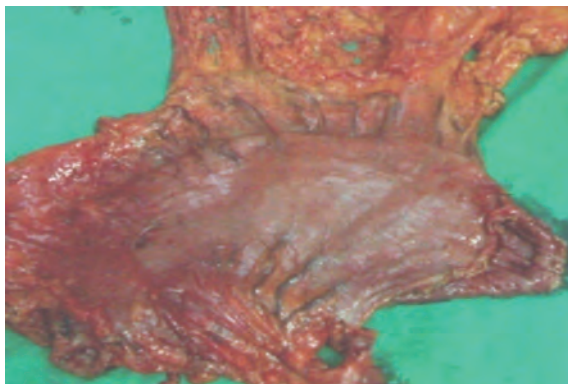


Figure (3)

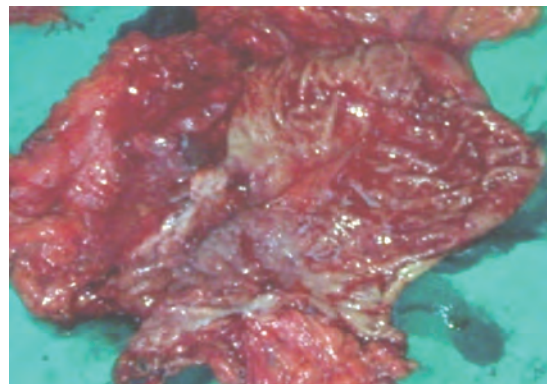


Figure (4)

Figures (3,4): Total gastrectomy for diffuse type of cancer stomach.



Figure (5)

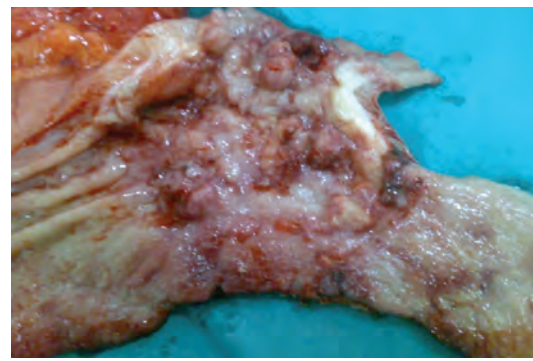


Figure (6)



Figure (7)



Figure (8)

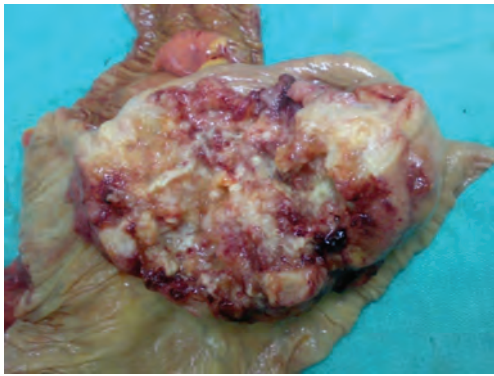


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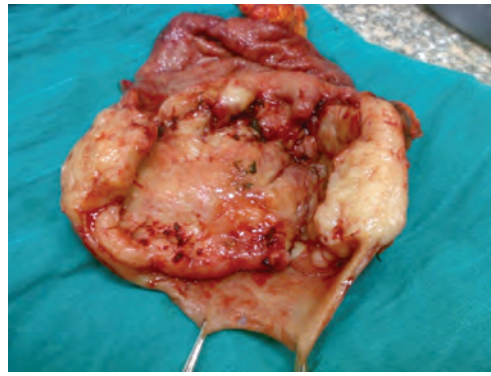


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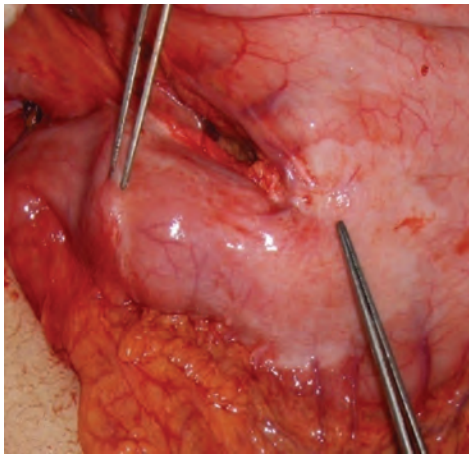


Figure (11)



Figure (12)



Figure (13)

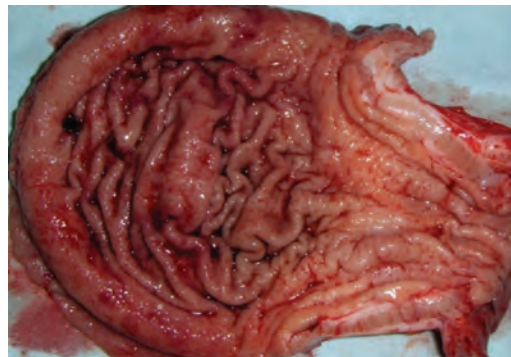


Figure (14)



Figure (15)

Figures (5-14): Distal gastrectomy with D2 lymphadenectomy for cancer stomach of the pyloric antrum and gastrojejunostomy Figure (15).

The clinicopathological characteristics of the 50 patients, the pathologic TNM stages of the patients, and the lymph nodes in the D2 dissections are shown in **Table(1)**.

Disease staging was based on the TNM classification included in the fifth edition (2005)

of the TNM atlas: illustrated guide to the TNM classification of malignant tumors, of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC).³⁰

Table (1): Clinicopathological characteristics of the 50 patients (gastrectomy with D2 lymphadenectomy).

	Patients (n= 50)	Percentage %
1- Age		
< 40	15	30
40-54	23	46
>55	12	24
2- Gender		
Male	36	72
Female	14	28
3- Co-morbidity		
0 factor	28	56
1 factor	10	20
2 factors	8	16
3 factors	4	8
4- Location		
Upper third	2	4
Middle third	10	20
Distal third	35	70
Diffuse (whole stomach)	3	6
5- Gastrectomy		
Total	15	30
Distal subtotal	35	70
6- Additional organ resection:		
Splenectomy	6	12
Transverse colectomy	1	2
Distal pancreatectomy	1	2
7- Operative time (hours), mean (range):	3 (2-4)	-
8- Operative blood loss (ml) mean (range):	507 (200-1200)	-
9- Blood transfused (units)	1 (0-3)	-
10-Stage (pTNM):		
Ia	0	0
Ib	2	4
II	10	20
IIIa	25	50
IIIb	11	22
IV (T4N2M0)	2	4

11-Tumor size		
< 10 cm in diameter	37	74
>10 cm in diameter	13	26
12-Lauren classification:		
Intestinal	28	56
Diffuse	13	26
Indeterminate	9	18
13-Type of resection margin:		
R0	42	84
R1	8	16
14-Number of metastatic lymph nodes (N stage, AJCC):		
N0	15	-
N1	18	-
N2	14	-
N3	3	-

N0: No positive nodes

N1: One to 6 positive nodes

N2: Seven to 15 positive nodes

N3: More than 15 positive nodes

The hospital mortality rate was 4% (2/50). The two patients underwent total gastrectomy; the first one, 64 years old, was hospitalized before the gastric operation with serious gastric bleeding from the stomach cancer; after blood transfusion and correction of the general condition, he was operated on and died on the 12th postoperative day due to anastomotic dehiscence (oesophagojejunostomy), septicemia and respiratory distress secondary to pneumonia. The second patient, 60 years old, had hypertension and chronic cardiac failure as a co-morbidity preoperatively, and despite preoperative hospitalization and control of hypertension and chronic cardiac failure, the patient died on the 25th postoperative day because of heart failure and chest infection.

Morbidity rate was 44% (22/50), some of them presented with more than one complication. Chest infection (n = 12); two of these patients had respiratory failure and required intensive support at the intensive care

unit (ICU) but none required artificial ventilation, wound infection (n=10), diabetic ketoacidosis (n=3), atrial fibrillation (n=2), upper gastrointestinal hemorrhage (n=2); which resolved spontaneously, deep vein thrombosis (n=1), pulmonary embolism (n=1), and intra-abdominal abscess (n=1). There were two patients with oesophagojejunal leak; one patient died postoperative because of intraabdominal abscess and respiratory failure and the other patient was treated conservatively with percutaneous drainage and medical treatment. Another patient with gastrojejunal anastomotic leak was successfully managed conservatively with percutaneous drainage and medical treatment (the anastomotic leak proved by a systematic water soluble X-ray imaging performed on the seventh postoperative day). No patient required surgical re-interventions. The statistics of the parameters according to mortality and morbidity are shown in **Table(2)**.

Table (2): Postoperative complications (morbidity) and mortality.

Morbidity	Patients	Percentage (%)
1- Non-surgical complications:		
Pneumonia (chest infection)	12	24
Cardiac complications(AF)	2	4
Diabetic ketoacidosis	3	6
Pulmonary embolism	1	2
Respiratory failure	2	4
Heart failure	1	2
Deep vein thrombosis	1	2
2- Surgical complications:		
Wound infection	10	20
Upper gastrointestinal hemorrhage	2	4
Anastomotic dehiscence		
Oesophagojejunostomy	2	4
Gastrojejunostomy	1	2
Intra-abdominal abscess	1	2
Re-operation	0	0
Mortality:	2	4
Hospital stay (days), mean (range):	22.3 (13-40)	-

The median time of hospital stay was 22 days (mean 22.3, range 13–40). Follow-up included clinical, laboratory and CT examinations of all patients during the first two years after surgery. In addition, when relapse was suspected, endoscopy with biopsy, and CT scan were performed. Tumor markers were performed; carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9. Recurrences were classified as locoregional, peritoneal, or distant metastasis. Locoregional recurrences were included (those located in the surgical bed, retroperitoneal lymph nodes of the upper abdomen, or in the site of anastomosis). Peritoneal recurrences were included [those affecting the ovaries, (Krukenberg tumor), carcinomatosis, and positive cytology]. Distant recurrences were those detected in other non-regional lymph

nodes or other organs.

During the first 2 years follow-up, locoregional relapses were observed in 2 patients (local lymph nodes relapse). One patient presented with peritoneal recurrence, and 2 patients showed distant spread.

The survival curve following D2 resections is shown in **Figures(16,17)**.

The overall actuarial one-year survival in D2 patients was 92% and 76% at two years.

Statistical analysis:

The SPSS version 12.0.1 statistical package was used for statistical analysis. Values for qualitative variables were given as percentages and those for quantitative variables were given as medians and ranges. Survival curves were calculated using the Kaplan-Meier method.

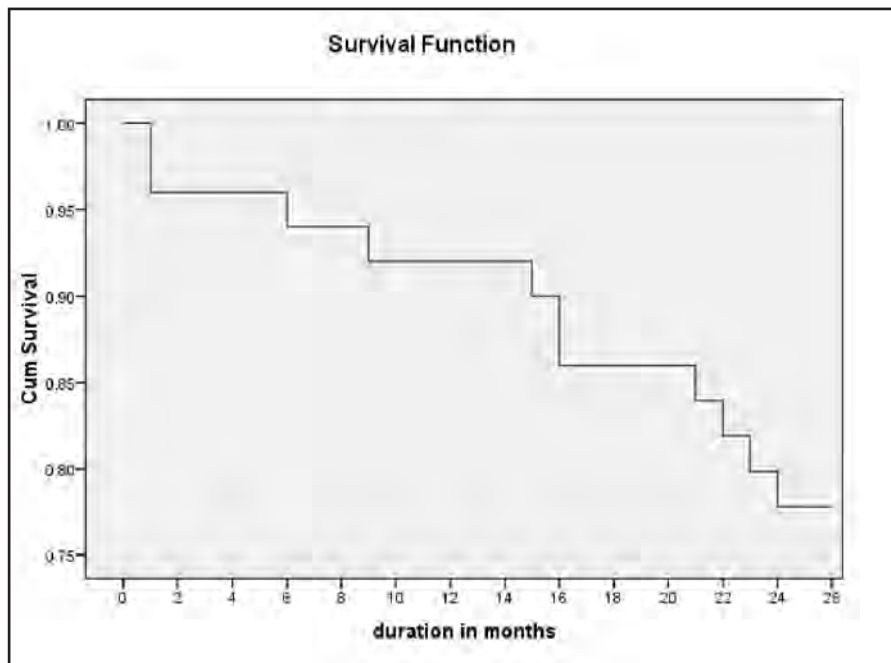


Figure (16): Survival curve following D2 lymphadenectomy and gastric cancer resection.

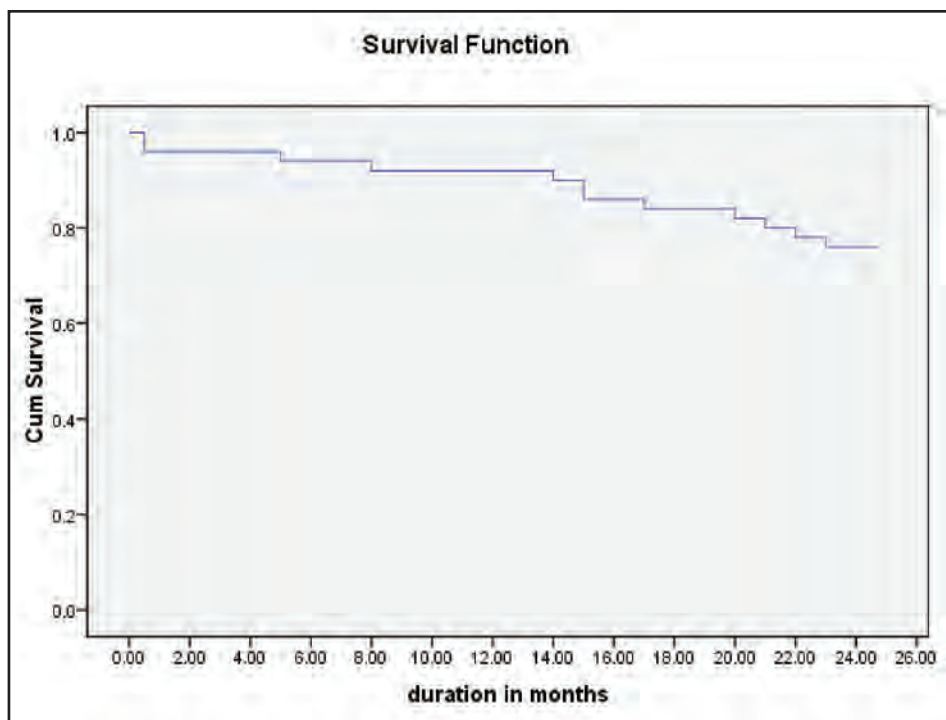


Figure (17): The overall actuarial survival curve for patients after total and distal subtotal gastrectomy for gastric cancer (2-year Kaplan-Meier survival curve).

Discussion:

Despite its recent decline, gastric cancer is still a common lethal disease in western countries.³¹ For apparently resectable cancers, surgery offers the best locoregional control; but unfortunately, average 5-year survival rates for treated patients remain low in the western world, ranging from 15 to 30%.^{32,33} The benefit

of D2 gastrectomy's potential for reducing locoregional recurrence may be nullified by the significant increase of post-operative morbidity and mortality.³¹

There is controversy over the use of D2 as a curative procedure for gastric cancer. Japanese surgeons have advocated its use since the 1960s and it is now the standard surgical treatment

for gastric cancer in Japan and in many centers in Hong Kong, Korea and China. Its use in Europe and the US has been limited to specialist units. This may reflect some therapeutic nihilism to gastric and other upper gastrointestinal cancers in the Western World, but in greater part it reflects the lack of supporting evidence from randomised studies which claim no survival benefit yet enhanced operative morbidity and mortality from the extended lymphadenectomy. The Medical Research Council (MRC) studied 400 patients undergoing gastrectomy (200 in both the D1 and D2 groups) in a multicentre trial and found significantly higher post-operative morbidity (33% D2 vs. 21% D1) and mortality (13% D2 vs. 6.5% D1) following D2 resection.³⁴ In support of this view, Wanebo et al³⁵ reviewed a prospectively gathered database of 18,346 cases of gastric carcinoma in the US. Among the 3,804 patients undergoing curative resection, five year survival rates for patients with N2, N1 and N0 nodes removed were 26.3%, 30% and 35.6% respectively. They concluded that lymph node dissection (D2) of N2 nodes did not confer a survival advantage. Overall mortality was very low, at 0.6%. This rate is comparable to those shown by eastern authors in series from experienced centers, and is strikingly different from the rates of both arms reported in MRC and Dutch trials.^{36,37}

Although morbidity and mortality rates of gastrectomy for gastric cancer were different, in a data analysis of 22 cancer centers; the mortality rate was reported between 3.1% and 31%.³⁸

In this study, the hospital mortality rate was 4%, and the mortality rate at one year was 8% and this is in agreement with literature reports.

The morbidity rate of our study was 44%. This figure is higher than the percentages reported by other authors in literature in which the morbidity has been reported as being 8-31%.^{39,40} Various studies^{41,42} have demonstrated that the morbidity increased with age but no significant correlation was found; however other studies emphasized that the age is a predictor factor of morbidity.^{43,44} In our experience; the mortality and morbidity increased with age but no significant correlation was found.

The most common non-abdominal complications in our series were of a respiratory nature, in agreement with many other literature sources.^{34,45-54} Among the abdominal complications, anastomotic leakage rates reported in the literature ranged from 2.1% to more than 8%.^{34,45-52,54} The overall incidence of dehiscence in our series was 6%.

It is now accepted that pancreatic and splenic resections are only justified in the rare situations where there is direct contiguous involvement of these organs by the gastric tumor and that a complete D2 lymphadenectomy can be effectively and safely performed with preservation of these organs.⁵⁵ In our study, six patients underwent splenectomy, one patient a distal pancreatectomy, and one patient a transverse colectomy in an attempt to achieve R0 resections in the locally advanced tumors.

The incidence of disease relapse varies greatly among the different series published in the literature. This is due to a number of factors, including the extent of surgery and the tumor stage at the time of the operation. Accordingly, the published relapse rates range from 20% to more than 60%; this figure is higher than the percentages reported by this study (recurrence rate was 10%) and this is because it includes both R0 and R1 patients, unlike many other studies that include only R0 patients.⁵⁶⁻⁶⁴ It is generally accepted that most relapses occur within the first 2 years after curative surgery for gastric cancer.^{8,60,65} Yoo et al⁵⁷ on classifying relapse into early and late groups (according to whether relapse occurred before or after 2 years), found 73% of all disease relapses to occur early. D'Angelica et al⁶⁰ in turn, reported a higher relapse rate, of 79%, in the first 2 years after surgery; this figure reached 94% before the fourth year. In our series, recurrence within the first 2 years after surgery was seen in 5 patients. Gastric cancer survival according to the type of surgery performed has been the subject of many studies—including those of Bonenkamp et al⁶⁶ and Cuschieri et al³⁴ who recommended the obviation of routine D2 gastrectomy due to its high morbidity and mortality, and because the overall 5-year survival in their group of D2 lymphadenectomized patients was not significantly different from that of the group

submitted to more conservative surgery. Other authors have also reported overall 5-year survival rates of fewer than 50%, with results in the range of 30%-47%.^{47,48,67-69}

The 5-year survival rates show marked differences between patients from the West and East, and although the prognosis of resectable gastric carcinoma in the West remains poor, in Japan it is two-fold to three-fold higher than those in the West mainly because extended lymph node dissection has been standard procedure during the last three decades.^{70,71} In recent years, the results of treatment in the West have also shown evidence of improvement. The 5-year survival rate after all resections has increased significantly from 21% in the series ending before 1970 to 28% in those ending before 2000, and the 5-year survival rate after curative resection has risen from 38% to 55% over the same period.^{72,73} In our study; the overall one-year survival in D2 patients was 92% and 76% after two years.

Conclusion:

Our experience is consistent with reports from other units in Western, European and the US and indicates that the extended lymph node dissection with gastrectomy can be performed with a low risk of mortality and morbidity, and acceptable outcomes. In conclusion, the results obtained in our series of patients submitted to gastrectomy with D2 lymphadenectomy suggest that this technique offers low morbidity, mortality and acceptable 2-year survival rates of 76%. We consider it essential for such surgery to be performed by specialized surgeons. In principle, the survival benefit with D2 is obtained when a tumor invades muscularis propria or penetrates serosa without invasion of adjacent structures.

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