

Evaluation of Extended (D2) Lymphadenectomy for Treatment of Gastric Cancer

*Hossam Abdelkader,¹ MD; Haitham Elmaleh,² MRCS, MD;
Rabbah Abdellateef,² MD; Ismael Morad³, MD*

- 1) Department of General surgery, Menofia University, Menofia, Egypt.
- 2) Department of General surgery, Ain Shams University, Cairo, Egypt.
- 3) Department of Surgical oncology, National Cancer Institute, Cairo, Egypt.

Background & objectives: Although gastric cancer is one of the most common causes of cancer-related death, its prognosis remains poor. Surgical resection with lymph node dissection is the only potentially curative therapy for gastric cancer. However, the appropriate extent of lymph node dissection remains controversial. In East Asian countries, D2 lymph node dissection has been performed as a standard procedure. In western countries, D2 dissection was associated with higher mortality and morbidity with no 5-year survival benefit compared to D1 dissection. More recent studies have demonstrated that western surgeons can be trained to perform D2 lymphadenectomies on achieving survival benefits comparable to those of reported in eastern countries. The aim of our study is to evaluate the feasibility, safety and outcome of extended (D2) lymphadenectomy for gastric cancer.

Patients and methods: Between July 2008 and June 2014, patients with gastric cancer in whom surgical resection was indicated, were prospectively included in this study. Enrolled patients underwent gastrectomy with D2 lymphadenectomy. The patients were followed up regularly after the operation. Postoperative parameters, disease-specific mortality & Kaplan-Meier survival analysis were used to assess the outcomes.

Results: 62 patients were included in the study. 33 patients had distal gastrectomy and 29 patients had total gastrectomy. 9 (14.5%) patients had postoperative complications with 2 cases of postoperative mortality recorded. The overall mean survival time was 17.13 ± 9.6 months and the disease free mean survival time was 13.4 ± 9.39 months. Kaplan-Meier survival analysis showed that the overall survival probability estimate in the study was 100% at 1 year, 88.7% at 2 years, 58.1% at 3 years and 32.3% at 4 years. Nodal disease class & N stage were found to have a statistically significant effect on survival.

Conclusion: D2 lymphadenectomy can be performed safely in well-equipped hospitals by experienced surgeons with acceptable morbidity & mortality. It can provide better survival for patients with gastric cancer and low degree of lymph node metastases (N1 or N0).

Key words: Stomach cancer, D2 lymphadenectomy, extended lymphadenectomy.

Introduction:

Gastric cancer is one of the most common causes of cancer-related death¹ and is second only to lung cancer worldwide.² The wide variation in incidence between eastern and western countries strongly suggests an ethnic background as a risk factor. Egypt falls into the low risk area, with an incidence of 2.9 per

100,000, in comparison to 5.3 per 100,000 populations in the United States. These rates are 5 to 15 times lower than in Japan, where the overall incidence is 50 per 100,000 population.² The prognosis of gastric cancer patients remains poor, with a 5-year overall survival of 25% or less, especially in the USA, Europe, and China.³ Lymph node metastasis

is an important prognostic indicator for the patients with gastric cancer. Surgical resection with lymph node dissection is the only potentially curative therapy for gastric cancer. However, the appropriate extent of lymph node dissection to be performed with gastrectomy remains controversial.⁴ The 5-year survival rate reported in most western series is 10% to 21%, which is a consequence of high proportion of patients that present in advanced stages.⁵ In East Asian countries, especially Japan and Korea, D2 lymph node dissection has been regularly performed as a standard procedure. In Western countries, surgeons used to perform gastrectomy with D1 dissection only because D2 dissection was associated with higher mortality and morbidity with no 5-year survival benefit compared to D1 dissection.^{6,7} However, more recent studies have demonstrated that western surgeons can be trained to perform D2 lymphadenectomies on western patients with a lower morbidity and mortality, and eventually achieving survival benefits comparable to those of reported in eastern countries.^{8,9,10} The question of whether these results can be repeated in Egypt is still a matter of research. The aim of our study is to evaluate the feasibility, safety and outcome of performing extended (D2) lymphadenectomy for gastric cancer in Egypt.

Patients and methods:

The study was conducted in three hospitals in Egypt (National cancer Institute, Menofya university hospitals & Ain Shams university hospitals) between July 2008 and June 2014, and it was a prospective interventional study. It included patients with gastric cancer in whom surgical resection was indicated.

Preoperative workup involved laboratory investigations (complete blood picture, renal functions, liver functions, serum electrolytes & coagulation profile); chest X-rays, enhanced computed tomography scans of the abdomen and pelvis, and gastric endoscopy and biopsy. All tumors were diagnosed as adenocarcinomas by histopathological assessment of biopsy specimens.

We used the D terminology according to

the guidelines of Japanese Research Society for Gastric Cancer (JRS GS). According to this classification, lymph nodes surrounding stomach are divided into 20 stations and these are classified into three groups depending upon the location of the primary tumor. This grouping system is based on the results of studies of lymphatic flow at various tumor sites, together with the observed survival associated with metastasis to each nodal station. In this grouping system, most perigastric LNs (Right paracardial, Left paracardial, Right and left gastric, Right and Left gastro-omental, Suprapyloric, and Subpyloric LNs [stations no. 1-6 respectively]) are defined as group 1, whereas the nodes along the left gastric artery (station no. 7), common hepatic artery (station no. 8), celiac axis (station no. 9), splenic artery (station no. 11) and hepato-dudenal ligament (station no. 12) are defined as group 2. D1 gastrectomy is defined as dissection of all the Group 1 nodes (plus station 7), and D2 is defined as dissection of all the Group 1 and Group 2 nodes.¹¹

All our patients underwent D2 lymphadenectomy, splenectomy was done for greater curve lesion attached to the spleen. No pancreatectomy was done.

All patients had follow-up visits after discharge from hospital every 3 months for the first year, and twice a year thereafter. The routine examination during follow-up included a physical examination, blood chemistry tests, chest X-ray, abdominal ultrasound. Pelvi-abdominal CT, bone scan and endoscopy were done for selected patients when indicated.

We used disease-specific mortality for controlling of unrelated causes of death. Stratified and Cox regression analyses were used to evaluate the association between survival and the number of positive node harvested. The parameters analyzed included operative time, blood loss, blood transfusion, morbidity, number of harvested lymph nodes (HLNs), number of positive LN, T stage, and overall survival. Kaplan-Meier survival analysis was conducted to measure the survival estimates and assess the effect

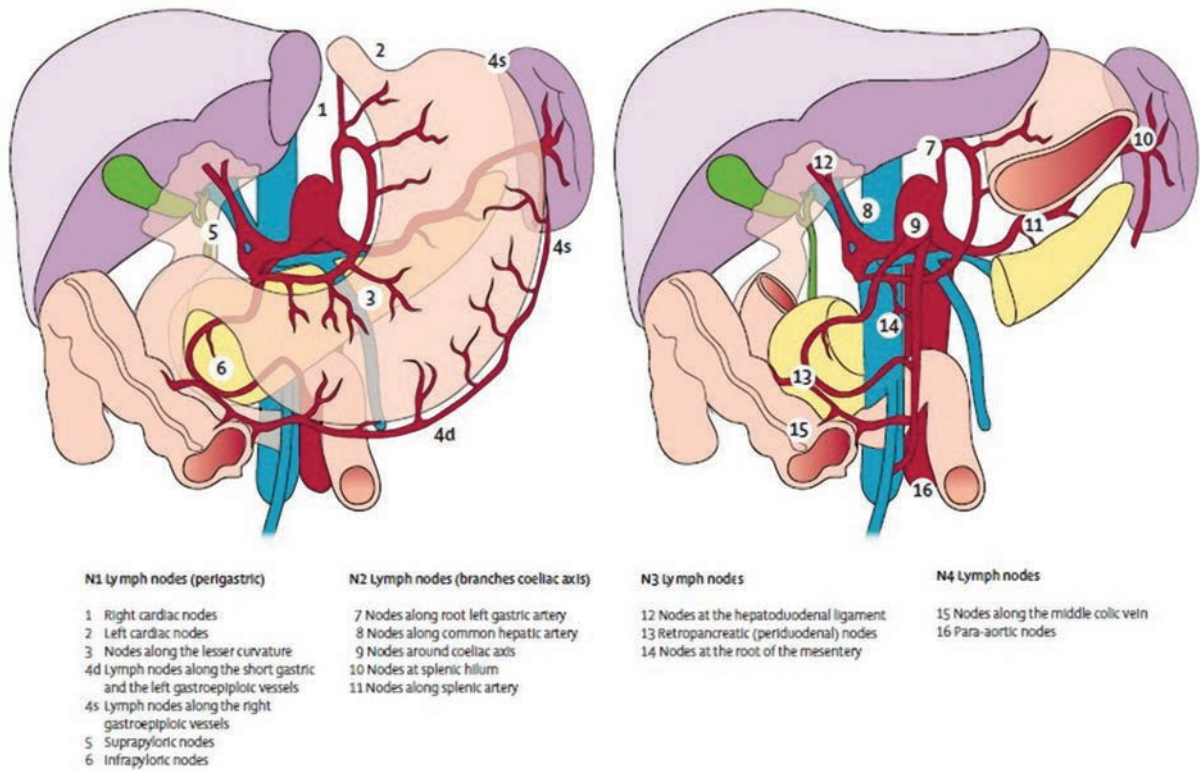


Figure (1): Location and grouping of the lymph nodes. D1 resection: Removal of the N1 lymph nodes. D2 resection: Removal of the N1 and N2 lymph nodes. {Quoted from Songun et al.¹²}

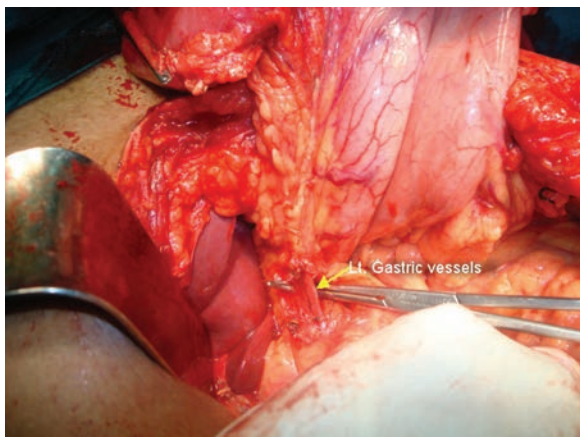


Figure (2): Intraoperative view of dissection of LNs along left gastric vessels (group 7).

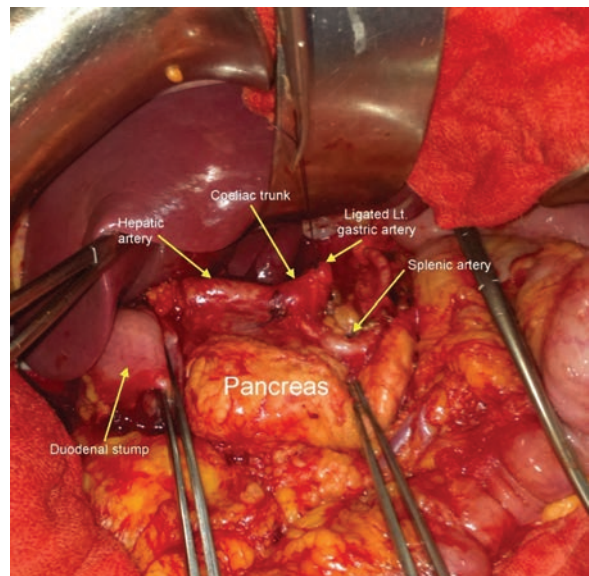


Figure (3): Intraoperative view of the field after dissection of LNs along the coeliac, hepatic, splenic & left gastric arteries (groups 7, 8, 9 & 10).

different parameters on survival. P values were considered significant if less than 0.05.

Results:

62 patients were included in the study, 37 males (59.7%) and 25 females (40.3%),

the mean age of patients was 52.29 ± 15.08 (range: 24-75) years.

According to the 7th AJCC's TNM staging system for gastric cancer, there were 10, 5, 19 and 28 patients in the N0, N1, N2 and N3 stage, respectively. Patients with low nodal

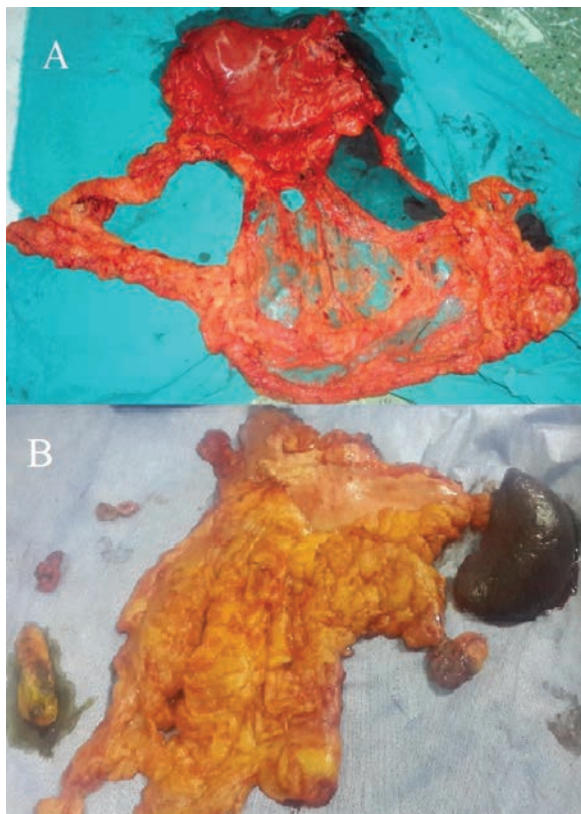


Figure (4): Resected specimens of: A: Distal gastrectomy, B: Total gastrectomy & splenectomy both with extended lymphadenectomy.

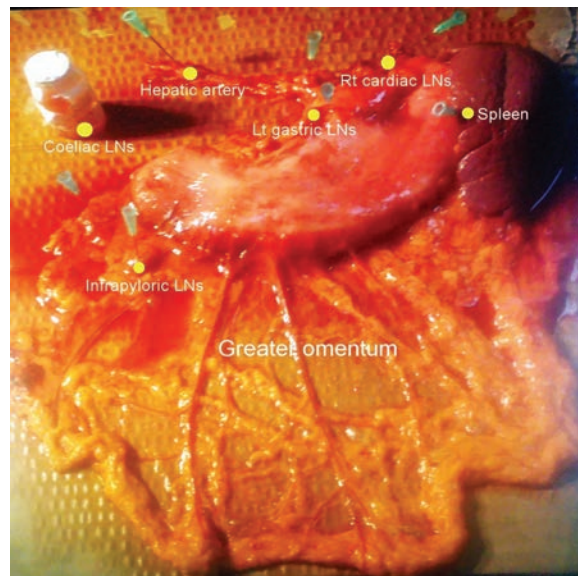


Figure (5): Resected specimen of total gastrectomy, splenectomy & D2 Lymphadenectomy with different parts and enlarged LN groups labeled.

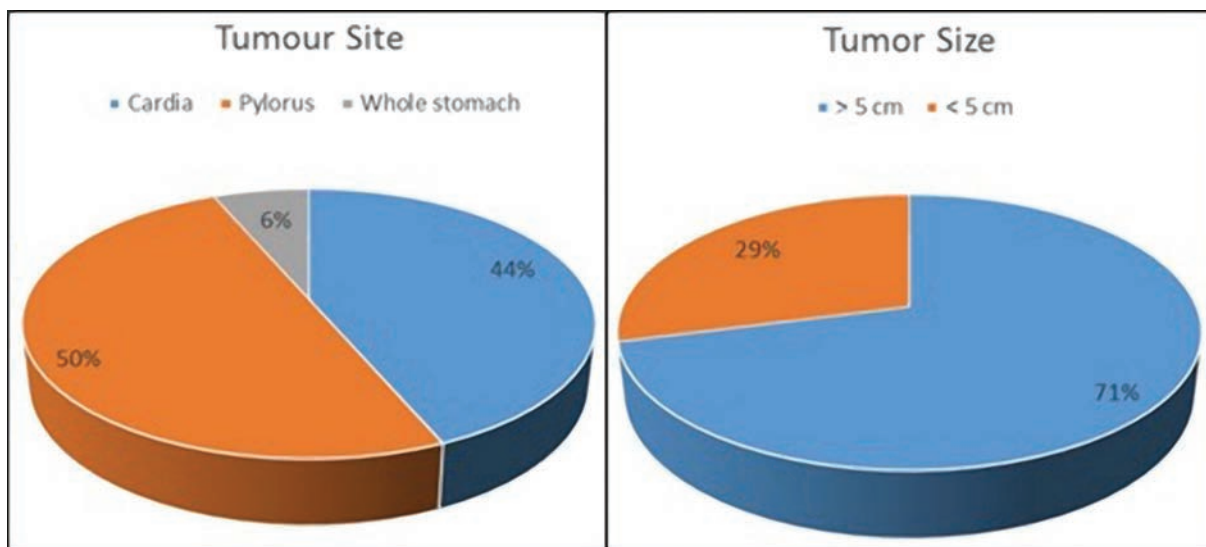


Figure (6): Tumor site & size distribution in the study group.

disease (N 0 or 1) were 15 and were termed early nodal disease patients, high or late nodal disease patients were 47. There were 9, 32 and 21 patients in the T2, T3 and T4 stage, respectively. The patients' clinicopathological characteristics are shown in **Figures (6-8)**.

33 patients had distal gastrectomy and

29 patients had total gastrectomy. D2 LN dissection was done in all cases. No intraoperative mortality was recorded. The mean average number of lymph nodes harvested was 33 ± 5 nodes (range: 21-41). The details of operative data are shown in **Table (1)**.

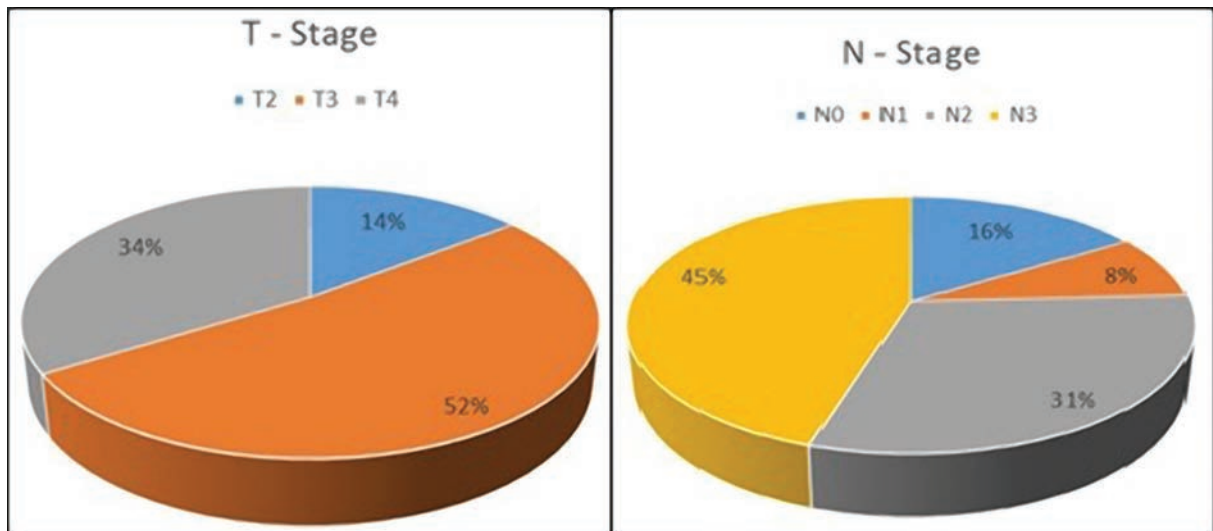


Figure (7): T & N stages distribution in the study group.

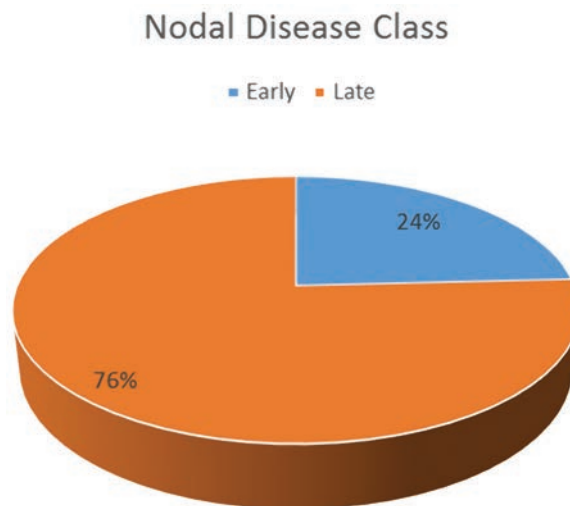


Figure (8): Nodal disease class distribution in the study group.

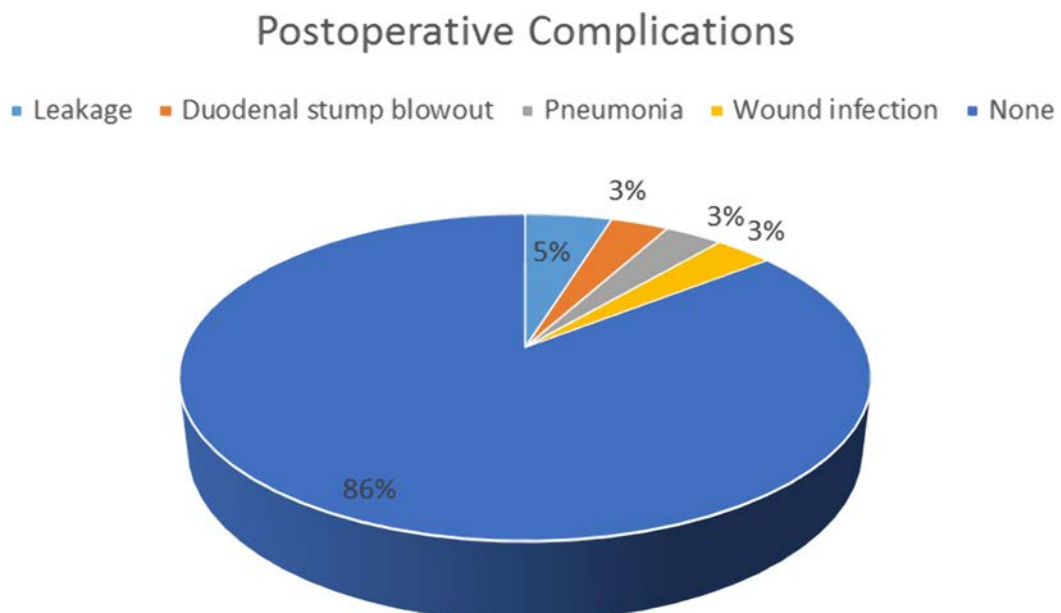


Figure (9): Post operative complications in the study group.

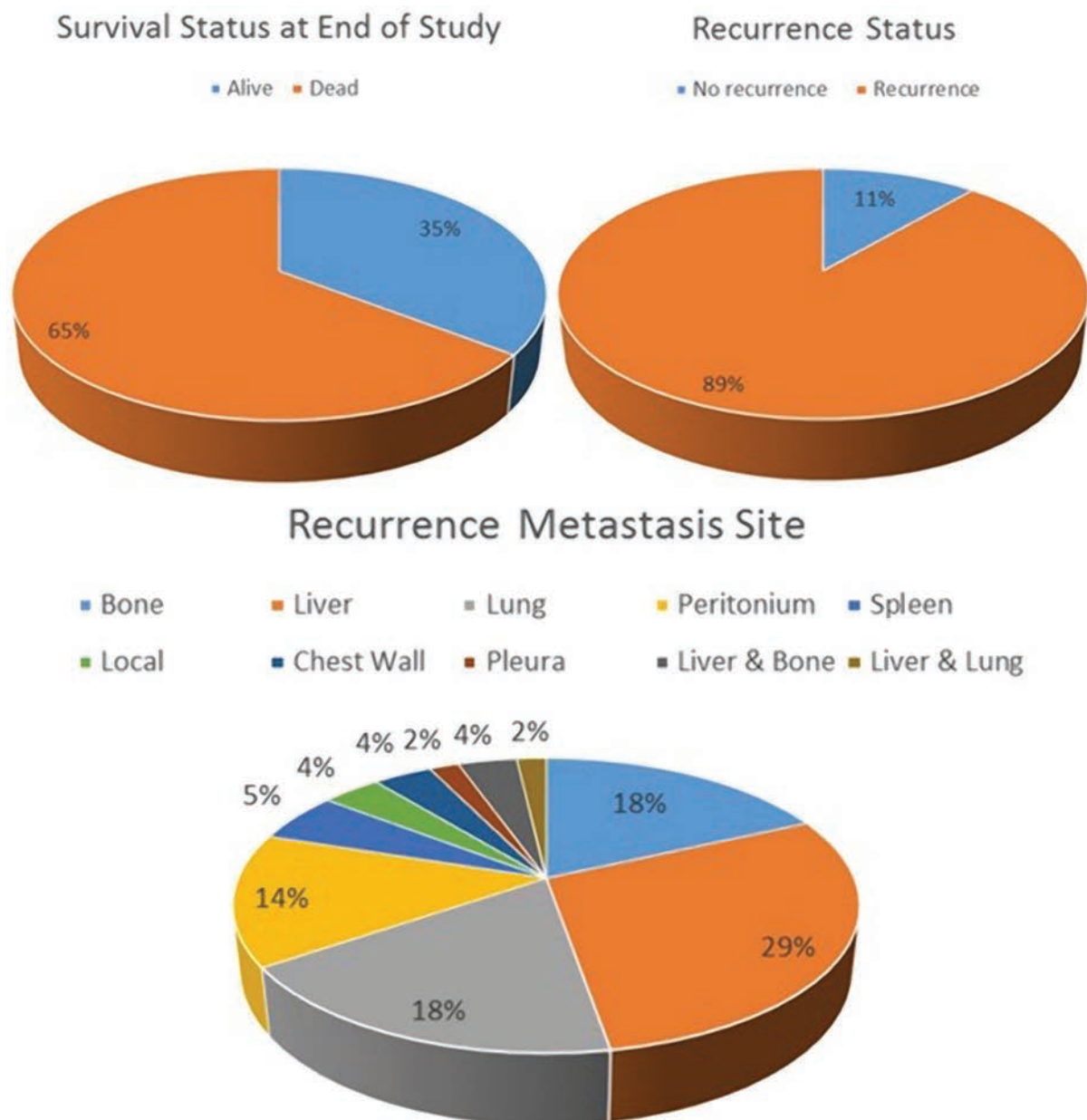


Figure (10): Survival & recurrence data in the study.

The mean follow-up period in our study was 32 months (range 12-48 months). 9 (14.5%) Patients had postoperative complications (3 cases of leakage from esophagojejunal anastomosis after total gastrectomy, 2 duodenal stump blowouts, 2 wound infection and 2 cases of pneumonia). Two cases (3.2%) of mortality were recorded in the first month after surgery (one after leakage from esophagojejunal anastomosis and 1 after duodenal stump blowout). Postoperative complications are shown in **Figure (9)**.

The overall mean survival time was 17.13 ±9.6 months. The disease free mean survival

time was 13.4 ±9.39 months. Kaplan-Meier survival analysis showed that the overall survival probability estimate in the study to be 100% at 1 year, 88.7% at 2 years, 58.1% at 3 years and 32.3% at 4 years. The majority of cases with recurrence had systemic metastasis not local recurrence. In addition, most of the cases of disease related death were from systemic metastasis not local recurrence. Follow up data are shown in **Table (2)** and **Figure (10)**.

Statistical analysis was done in order to define the relation between disease parameters and survival pattern with D2 resection.

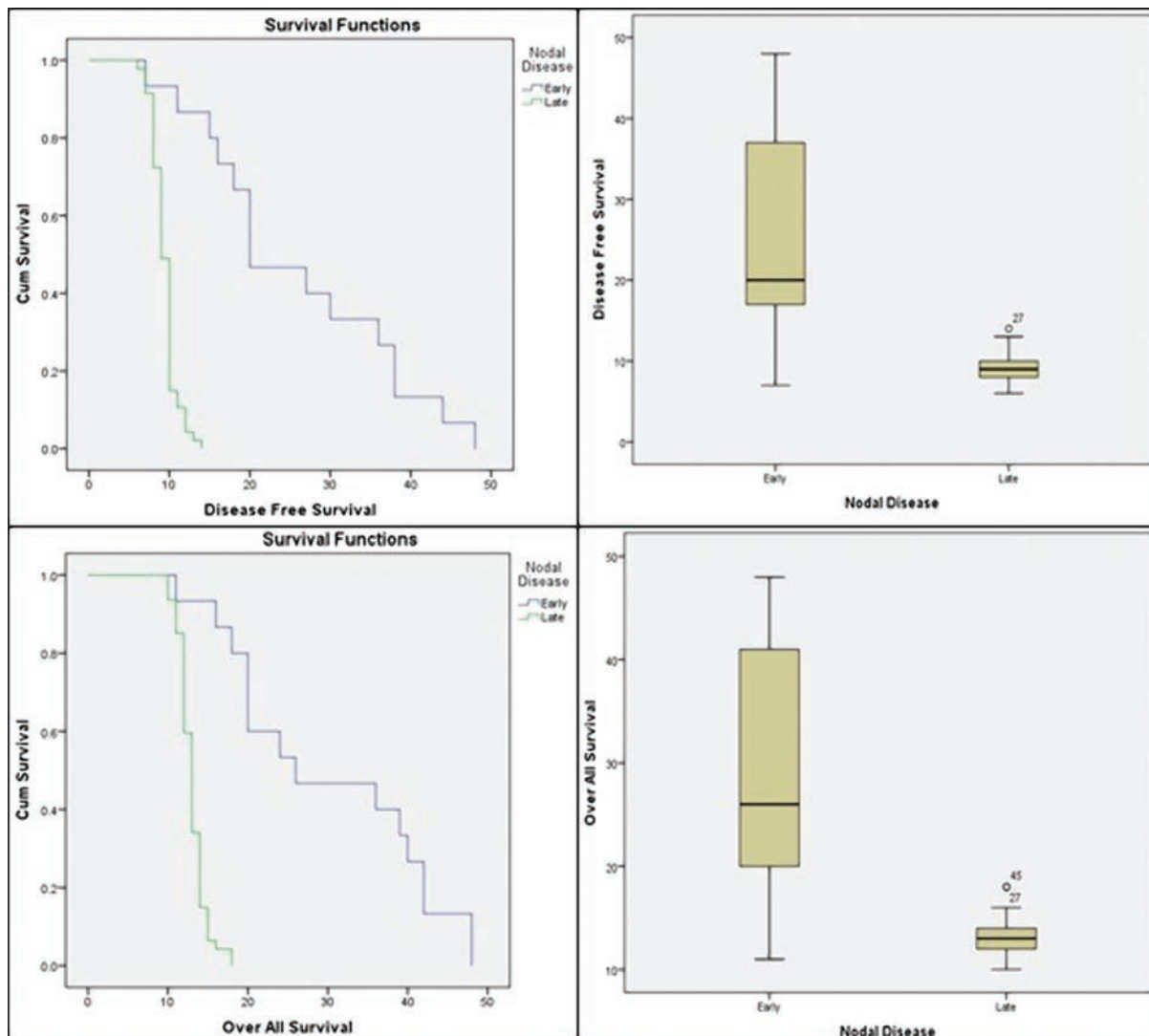


Figure (11): Kaplan-Meier survival analysis curves of the relation between LNs status and survival.

Relation between the numbers of harvested lymph nodes and survival: Cox regression analysis revealed that there was no significant relation between the number of harvested LN and overall survival or disease free survival as shown in **Table (3)**.

Relation between lymph node status and survival: We categorized the patients in study by their metastatic lymph node status into early nodal disease group (N0 and 1) and late nodal disease group (N2 and 3).

Kaplan-Meier survival analysis showed a highly significant difference in disease free and overall survival between early and late nodal disease. The mean disease free survival times were 25.87 ± 3.23 and 9.42 ± 0.23 months for early and late nodal groups respectively, and the mean overall survival

times were 30 ± 3.24 and 13.02 ± 0.25 months for early and late nodal groups respectively as shown in **Table (4)** and **Figure (11)**.

Relation between the N stages and survival:

Kaplan-Meier survival analysis showed a highly significant difference in disease free survival and overall survival between different nodal stages. The median disease free survival times were 30, 16, 9 and 9 months for N0, N1, N2 and N3 respectively. The median overall survival times were 39, 18, 13 and 13 months for N0, N1, N2 and N3 respectively, as shown in **Table (5)** and **Figure (12)**.

Discussion:

The proper surgical management of

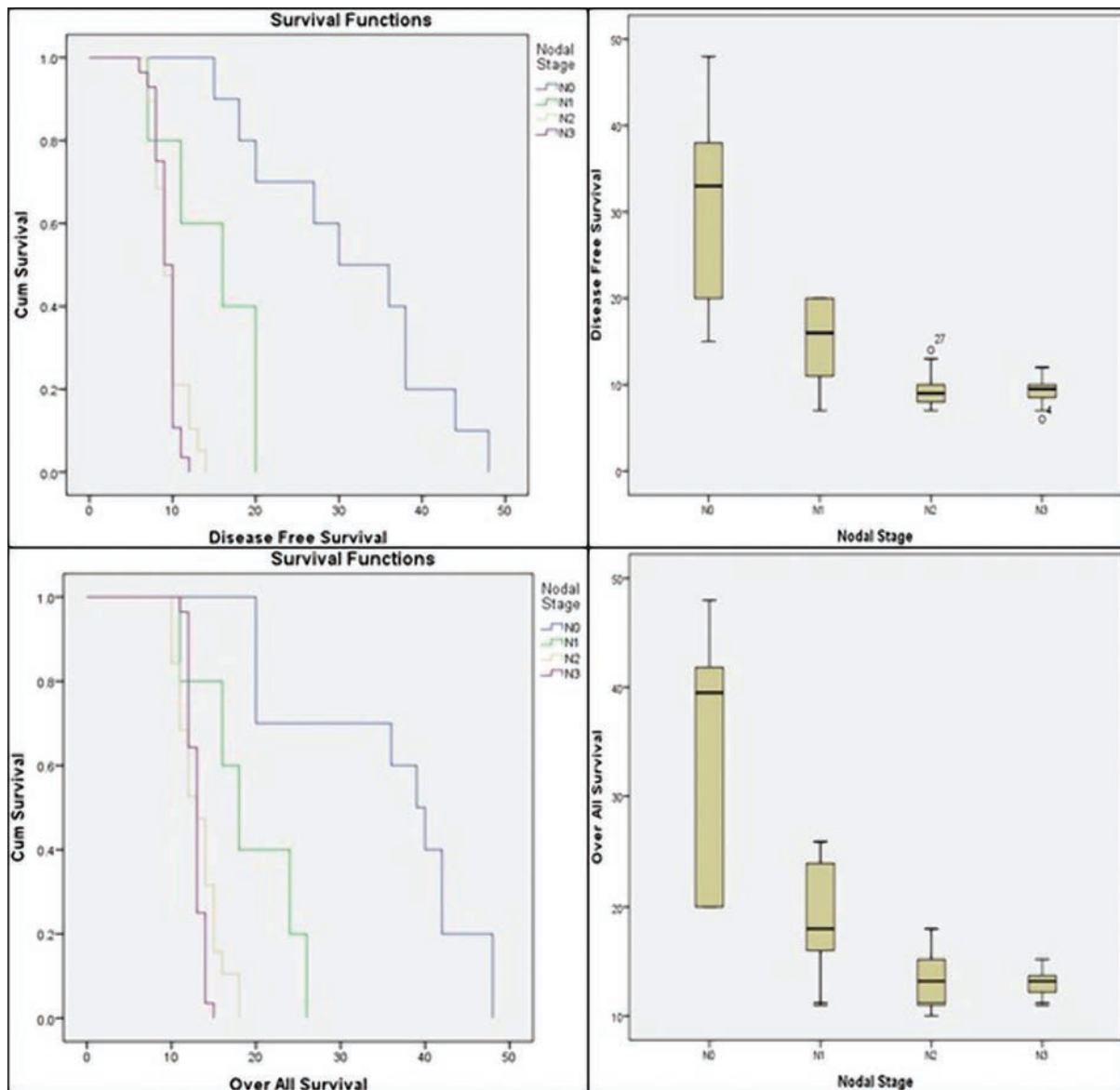


Figure (12): Kaplan-Meier survival analysis curves of the relation between LNs status and disease free survival.

Table (1): Operative data in the study group.

Item		Mean	Std. Deviation	Minimum	Maximum
Total LNs harvested		33	5	21	41
Operative time	Distal gastrectomy	127.8	19.1	96	180
	Total gastrectomy	155.1	25.9	120	220
Intraoperative blood loss	Distal gastrectomy	105.9	54.7	50	250
	Total gastrectomy	193	93	50	400

Table (2): Survival data in the study.

Item	Minimum	Maximum	Mean	Std. Deviation
Over all survival	10	48	17.13	9.601
Disease free survival	6	48	13.40	9.390

Time	Survival probability estimate
1 Month	100
1 Year	88.7
2 Years	58.1
3 Years	46.2
4 Years	32.3

Table (3): Cox regression analysis of the relation between harvested LNs and survival.

	B	SE	Wald	P value	Odds Ratio
Overall Survival	-.016	.032	.251	.616	.984
Disease Free Survival	-.022	.028	.641	.423	.978

Table (4): Kaplan-Meier survival analysis of the relation between LNs status and disease free survival.

Survival	Nodal disease	Mean				Median	
		Estimate	Std. Error	95% Confidence interval		Estimate	Std. Error
				Lower Bound	Upper Bound		
Disease free	Early	25.867	3.231	19.535	32.199	20.000	4.347
	Late	9.426	.229	8.976	9.875	9.000	.254
	Overall	13.403	1.193	11.066	15.741	10.000	.233
Overall	Early	30.000	3.241	23.647	36.353	26.000	10.305
	Late	13.021	.254	12.524	13.518	13.000	.271
	Overall	17.129	1.219	14.739	19.519	13.000	.375

stomach cancer had been subjected to much debates for years. Despite that, controversy still exists regarding the role of extended lymphadenectomy in the treatment of gastric cancer.⁵ Radical lymphadenectomy was adopted based on an initial report published in 1981 by Kodama and his colleagues who described a survival benefit for patient with serosal or regional lymph node involvement who underwent D2 or D3 lymphadenectomy.¹³ There have been significant differences in Eastern and Western philosophies regarding the role and extent of lymph node dissection for gastric cancer. The Eastern view generally contends that extensive lymphadenectomy

provides better cancer clearance and therefore improves survival, whereas the Western view generally holds that lymphadenectomy provides prognostic information and when done adequately, improves staging and guides adjuvant treatment decisions. From either perspective, there is strong agreement that lymphadenectomy is an integral part of high-quality gastric cancer operation, but debates are still present that eastern results of better survival can be reproduced in other parts of the world.¹⁴ Our study tried to address this point from the practice point of view in Egypt.

In our study, 62 patients with stomach cancer underwent D2 lymphadenectomy

Table (5): Kaplan-Meier survival analysis of the relation between N stage and survival.

Survival	Nodal stage	Mean				Median	
		Estimate	Std. Error	95% Confidence interval		Estimate	Std. Error
				Lower bound	Upper bound		
Disease free	N0	31.400	3.563	24.417	38.383	30.000	7.115
	N1	14.800	2.557	9.788	19.812	16.000	5.477
	N2	9.632	.447	8.755	10.508	9.000	.484
	N3	9.286	.240	8.814	9.757	9.000	.294
	Overall	13.403	1.193	11.066	15.741	10.000	.233
Overall	N0	35.500	3.575	28.492	42.508	39.000	3.162
	N1	19.000	2.720	13.668	24.332	18.000	2.191
	N2	13.211	.580	12.073	14.348	13.000	.933
	N3	12.893	.173	12.553	13.232	13.000	.208
	Overall	17.129	1.219	14.739	19.519	13.000	.375

in 3 large referral hospitals by experienced surgical teams. All cases were completed without intraoperative morbidity or mortality. The mean average number of lymph nodes harvested was 33 ± 5 nodes. 9 (14.5%) Patients had postoperative complications (3 anastomotic leakage, 2 duodenal stump blowout, 2 wound infection and 2 had pneumonia). Two cases (3.2%) of mortality were recorded in the first month after surgery. The overall mean survival time was 17.13 ± 9.6 months. The disease free mean survival time was 13.4 ± 9.39 months. 89% of patients had recurrence during the follow up period. The overall survival probability estimate in the study was 100% at 1 year, 88.7% at 2 years, 58.1% at 3 years and 32.3% at 4 years.

Comparing our results to the published literature outside Japan. In 2006, Wu and his colleagues¹⁵ from Taiwan published their randomized controlled trial of D1 versus “D3” dissection in *Lancet Oncology*. The D3 lymphadenectomy described in this study essentially included a JGCA D2 lymphadenectomy together with nodes around the retropancreatic region and superior mesenteric vein. The study included 221 patients, and the primary endpoints were 5-year overall- and disease-free survival. At a median follow-up of 95 months, there was a 5-year overall survival rate of 63%

for patients who underwent D3 surgery and 58% for patients undergoing D1 surgery ($p = 0.006$). The recurrence rate at 5 years was 51% after D1 surgery and 40% after D3 surgery.¹⁵ The Dutch Gastric cancer Group had a study of 711 patients undergoing surgical treatment of stomach cancer, their first results were published at 2004. In 2010, the Dutch trial was updated with a 15-year follow-up results.¹² Gastric cancer-related death was 37% for the D1 group and 48% for the D2 group ($p = 0.01$), whereas death from other causes was the same in both groups.¹² Hanna and his colleagues published in 2012 their experience with D2 gastrectomy.¹⁶ From 2003 to 2010, 100 patients underwent gastrectomy. He reported anastomotic leak rate of 2%. Postoperative mortality and technical complications for gastric cancer resections were similar to Japanese rates. Kaplan-Meier estimates of overall survival after gastrectomy was 90.6% at 1 year, 74.3% at 2 years, 67.8% at 3 years, 64% at 4 years and 58.4% at 5 years.¹⁶ The early postoperative morbidity and mortality results in our study are higher than those published in the studies mentioned. Also, our survival results especially after 2 years are significantly worse than those reviewed being only close to those of the Dutch trial. That can be explained by two reasons. First, the majority of our patients

had advanced disease (86% were T stage 3 or 4 and 76% were N stage 2 or 3). This fact may be the cause of high recurrence rates. Second, the volume of cases is less than those reported in the mentioned trials especially the one done in Taiwan, meaning that we are still in the phase of gaining experience. The higher case volume results in better surgical experience and improved technical expertise leading to better overall results. In spite of that, our study showed that the recurrence was mainly metastatic not local, meaning that D2 lymphadenectomy had actually improved the outcome regarding the local control of the disease.

Lymph node metastasis is one of the most important prognostic factors in gastric cancer. We tried to assess the effect of different parameters related to LN metastases on survival after D2 dissection. Our study found that there was no significant relation between the number of harvested LN and overall or disease free survival. On the contrary, analysis demonstrated a significant relation between N-stage and survival with patients with late nodal disease (N stage 2 or 3) having shorter disease free survival and overall survival times (9 and 13 months respectively) than those with early nodal disease despite the extended nodal dissection done. These findings are opposite to those of the Dutch trial, which had found that patients with N2 disease have benefited from the extended lymphadenectomy.¹²

Our study have its limitation. The number of cases is not large enough as other trials and follow up period was variable and no 5 year follow up data were documented.

Conclusion:

D2 lymphadenectomy can be performed safely in well-equipped hospitals by experienced surgeons with acceptable morbidity and mortality. It can provide hope for better survival for patients with gastric cancer and low degree of lymph node metastases (N1 or N0). Further studies with larger case numbers and longer follow up period are needed to address the limitations of our study.

Reference:

- 1- Pisani P, Parkin DM, Bray F, Ferlay J: Estimates of the worldwide mortality from 25 cancers in 1990. *International Journal of Cancer* 1999; 83(1): 18–29.
- 2- Freedman LS, Edwards BK, Ries LAG, Young JL (eds): Cancer incidence in four member countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium (MECC) compared with US SEER. *National Cancer Institute* 2006; NIH Pub. No. 06-5873. Bethesda, MD.
- 3- Jemal A, Siegel R, Ward E, Hao Y, Xu J: Cancer statistics, 2008. *CA Cancer J Clin* 2008; 58: 71–96.
- 4- Tamura S, Takeno A, Miki H: Lymph node dissection in curative gastrectomy for advanced gastric cancer. *Int J Surg Oncol* 2011; 2011: Article ID: 748745, 8 pages.
- 5- Seevaratnam R, Bocicariu A, Cardoso R, Mahar A, Kiss A, Helyer L, Law C, Coburn N: A meta-analysis of D1 versus D2 lymph node dissection. *Gastric Cancer* 2012; 15 Suppl 1: 60–69.
- 6- Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW, et al: Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995; 25: 345(8952): 745–748.
- 7- Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P: Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: Preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996; 13: 347(9007): 995–999.
- 8- Roviello F, Marrelli D, Morgagni P, de Manzoni G, Di Leo A, Vindigni C, Saragoni L, Tomezzoli A, Kurihara H; (Italian Research Group for Gastric Cancer): Survival benefit of extended D2 lymphadenectomy in gastric cancer with involvement of second level lymph nodes: A longitudinal multicenter study. *Annals of Surgical Oncology* 2002; 9(9): 894–900.
- 9- Degiuli M, Sasako M, Calgaro M, Garino M, Rebecchi F, Mineccia M, Scaglione D, Andreone D, Ponti A, Calvo F; (Italian Gastric Cancer Study Group): Morbidity and mortality after D1 and D2 gastrectomy for cancer: Interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised

- surgical trial. *European Journal of Surgical Oncology* 2004; 30(3): 303–308.
- 10- Dikken JL, Verheij M, Cats A, Jansen EP, Hartgrink HH, van de Velde CJ: Extended lymph node dissection for gastric cancer from a European perspective. *Gastric Cancer* 2011; 14(4): 396–398.
 - 11- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; 14(2): 113–123.
 - 12- Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ: Surgical treatment of gastric cancer: 15-year follow-up results of the randomized nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; 11(5): 439–449.
 - 13- Kodama Y, Sugimachi K, Soejima K, Matsusaka T, Inokuchi K: Evaluation of extensive lymph node dissection for carcinoma of the stomach. *World J Surg* 1981; 5(2): 241–248.
 - 14- Strong VE, Yoon SS: Extended lymphadenectomy in gastric cancer is debatable. *World J Surg* 2013; 37(8): 1773–1777.
 - 15- Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY, Whang-Peng J: Nodal dissection for patients with gastric cancer: A randomised controlled trial. *Lancet Oncol* 2006; 7(4): 309–315.
 - 16- Hanna GB, Boshier PR, Knaggs A, Goldin R, Sasako M: Improving outcomes after gastroesophageal cancer resection: Can Japanese results be reproduced in Western centers? *Arch Surg* 2012; 147(8): 738–745.