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Surgical Treatment of Gastric Cancer the Role of Extended Lymphadenectomy

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ABSTRACT

Purpose: For patients with gastric cancer, surgical resection with a lymph node dissection is considered a potentially curative treatment. The prognostic benefit of extended lymph node dissection (D2) is still controversial. Accordingly, our objective in this study is to investigate the feasibility of this type of dissection and the value of intraoperative contrast medium in the demonstration of the lymphatic system and lymph node's draining area and to evaluate the different prognostic factors using univariate and multi-variate analysis and to compare the survival of patients subjected to D2 dissection to a historical group of patients with gastric cancer treated at the NCI Cairo University.

Patients and Methods: Thirty-three patients with gastric carcinoma underwent radical gastrectomy with systematic lymph node dissection (D2 dissection) as described by the Japanese Research Society for Gastric Cancer (JRSGC, 1998).

In NCI. Cairo University and South Egypt Cancer Institute (S.E.C.A) Assiut University and Aswan Cancer Center between October 1999 and September 2001 using black contrast medium (CH-40) India ink for lymphatic mapping intra operatively. The prognostic factors using univariate and multivariate analysis and the survival were compared to the results of a group of patients with gastric cancer treated in NCI before 1998.

Results: The 2 year overall and disease free survival rates were 43.6% and 42.5% respectively. Serosal invasion, curability of resection, combined resection, depth of invasion and number of resected lymph nodes were the most significant prognostic factors. Type of operation, lymph nodes metastasis, ratio of involved to resected nodes, level of lymph node metastasis (N stage by the Japanese Staging System), tumour location, histology and UICC stage also had prognostic significance on univariate analysis. The number of resected lymph nodes was a highly significant prognostic factor suggesting the importance of an extended lymph node dissection. The operative morbidity was 15% and hospital mortality rate was 3%. These results were much better than the historical group (97 patients) treated in NCI before 1998 without the extended lymph node dissection where the mortality rate was 18.5% and morbidity was 23.7% while the 2 year overall and disease free survival rates were 30.1% and 28.8% respectively.

On multivariate analysis, serosal invasion, tumour location, level of lymph node metastasis (N) stage by the Japanese Staging System and tumour histology were independent significant prognostic factors.

Intraoperative lymphography using fine activated carbon particle solution proved to be effective in facilitating an extended lymphadenectomy in node -ve patients.

Conclusion: In Egypt gastric cancer usually presents late in advanced stage with a poor outcome. Early diagnosis, appropriate staging and adequate surgical resection with extended lymphadenectomy (D2) are the most important requirements for a successful outcome. Extended lymph node dissection is feasible and not associated with an increased morbidity or mortality and can improve results of surgery in cases with curable gastric cancer. Intraoperative lymphography facilitates such extended lymph adenectomy.

Key Words: *Surgical treatment - Gastric cancer extended lymph adenectomy.*

INTRODUCTION

Radical resection for gastric cancer comprises adequate resection of the stomach together with lymph node dissection [1].

The philosophical basis of extended gastric resection and lymph node dissection is that gastric cancer often remains a locoregional disease with only local lymphatic spread, which can be cured by gastric resection with sufficient margins and extended lymph node dissection. On this theoretic basis, it is assumed that cancer cells disseminate principally via lymphatic vessels and the removal of metastatic lymph nodes affected cure by preventing subsequent systemic spread [2]. As opposed to other cancers, the incidence of distant metastasis is kept very

low until a tumor becomes T3. The major pattern of recurrence is either locoregional or peritoneal. On the other hand, the frequency of lymph node metastasis is rather high already in T2 tumours and increases in parallel with the depth of tumour infiltration [2]. However, in many Western countries, carcinoma with lymph node metastasis is regarded as a systemic disease, an opinion supported by observations in various cancers [3].

The proportion of early gastric cancers is over 50% in many Japanese institutions, much higher than in the West where early gastric cancer accounts for only 5-15% in most series [4,5,6]. However, when compared stage for stage, Japanese and Western tumours behave exactly the same if they are treated by extended surgery [7]. Even on the molecular biological level there was no difference in expression of onco-and tumour-suppressor genes between Japanese and British gastric cancer [8].

Based on the above facts it is logical to remove not only the cancer and surrounding normal stomach, but also the lymph nodes to which the tumour drains, including those along the hepatic, splenic and coeliac arteries. This is known as the D2 radical gastrectomy with extended lymph node dissection, and has been practised as standard surgery in Japan for the past 30 years and has given an improved five-year survival [1].

The general rules of the Japanese Research Society for Gastric Cancer (JRSGC, 1995) [9], are widely accepted and adopted in many countries. In these rules, lymph nodes are classified into 16 stations by location. In gastric cancer, all nodes should be retrieved from the en bloc resection specimen and examined to detect metastases, because even small, apparently normal nodes sometimes contain metastases as 26.4% of the nodes less than 5mm were found to contain metastases in 3141 metastatic nodes [1].

From perigastric to paraaortic nodes, the regional lymph nodes are classified into 16 stations (Table 1).

The location of a gastric tumour can be precisely determined before operation by endoscopy with or without barium meal study. Intraoperative lymphography has enabled surgeons to recognize the anatomical structure of the lymphatic system and to perform a precise lymphadenectomy. The dye in the nodes also makes the postoperative nodal retrieval by surgeons or pathologists easy [11]. Intraoperative injections of radioisotopes were tested and proved efficient [12].

The solution of activated carbon particles CH40 developed by Hagiwara et al. [11] showed high affinity with lymphatic tissue and remained in nodes for a long time. A direct injection of CH40 to a perigastric node immediately visualized the lymphatic channels and connected nodes.

Sano [12] studied the location of the first metastasis from small gastric cancers and he found that in 62%, the single positive node was located in the perigastric area close to the primary tumour and in 13%, the node was in N2 area without involvement of N1 nodes, indicating that the blind examination of the nodal area close to the primary tumour cannot be a reliable method to detect the first metastasis [12].

Systematic lymph node (D2) dissection is very effective for treatment of lymph node metastasis. The lymph node dissection technique is based on the studies of lymphatic flow, incidence of metastasis and benefit in survival. Table (1) shows the number and the anatomical name of regional lymph nodes and N categories (N1, N2, N3) for each primary gastric cancer located in the upper (U), middle (M), lower thirds (L) and whole stomach. Standard lymph node dissection (D2) is the removal of all lymph node groups of N1 and N2.

A minority of Western surgeons followed the Japanese strategy of extended lymph node dissection and in the late 1980s, several specialized centres in the West started to report a significant benefit from extended lymphadenoctomy over conventional limited resection (even more limited than D1 dissection). They reported that postoperative mortality after D2 dissection did not increase and was 3-5% [14,15,16].

Sasako and associates [17] estimated the incidence of metastasis and the 5-year survival rates of the patients with positive nodes station by station, according to the tumour location in 1281 potentially curable advanced gastric carcinomas. They found that the incidence of me-

tastasis ranged from 2.4% to 66% according to T stage. The 5-year survival rate of affected patients from 0 to 58.7% in perigastric stations (N1) Japanese staging. The incidence of metastasis was between 3.0% and 44.4% in the second tier nodes (N2) according to T stage and the 5-year survival rate ranged from 0% to 47.5% [17]. Even in the presence of advanced gastric cancer cases with high incidence of lymph nodes in the second tier nodes, there was fair prognosis following D2 dissection [1].

So the systematic LN dissection is the most effective procedures in the surgical treatment of gastric cancer. However, this treatment is not indicated for patients with distant metastasis. In addition, it does not increase postoperative mortality or morbidity. Even if it will not increase the survival for the individual, it will definitely improve classification with subsequent staging, which is a necessity if any future adjuvant treatment is to be evaluated [17]. The minimal requirement for radical gastric resection is to completely remove the N1 and N2 lymph nodes [18].

PATIENTS AND METHODS

This prospective single arm study included 33 patients with gastric carcinoma treated by D2 surgical resection at NCI Cairo University and SECI Assiut University and Aswan Cancer Center between Oct. 1999 and Sep 2001. Their results were compared to the results of a group of patients with gastric cancer treated at NCI before 1998 with curative resection [19].

Operative procedure:

The patients were subjected to surgical exploration and radical gastrectomy (total or subtotal), with systematic lymph node dissection: (D2 dissection) as described by the Japanese Research Society for Gastric Cancer (JRSGC, 1998) [20] following the steps of Van De Veled and Sasaco [21].

1- Exploration was performed to exclude metastatic disease and to assess site and extent of the tumour.

2- Injection of 0.5 ml of the black contrast medium (CH-40) India ink, in the subserosa of the tumour vicinity and in perigastric nodes along the greater and lesser curvatures was done. This demonstrates clearly lymphatic vessels and nodes which are stained black in one minute. This facilitates systematic lymph node dissection and is described as a routine in the Japanese technique of D2 gastrectomy (Figs. 1,2).

3- Mobilization of the duodenum: (Kochers procedure). The duodenum, starting by the second part and the pancereatic head are mobilized until the left margin of the aorta is recognized.

4- Dissection of the greater omentum and excision of the anterior layer of the transverse mesocolon.

5- Dissection of lymph nodes at the root of the mesentry by freeing the pancereatic capsule from the inferior margin of the pancereatic body to the anterior aspect exposing the superior mesenteric vein (SMV) and dissecting lymph nodes around (Fig. 3).

6- Dissection of infrapyloric nodes (no 6): The trunk of the gastrocolic vein is exposed and the lymph nodes along it are dissected and the right gastroepiploic vein and artery are ligated and cut. Continuous dissection is performed from the anterior layer of the mesocolon to upper margain of pancreatic capsule exposing the common hepatic artery and the lymph nodes in the anterosuperior group (Fig. 4).

7- The lymph nodes are freed along the upper margin of the pancreas, Then, subpyloric lymph nodes and lymph nodes of the greater curvature are completely dissected with the greater omentum. And the lymph nodes behind the pylorus and anterior to the head of the pancreas are dissected (Fig. 5).

8- Dissection of the lymph nodes at the anterior aspects of the hepatoduodenal ligament with ablation of the lesser omentum, as close as possible to the point of attachment with the liver exposing the right gastric artery that is ligated, The accompanying lymph nodes were stripped with it. (Suprapyloric nodes) (Fig. 6).

9- Dissection of the lymph nodes in the hepatoduodenal ligament (no. 12a) was carried out along its left wall and the connective tissue around the hepatic artery is dissected (Fig. 7).

10- Transection of the duodenum was done using a GIA stapler or between noncrushing clamps.

11- Transection of the lesser omentum: from

the point of attachement to the liver, as far as the lower margin of the esophagus was done.

12- Dissection of the lymph nodes anterosuperior to the common hepatic artery (No. 8a) (Fig. 7): The lymph nodes of the anterosuperior group along the common hepatic artery with the connective tissue at the root of the gastroduodenal artery and around the trunk of the common hepatic artery was performed and the coronary vein ligated and cut.

13- Dissection of lymph nodes along the bile duct behind the hepatoduodenal ligament was carried out through an incision made from Winslow's foramen (Fig. 7).

14- Dissection of the area around the celiac artery (N9): Dissection was continued in the direction of the base of the common hepatic artery and from the right side of the celiac artery towards the root of the left gastric artery with dissection of lymph nodes around them (Fig. 8).

15- Dissection of the lymph nodes along the trunk of the splenic artery (N 11) was then carried out.

16- Dissection of the right cardial lymph nodes and the lymph nodes along the lesser curvature was done (Fig 9).

17- The greater omentum was incised from the splenic flexure through the inferior splenic margin to the greater curvature of the stomach (Fig. 10).

18- Procedures for proximal tumours or tumours recquiring total gastrectomy with either mobilisation and preservation of the spleen or with splenectomy and pancereas preserving gastrectomy (PPG), avoiding pancereatectomy with removal of no. 10 and 11 nodes.

Pathological study: The surgical specimen was examined pathologically, grossly and microscopically for tumour site, size, histological type, grade, tumour invasion, surgical margin, number of lymph nodes excised and the number and groups of nodes involved by metastasis (Fig. 11).

Follow up of the patients and evaluation of prognostic factors and contrast medium:

After surgery all the patients were followed up to detect early and delayed post operative complications. Regular follow up was continued to detect locoregional failure, distant metastasis and survival. The different prognostic indicators were studied using univariate and multivariate analysis. The value of intraoperative use of the black contrast medium in the demonstration of the lymphatic system and lymph nodes was also studied.

The data of this study was compared to data of another series performed before 1998 in the NCI [19].

RESULTS

This prospective study included 33 patients. Their mean age was 53.0 years (range, 27-83), with peak incidence (60.6%) between 40-60 years. There was a slight male predominance 54.5%. The majority (63.6%) suffered from dyspepsia, (27.3%) from pain and (6%) from general symptoms as loss of weight and appetite and (3%) from haemtemsis.

Fifty one percent of the lesions were located at the distal two thirds of the stomach. However, upper third lesions represented 45.5% and there was only one case (3%) in which the tumour involved the whole stomach.

The mean size of the tumours was 5.5 cm (range 2-11). The most common histological type was adenocarcinoma (60.6%) followed by signet ring carcinoma (24%) and undifferentiated carcinoma (12%). There was only one case that showed squamous cell carcinoma (3%). Grade 3 was detected in 63.6% of cases and grade 2 in 30.3%, grade 1 in 6%. According to the TNM staging, T3 represented 48.5% of the cases, T4 (27.3%) and T2 (18.2%) of the cases. Lymph node metastasis were found in 66.7% of the patients. N stage was estimated according to both the Japanese Research Society of gastric cancer system (site) and the UICC TNM system. According to the Japanese system: 33.3% of patients were N0, 36.4% were N1 and 30.3% were N2 there were no N3 cases. According to the UICC TNM (N) stage: 33.3% of the patients were N0, 51.5% were N1, 12.1% were N2 and 3.1% were N3.

According to the UICC TNM stage classification (1997) 33.3% were stage IIIa, 24.2% stage II, 18.2% stage IV, 12.1% stage IIIb, 6.1% for stage Ia and 6.1% for stage Ib. The average

number of resected and involved lymph nodes for each patient was 18.7 (11-45) and 3.5 (0-21) respectively.

The calculated ratio of involved to resected lymph nodes expressed as percentage was categorized into 4 groups 0, 30%, 30-50% and > 50% was as follows: (0%) in 33.3% of cases, (30%) in 36.4% of cases, (30-50%) in 12.1% of cases and (> 50%) in 15.2% of cases.

Serosal invasion was detected in 57.6% of the cases.

Radical resection (D2 Gastrectomy) with extended lymphadenectomy, was performed in all cases, the extent of gastric resection varied from a distal gastrectomy in 39.4% of the cases, total gastrectomy in 36.4% and proximal gastrectomy in 24.2% of the cases. Combined resection of adjacent organs was performed in 63.6%; splenectomy in 36.4%, splenectomy and hiatal resection of the diaphragm in 12%, pancereaticosplenectomy 9%, hepatic resection in one case and colectomy in one case (3%).

The reconstruction method was Billroth II gastrojeujenostomy in 33.4%, oesophagogastrostomy in 27.3%, Rue-en-Y in 27.3% and Billroth I gastroduodenostomy in 6% and oesophagojeujenostomy in 6% of cases for each type. The mean operative time was 3.9 hours and mean blood loss was 404.5 ml. Curability of the resection was A in 69.7% of cases and B in 30.3% of cases.

Intraoperative lymphography was done in 30 cases and staining of further lymph node stations was evaluated and graded as: poor (-) in 5 cases (16.7%) average (+) in 3 cases (10%) and good (++) in 22 cases (73.3%).

Operative morbidity was 15%, mostly due to anastomotic leakage and abscess. Operative mortality was 3% (only one patient died of massive pulmonary embolism).

The two year overall survival (OS) rate for patients in this study was 43.6% and disease free survival (DFS) was 42.5% Fig. (12).

The survival rates according to the UICC TNM staging was 68% for stages I and II (grouped together), 38% for stage III and 0% for stage IV.

Univariate analysis:

The results of univariate analysis were summarized in Table (2).

Serosal invasion, curability of resection, combined resection, number of resected lymph nodes and depth of invasion were the most significant variables ($p < 0.02$) clinico - pathological variables were studied for two year (DFS) disease free survival. Age and sex did not show prognostic significance in this study in univariate analysis.

Tumor histology, tumor location, number of resected lymph nodes, presence of lymph node metastasis, ratio of involved to resected lymph nodes, N stage in the Japanese staging system (JRSGC, 1998), type of operation, UICC stage and operative blood loss had prognostic significance on univariate analysis.

Most of the tumors were located in the distal two thirds of the stomach. Patients with tumors in the distal stomach showed better survival (70%) than patients with tumors of the middle and upper third (50% and 20%) ($p = 0.028$) (Table 2, Fig. 13).

Tumor histology was a significant prognostic variable ($p = 0.04$), where the two year disease free survival for well and moderately differentiated adenocarcinoma cases was 42%. Tumors with signet ring carcinoma showed survival of 18% while there were only 4 cases with undifferentiated histology, those showed a 2 year survival of 90% (Table 2, Fig. 14).

Depth of invasion of the gastric wall showed significance in univariate analysis when T1 and T2 were grouped together due to the small number of cases, also T3 and T4 were grouped together. The two year disease free survival for T1 and T2 group was 70% and for T3 and T4 group was 34%, this difference was statistically significant ($p = 0.02$) (Table 2, Fig. 15).

Serosal invasion was the most significant prognostic variable in univariate analysis ($p = 0.001$). Patients with no serosal invasion had a much better two year disease free survival than those with serosal invasion, 73% versus 19% respectively (Table 2, Fig. 16).

The two year disease free survival was related to presence of lymph node metastasis, the number of metastatic nodes: (UICC, N stage),

the level of lymph node metastasis (N stage by the Japanese staging system), the number of resected lymph nodes and the ratio of involved to resected lymph nodes.

The number of resected lymph nodes was the most significant variable on univariate analysis where the 2 year disease free survival was 59% when 15 or more lymph nodes were resected while it was only 11% in cases in whom less than 15 nodes were resected, this was statistically significant ($p = 0.009$) (Table 2, Fig. 17).

The UICC (TNM) N stage did not show significance on univariate analysis ($p = 0.09$). The presence of metastatic lymph nodes was associated with worse prognosis ($p = 0.014$). Patients with lymph node metastasis had a survival of 29% and those with no lymph node metastasis had a survival of 78% (Table 2, Fig. 18).

Patients were divided into four groups according to the ratio of involved to resected lymph nodes: 0, < 0.3, 0.3-0.5, > 0.5. The two year disease free survival rates were 78% for patients with a ratio of 0, 35% for those patients with a ratio less than 0.3, 25% for those with a ratio between 0.3 and 0.5, 18% for patients with a ratio of more than 0.5. these results were statistically significant ($p < 0.04$) (Table 2, Fig. 19).

The level of lymph node metastasis expressed here by the Japanese staging system was of value on survival. Patients with N0 had a two year disease free survival of 78%, patients with N1 stage 40% and those with N2 stage 0% (at 14 months). These results were statistically significant ($p = 0.04$) (Table 2, Fig. 20).

The two year disease free survival rates according to the extent of resection (type of operation) were 73% for distal gastrectomy, 28% for total gatrectomy and 15% for proximal gastrectomy (Table 2, Fig. 21).

Combined resection of adjacent organs was performed in 63.6% of cases. There was a significant difference in survival between cases with and without combined resection ($p = 0.004$). The two year disease free survivals rates were 91% for cases without combined resection and 19% for cases in which combined resection was performed (Table 2, Fig. 22).

The two year disease free survival rates were 60% for patients in whom a resection (A) was performed and 0% (at 14 months) in patients in whom a resection (B) was performed Fig. (23).

The two year disease free survivals were 68% for stages (I and II), 38% for stage III and 0% (at 8 months) for stage IV ($p = 0.02$) (Table 2, Fig. 24).

In this study age, sex, presenting symptom, tumour size and morbidity, did not show survival significance by univariate analysis.

Multivariate analysis:

Multivariate analysis using treatment outcome as the dependent variable, showed that serosal invasion, N stage by the Japanese classification (JRSGC, 1998) **[20]**, tumour location and histology had statistical influence.

Sex, age, tumour size, type of oepration, combined resection, curability of resection, depth of invasion (T stage), number of resected lymph nodes with (UICC "N" stage), lymph node metastasis, ratio of involved to resected nodes, tumour grade were not proven as independent prognostic factors by multivariate analysis.

Results of lymphography:

In this study the use of intraoperative lymphography using (CH-40) fine activated carbon particle solution, to facilitate an extended lymphadenectomy was evaluated. Lymphography was related to the number of retrieved nodes, and positive nodes. More than 15 lymph nodes were resected in 19 (90%) of cases that showed good staining, in only 2 (67%) of cases in whom staining was average and in 3 (60%) of cases in whom staining was poor. Also all cases with average and poor staining were associated with lymph node metastasis but only 44% of cases with good staining had lymph node metastasis. This was probably due to obstruction of the lymphatics by tumour emboli preventing spread of the dye and limiting its value.

Comparing our results with D2 dissection to a historical group of 97 patients with gastric cancer treated with curative resection in the NCI before 1998 **[19]** we found the following in the historical group:

The tumours were located in the distal third of the stomach in most of the cases 46.4%, proximal tumours were in 19.6% of cases, middle third tumours were present in 16.4%.

The operative procedures were: distal gastrectomy in 33% of cases, total gastrectomy in 27.8% and proximal gastrectomy in 13.4%. Exploration only was done in 25 cases which were either irresectable or metastatic cases. Combined resection of other organs was performed in 39% of cases (52.8% of resected cases) most of these comprised a splenectomy alone in 33% pancereaticosplenectomy in 3% only and splenectomy and colectomy in 3%.

The incidence of a positive surgical margin: was 17.5% of all cases (23.6% of resected cases). That was quite high compared to 3% in our prospective study.

Operative mortality was 14.5% of all cases and 18.5% of resected cases. Morbidity was also around 14% of all cases and 23.7% of resected cases.

The mean number of resected lymph nodes was 4 with a minimum of 0 and a maximum of 26. Some forms of limited lymphadenectomy were performed in only 56 cases (57.7% of all cases and 77.7% of resected cases). The mean number of positive lymph nodes was 4 and the mean ratio of involved to resected lymph nodes was 0.47.

Metastatic lymph nodes were detected in 71.4% of the performed lymphadenectomy and the N staging (UICC TNM) was N0 in 28.5%, N1 in 48.2% and N2 in 23.2% of cases performing lymphadenectomy.

Survival analysis showed that the 2 year overall and disease free survivals were 31.5% and 28.8% respectively while the five year overall and disease free survivals were 27.1% and 26.9% respectively Fig (25).

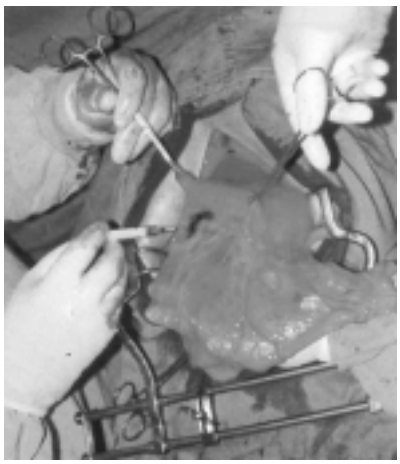

Fig. (1): Injection of the dye (CH-40).

Fig. (2): After injection of the dye.

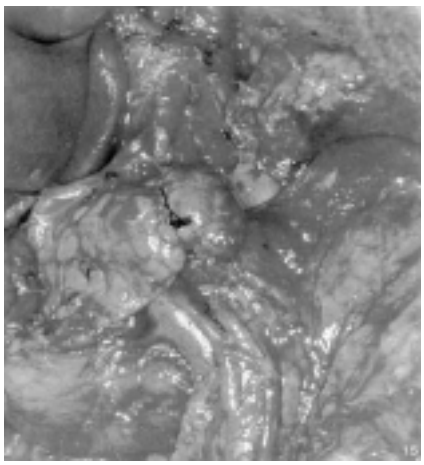

Fig. (3): Location 14 (Root of mesentery after dissection).

Fig. (4): Stained nodes along the common hepatic artery (Gp. 8).

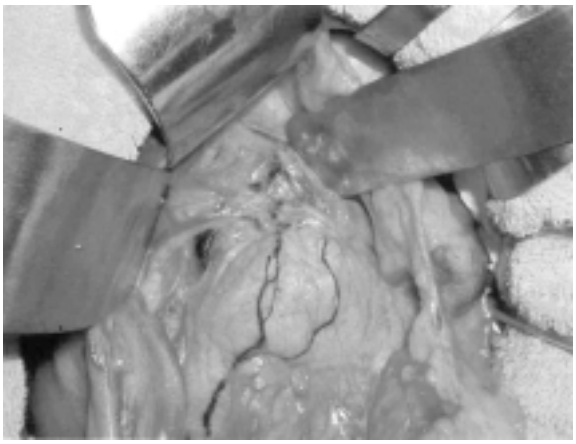

Fig. (5): Stained lymphatics and suprapancreatic nodes.

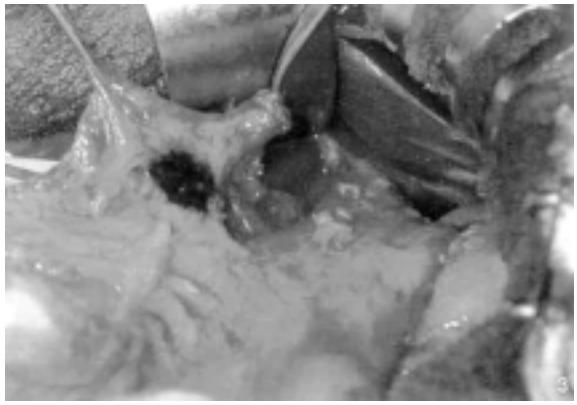

Fig. (6): Location 5 and lesser omentum dissected.

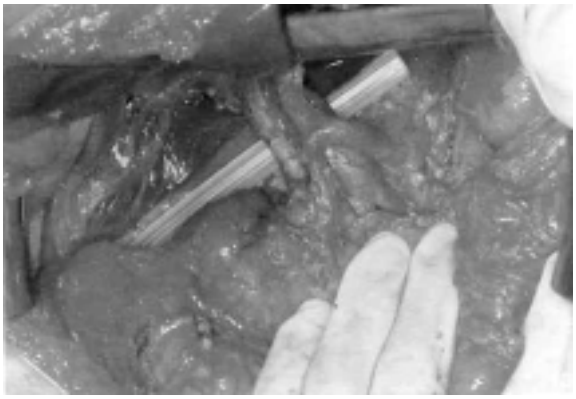

Fig. (7): Hepatoduodenal ligament after dissection.

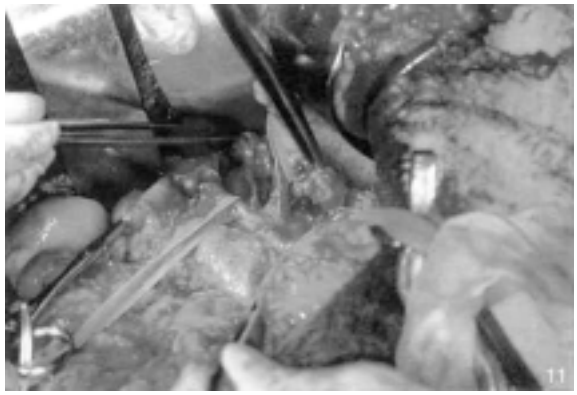

Fig. (8): Location 7,8 and 9 after dissection.

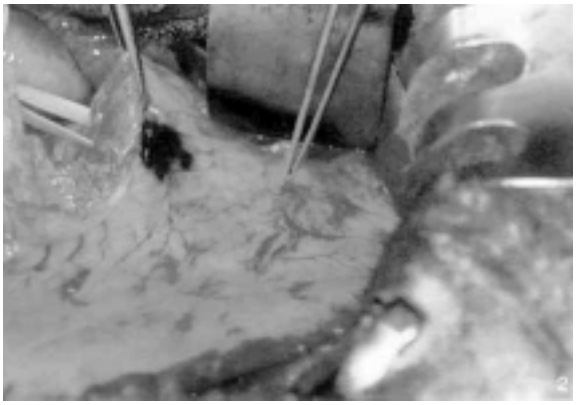

Fig. (9): Location 1 (Rt cardial nodes).

Fig. (10): Dissection of location 4 sb and 4d (LT & RT) gastroepiploic lymph nodes.

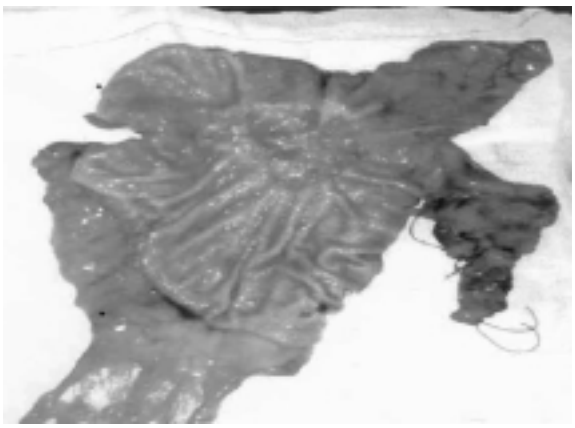

Fig. (11): Open specimen of distal gastrectomy showing the tumour, stained lymphatics and nodes.

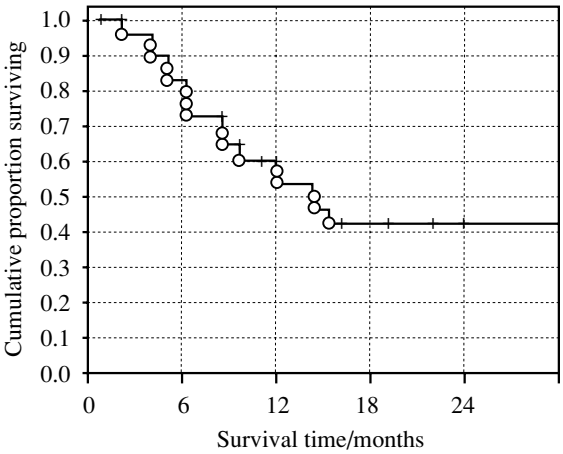

Fig. (12): DFS among the whole group.

○ Complete + Censored
DFS = 42.5 SE = 9.6

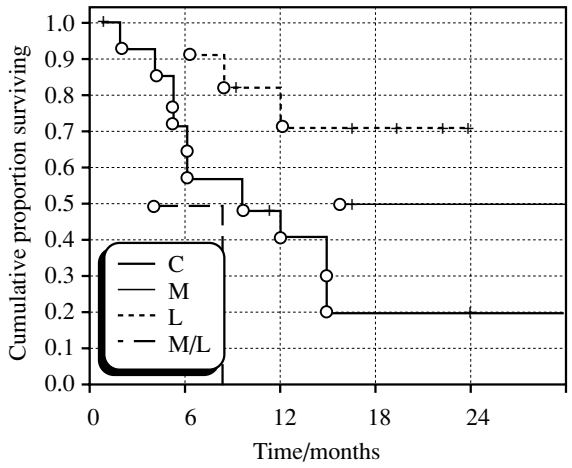

Fig. (13): DFS in relation to site.

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p value = 0.028*

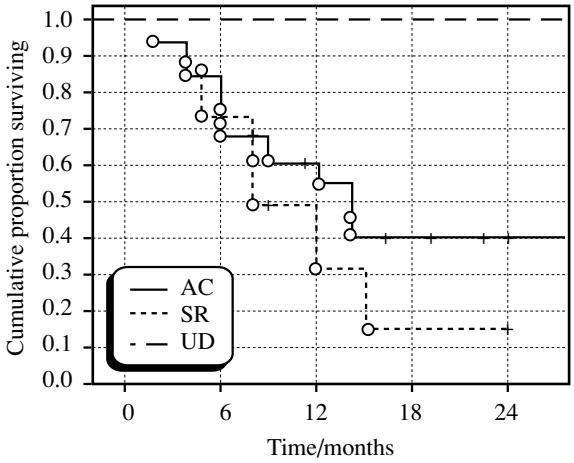

Fig. (14): DFS in relation to histopathology.

○ Complete + Censored
p value = 0.04*

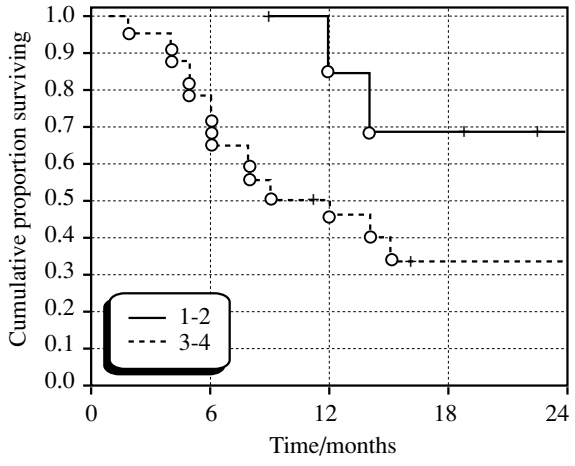

Fig. (15): DFS in relation to T stage.

○ Complete + Censored
p value = 0.023

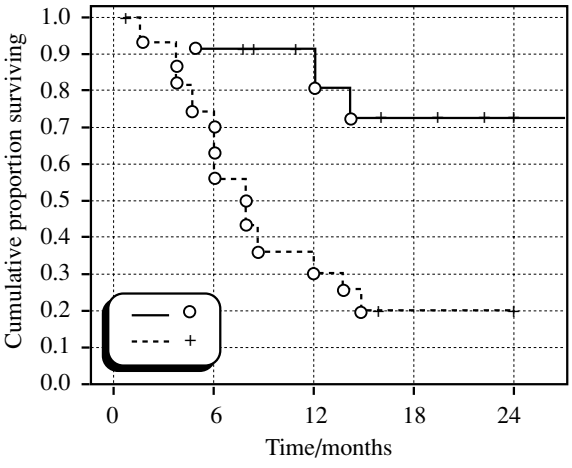

Fig. (16): DFS in relation to serosal invasion.

○ Complete + Censored
p value = 0.0019*

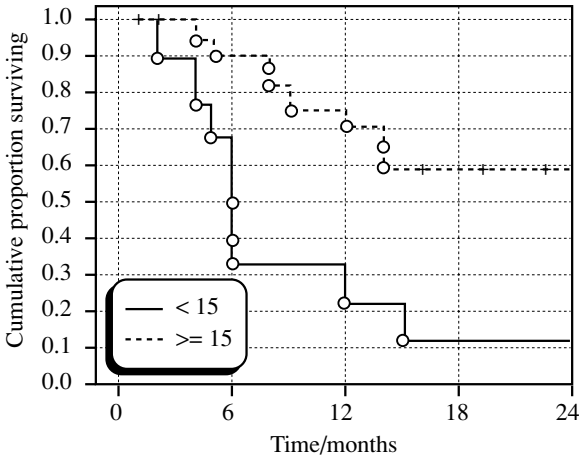

Fig. (17): DFS in relation to number of resected nodes.

○ Complete + Censored
p value = 0.009**

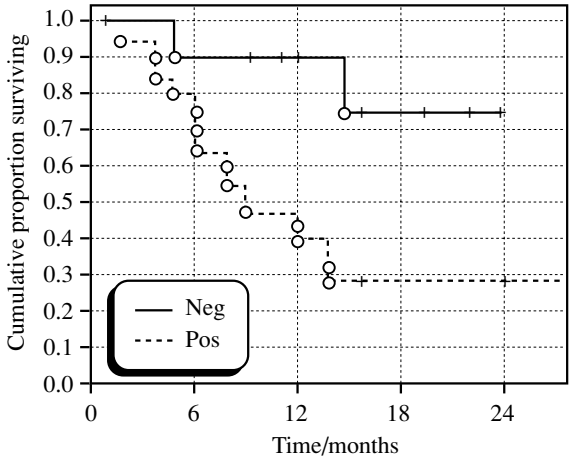

Fig. (18): DFS in relation to lymph nodes.

○ Complete + Censored
p value = 0.014*

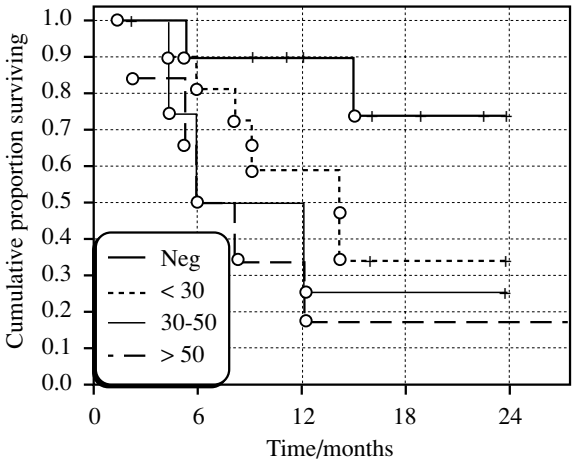

Fig. (19): DFS in relation to nodes ratio.

○ Complete + Censored
p value = 0.049*

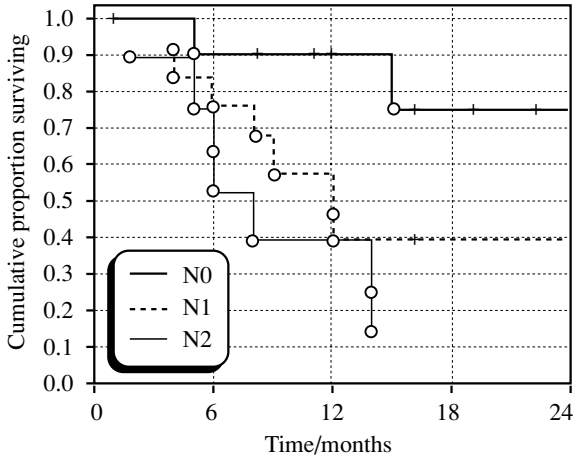

Fig. (20): DFS in relation to N stage.

○ Complete + Censored
p value = 0.04*

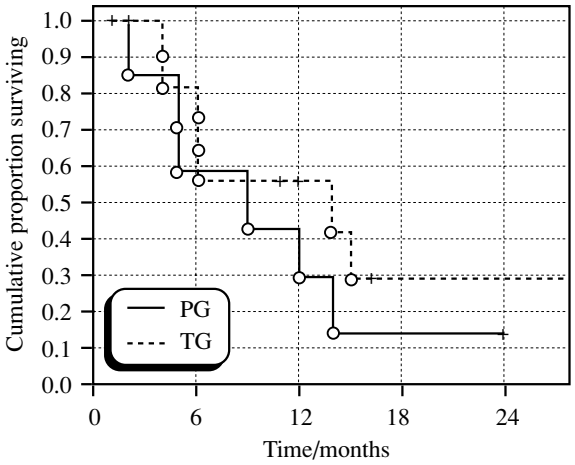

Fig. (21): DFS in relation to operation type.

○ Complete + Censored
p value = 0.35

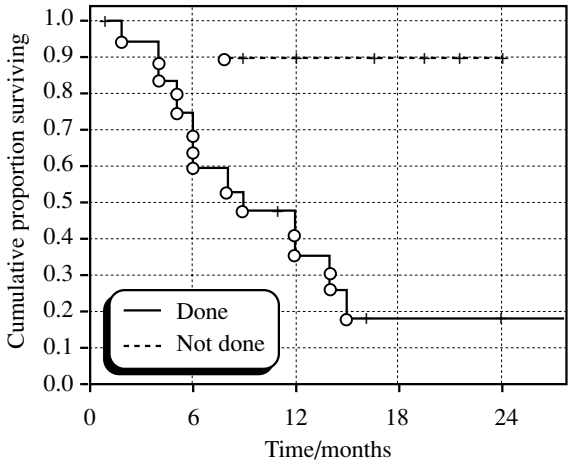

Fig. (22): DFS in relation to combined resection.

○ Complete + Censored
p value = 0.004**

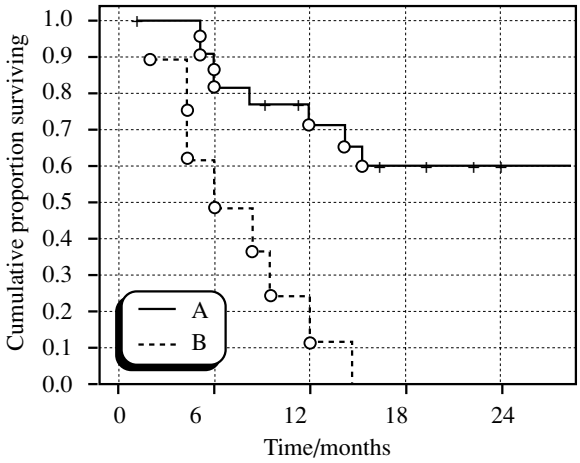

Fig. (23): DFS in relation to curability of resection.

○ Complete + Censored
p value = 0.002**

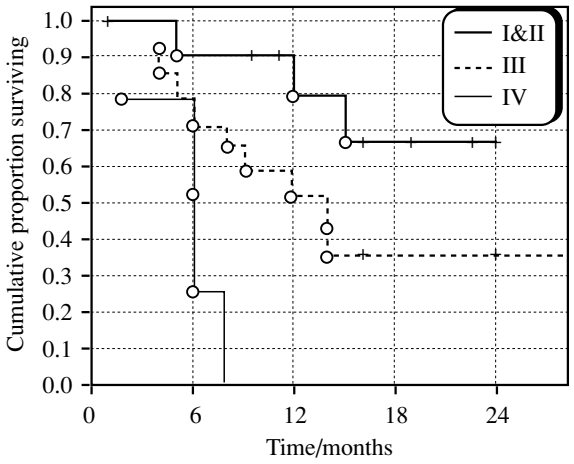

Fig. (24): DFS in relation to stage.

○ Complete + Censored
p value = 0.02*

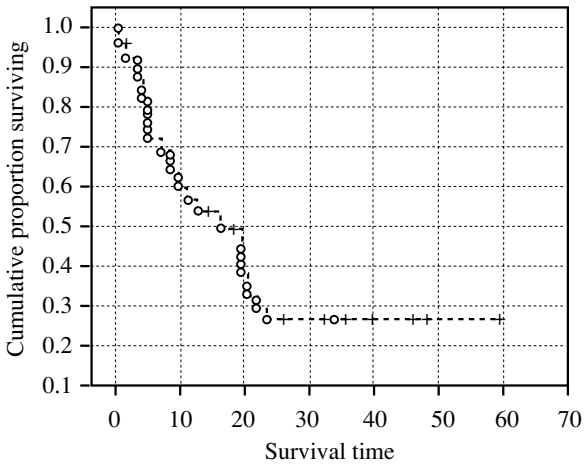

Fig. (25): DFS among the historical group.
DFS = 27.1% after 24 month and 26.9% after 60 month.

Table (1): Lymph node stations and staging.

LN station number	Location				
	LMU/ MUL MLU/ UML	LD/ L	LM/ M/ML	MU/ UM	U
1 Rt paracardial	1	2	1	1	1
2 Lt paracardial	1	M	3	1	1
3 Lesser curaveature	1	1	1	1	1
4sa Short gastric	1	M	3	1	1
4sb L.gastroepiploic	1	3	1	1	1
4d R.gastroepiploic	1	1	1	1	2
5 Surapyloric	1	1	1	1	3
6 Infrapyloric	1	1	1	1	3
7 Lt gastric	2	2	2	2	2
8a Ant. Com. Hep.	2	2	2	2	2
8b Post. Com. Hep.	3	3	3	3	3
9 Celiac artery	2	2	2	2	2
10 Splenic hilum	2	M	3	2	2
11p Prox. splenic	2	2	2	2	2
11d Distal splenic	2	M	3	2	2
12a Lt hep. duod.	2	2	2	2	3
12b, p Post-hep. duod.	3	3	3	3	3
13 Retropancreatic	3	3	3	M	M
14v Sup. mes. v.	2	2	3	3	M
14a Sup. mes. a.	M	M	M	M	M
15 Middle colic	M	M	M	M	M
16a1 Aortic hiatus	M	M	M	M	M
16a2, b1 Paraaortic middle	3	3	3	3	3
16b2 Paraaor caudal	M	M	M	M	M

Adopted from Japanese classification of gastric carcinoma (1995), (1st edn) **[9]** and the Japanese Research Society for Gastric cancer. (JGCA, 19998) **[10]**. M = Metastasis.

Table (2): Univariate analysis of clinicopathologic variables.

Variable	2-YSR (%)	*p* value	Variable	2-YSR (%)	*p* value
Age (years):		0.7	*Serosal invasion:*		0.0019*
< 40	0 at 1 year		(–)	73	
40-60	45		(+)	20	
≥ 60	50		*(T) Depth of invasion:*		0.006*
Sex:		0.46	Mucosa T1	60	
Male	31		Submucosa T1		
Female	52		Muscle T2	43	
UICC stage:		0.02*	Subserosa T3	15	
I&II	68		Serosa T4	0	
III	39		Adj. Organ T4		
IV	0 at 8 mons.		*No. of res LN:*		0.009*
Location:		0.028*	< 15	11	
Lower 1/3	73		≥ 15	58	
Mid 1/3	50		*No. of inv. LN (N):*		< 0.04*
Upper 1/3	21		0	78	
Extent of op:		0.035*	1-6	30	
PG	16		7-15	25	
TG	28		> 15	0	
DG	74		*LN status:*		0.014*
Combined resection:		0.004*	(+)	78	
(–)	91		(–)	28	
(+)	19		*Curability of resection:*		0.002*
Tumour size:		0.46	A	60	
2-5 cm	70		B	0 at 14 mons.	
> 5 cm	28		*Histology:*		0.04*
Ratio of inv to res LN:		0.049*	AG (G2)	45	
0	78		Signet ring	35	
≤ 0.3	60		*Reconst:*		0.04*
≤ 0.3	26		R-Y	33	
> 0.5	18		OG	11	
			Bill 1	68	

* *p* value < 0.05 (significant).

PG, TG, DG: Proximal, total and distal gastrectoy; adj.: Adjacent; inv.: Involved; res.: Resected; 2-YSR: 2-year survival rate; LN: Lymph nodes; mons.: Months; R-Y: Rue-en-Y; OG: Oesophago-gastrostomy; AC: Adenocarcinoma; Bill: Billroth.

DISCUSSION

Results of surgery in gastric cancer has markedly improved with 5 year survival rates between 50% and 60% in eastern studies **[22,24,25]**, this is in contrast to the still poor results in most western studies (< 20%) **[8,26,27]**. Potential reasons for improved survival in Japan and eastern sutudies include earlier diagnosis, a more aggressive operative approach and possible different biological charactrestics **[25,28]**.

This study showed that serosal invasion, depth of invasion of the gastric wall (T stage), curability of resection, combined resection, number of resected nodes, lymph node metastasis, ratio of involved to resected lymph nodes and level of lymph node metastasis: (N stage in the Japanese staging) were the most significant prognostic factors by univariate analysis. Also tumour location, tumour histology, UICC stage and type of operation were significant by univariate analysis Table (2).

Independent prognostic factors identified by multivariate analysis of the clinicopathological variables were serosal invasion, level of lymph node metastasis: (N stage in the Japanese Classification), tumour location and tumour histology.

In this study, proximal tumours represented 45% of cases which is a quite high proportion, especially when compared to the previous study in NCI **[19]** where proximal tumours represented 19.6% of the cases. But the proportion of distal

tumours didn't show a significant difference: 39% in this study and 46.4% in the retrospective data. The two year disease free survival was much poorer in proximal tumours 20% compared to 72% for distal tumours and 50% for mid third tumours. This was statistically significant by univariate analysis ($p = 0.02$) (Table 2, Fig. 13). Also tumour location was an independent prognostic factor by multivariate analysis. Several reports supported these observations **[22,25,29]**.

In the present study depth of invasion was a significant prognostic factor by univariate analysis after grouping T1 and T2 stages together due to the small number of cases in each. Also T3 and T4 were grouped together. As almost 50% of our cases were T3 tumours and incidence of EGC was 6% (2 cases), which did not differ significantly from previous reports where incidence EGC was reported to be 4% in a study performed in the NCI (1996) **[30]**. The two year disease free survival rates for (T1+T2) group and (T3+T4) group were 70% and 34% respectively, (Fig. 15). These observations showed the problem of advanced disease at presentation and the need for early diagnosis to improve the results. The results of advanced tumours are almost similar to the other reports. The depth of tumour invasion in the gastric wall expressed as T stage in both the UICC (TNM) and JRSGC staging system was reported as an important prognostic factor by both univariate and multivariate analysis in many studies **[1,25,29,31]**.

Serosal invasion was a highly significant prognostic factor using both univariate and multivariate analysis. The two year disease free survival rates for cases with and without serosal invasion were 73% and 19% respectively ($p = 0.0019$), (Table 2 Fig. 16). This was reported by other authors **[2,18,25]**.

In this study curability of resection was a highly significant prognostic factor ($p = 0.002$), (Table 2, Fig. 23). 68.2% of cases had a curative resection A or (R0: UICC), 31.8% had a resection B or (R1: UICC). Curative resection is defined as a complete tumour removal with adequate margins of clearance and lymphatic drainage **[25]**. Cases with resection A had a much better two year disease free survival rate than cases with resection B: 60% for cases with resection A versus 0% with resection B. This is supported by other studies **[25,33]**. In this study combined resection of adjacent organs was performed in 63.6%, most of these cases underwent splenectomy alone, 5 cases performed (15%) pancereaticosplenectomy.

In the present study the two year disease free survival rates were 19% in cases associated with combined resection and 91% in cases without combined resection, this was statistically significant by univariate analysis ($p = 0.004$), (Table 2, Fig. 22). Some reports showed better survival rates after gastrectomy without splenectomy than with splenectomy **[1,2,4,35]**. In two prospective trials for D2 dissection in Netherland and England, the post operative morbidity and mortality were significantly high in patients who underwent total gastrectomy and pancreaticosplenectomy than those who didn"t have combined resection **[36,37]**. In the Dutch trial, splenectomy showed higher risk of operative mortality higher than D2 dissection **[38]**. The indications of splenectomy include tumour invasion, enablity to remove hilar or splenic nodes and splenic injury **[35-38]**.

Extent of gastric resection showed some significance as a prognostic factor on univariate analysis in this study, with $p = 0.035$ (Table 2, Fig. 13). Distal gastrectomy had a two year survival of (73%) which was much better than total gastrectomy (28%). Proximal gastrectomy showed the worst survival (15%), this may be due to the already worse survival for proximal tumours as reported in other studies **[2,15,25]**.

In the present study we performed a D2 radical gastrectomy removing N1 and N2 groups in the 33 cases, the mean number of resected lymph nodes was 18.7 range (11-45). The number of resected nodes was a highly significant prognostic factor ($p = 0.009$), (Table 2, Fig. 17). Patients in whom 15 or more lymph nodes were resected had a much better survival than those in whom less than 15 lymph nodes were resected: 59% versus 11%. These results support the Japanese reports that D2 extended lymph node dissection should be the standard treatment for gastric cancer. There have been controversies over the value of extended lymph node dissection for the treatment of gastric cancer. Japanese literature supports the survival benefit of extended lymph node dissection (D2). The results of curatively treated cases (cases treated by a radical D2 gastrectomy show much better sur-

vival even in N2 cases and 5 year survival may reach above 60% [1].

Several reports from outside Japan supported this view. In 1998, Kim and Colleagues from Korea, stated that curative gastric resection with extended lymphadenectomy contributed to improved survival, and dissection of more than 25 lymph nodes had a survival benefit in patients with stage II and IIIa disease. They limited the value of extended lymph node dissection to stage II and IIIa which may be quite reasonable to exclude early and advanced cases in whom lymph node dissection may not have a strong influence on survival [25].

In this study the operative morbidity was 15% mainly in the form of anastomotic leak. The thirty day hospital mortality was 3% which was quite acceptable especially when compared to the previous study in the NCI [19] where morbidity was 23.7% and mortality was allmost 18.5%. Extended lymph node dissection D2 was not performed in the later study. The mean number of resected nodes was 8.8. The overall and disease free survival rates for the prospective study were 43.6% and 42.5% respectively which is much better than in the historical study, where overall and disease free survival rates were 31.5% and 28.8% after 2 years and 27.1% and 26.9% respectively after 5 year of follow up. Figs. (12,25).

The reported mortality and morbidity in Japanese studies were much less than in Western Literature. Reports from the Japanese Research Society for gastric cancer showed mortality of 1.2% for D2 versus 1.8% and 2.2% for D1 and D3 respectively [29]. Recent reports showed mortality around 1% [33]. Morbidity was reported between 1-10%, where anastomotic leakage ranged around 7% and pancereatic fistula 6%, other complications were much less common, around 1-2% each [2]. Other reports from non Japanese centres advocating the D2 extended lymphadenectomy, reported that mortality after D2 dissection did not increase and was 3-5% [14,15].

In 2001. Yildrim and Colleagues, conducted a retrospective cohort study in patients undergoing curative D1 or D2 gastrectomy for operable gastric carcinoma in Turkey. Mortality rates were 3.1% in the D1 group and 4.3% in the D2 group, while morbidity rates were 6.2% and 27.9% for D1 and D2 groups respectively. The 5 year disease free and overall survival rates were 19% and 36% in D1 and 49% and 54% in D2 respectively. This study concluded that D2 dissection can be carried out with low mortality but with high morbidity and a survival benefit over D1 of 18% [40].

In the United Kingdom, the Medical Research Council (MRC) conducted a trial for D2 gastrectomy. Postoperative morbidity was significantly greater in the D2 group (46% vs. 28%; $p < 0.001$). Hospital mortality was an alarming 13% for the D2 group and 6% for D1 ($p < 0.04$). The excess morbidity and mortality seen in the D2 group was associated with the routine use of distal pancreatectomy and splenectomy [36].

The Dutch Gastric Cancer Group conducted a subsequent larger trial on 711 patients (380 in D1 group and 331 in D2 group). The postoperative morbidity was again higher in the D2 group (43% vs. 25%, $p < 0.001$). The mortality rate also was significantly higher in the D2 group (10% vs. 4%, $p = 0.004$) [32]. Long-term results could not show any significant difference in survival between the two treatments as the 5-year survival rates of the D2 and D1 groups were 45% and 47%, respectively. Disease-free survival rates of the patients who had R0 resection were 57% and 63% after D1 and D2 dissection, respectively [37].

In another study from Hong Kong, Hayes and colleages reported morbidity of 50% and perioperaive mortality of 5% for radical gastrectomy with extended lymphadenectomy. Survival was predicted by tumour stage, where patients without serosal invasion showed a 5 year survival rate of 64% and those with serosal invasion survival was 10% [41]. These results are close to the results of the present study relating survival to serosal invasion, where two year survival was 73% and 19% for patients without and with serosal invasion respectively. Morbidity in our study was much less (15%), compared to the morbidity reported by Hayes and Colleagues (50%) [41].

Lymph node metastasis proved to be a segnificant prognostic factor when expressed in the form of the ratio of involved to resected lymph nodes ($p = 0.04$) and lymph node status (positive or negative) and N stage (JRSGC).

The relevance of lymph node metastasis did not depend on the number of positive nodes when grouped according to the UICC TNM (N staging) in the present study. Other reports suggesed that staging of lymph node metastasis should be based on the number of involved lymph nodes **[41,42]**.

The ratio of involved to resected nodes proved to be a significant prognostic variable in the present study. ($p = 0.04$), (Table 2, Fig. 19), ratios were grouped as 0, <0.3, 0.3-0.5 and > 0.5 and survival was 78%, 35%, 25% and 12% for each group respectively. The ratio of involved to resected lymph nodes has been identified as an important significant prognostic factor in centers where D2 lymphadenectomy is already established as a standard procedure **[43,44,45]**.

The ratio of involved-to-resected lymph nodes was an independent prognostic factor on multivariate analysis, while the number of involved or resected lymph nodes was not. Thus, when radical lymph node dissection is the standard operation for gastric cancer, the ratio of involved-to-resected lymph nodes has a more comprehensive and precise prognostic value than the number of involved or resected lymph nodes **[25]**.

In the present study, lymph node metastasis were staged according to the level of lymph node metastasis using the Japanese staging system (JRSGC, 1998) **[20]**. N stage by the JRSGC system was a significant prognostic variable by univariate analysis. The two year disease free survival rates for N0, N1 and N2 cases were 78%, 39% and 0%, (Table 2, Fig. 20). In 1997 Sasako and colleagues published their results after 5 years of follow up of surgically treated gastric cancer patients where the survival ranged between 63% and 92% for N0, 60% and 90% for N1 and 35% and 86% for N2 according to T stage **[1]**. This was also supported by other studies **[24,42]**.

The UICC 1997 TNM classification adopted the number of involved lymph nodes as a prognostic factor for gastric cancer. Yildrim and Colleagues supported this view and they found that the 5 year survival rates for the groups N0, N1, N2 and N3 were 80%, 46%, 8% and 0% respectively **[40]**. In the prospective multicenter German Gastric Cancer Study, the 5 year survival was 89.7% for patients with N1, 45.5% for patients with N2 and only 10.4% for patients with N3. The location of the involved lymph nodes did not significantly alter the prognosis **[46]**. In 2003 Gunji and colleagues stressed the importance of the number of metastatic lymph node in early gastric cancer after D2 dissection where he found that no patients with 1-3 metastatic lymph nodes had recurrence but 6 patients out of 7 with 4 or more metastatic nodes died of haematogenous spread **[47]**.

In another study, the 5 year survival rates for UICC N0, N1 and N2 were 69.4%, 35% and 10.7% respectively **[29]**. Ichikawa and colleagues **[48]** studied the prognostic value of lymph node staging in gastric cancer according to TNM Classification and the Japanese Classification for gastric cancer (JCGC) and they found that both nodal staging systems were significant prognostic factors by multivariate analysis.

With respect to the tumour histology adenocarcinoma was the commonest histology (60.6% of cases). Adenocarcinoma cases showed a two year disease free survival of 42%. Patients with signet ring histology showed a survival of 18%, (Table 2, Fig. 14). Some reports ignored tumour histology, stressing on cell differentiation and grade **[29,40]**, which did not show significance in our study (Table 2). Tumour histology was a significant independent prognostic variable by multivariate analysis in the present study.

The use of intraoperative lymphography using (CH-40) which is used in the Japanese technique routinely, **[21,22]** was evaluated crudely according to operative observation and related to the number of resected lymph nodes and lymph node metastasis. The use of the (CH-40) intraoperatively facilitated the technique of D2 lymphadenectomy especially in dissection of lymph nodes along the upper border of the pancreas, where stained lymph nodes could be identified from pancreatic tissue and the proper plane of dissection could be reached easily. The use of the dye was valuable especially in absence of grossly positive nodes where staining was good. Extensive lymph node metastases block lymphatics and prevent the spread of the dye to stain the lymph nodes adequately. This indicates that lymphography is useful in cases with -ve nodes and not in heavily infilitrated nodes. The number of resected lymph nodes (which proved to have a significant prognostic influence

by univariate analysis) was higher when the staining was good, where more than fifteen lymph nodes were resected in 90% of cases showing good staining and only 67% and 60% when staining was average or bad respectively.

In our study the mean size was 5.5 cm (range 2-11 cm) with $p = 0.46$ (Table 2) but still tumour size did not show statistical significance. Several studies showed that tumour size correlated with survival.

Patient age, sex, presenting symptom tumour size, operative time and morbidity did not show statistical significance on both univariate and multivariate analysis. Some studies showed that young patients with gastric cancer had a poorer survival than older patients due to a high proportion of advanced tumours and aggressive tumour biology **[49]**.

In conclusion, the D2 operation is a systematic approach toward the removal of high risk perigastric lymph nodes. Most retrospective single center reports indicate that the routine use of extended lymphadenectomy for potentially currable gastric cancer can be performed safely. Some published prospective randomized trials did not show survival advantage for the D2 lymph node dissection and did not support the routin use of extended D2 gastrectomy. A modified D2 operation avoiding pancreaticosplenectomy will provide superior staging information and may avoid the added morbidity and mortality assosiated with the additional organ resection. The advanced stage of disease at surgery in most patients remains the key determinant of survival. If there is a survival benefit from the D2 lymph-adenectomy, it is limited to those with few lymph node metastases.

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