Lymph Node Metastasis in Gastric Cancer: Result of D2 Dissection

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***Background**: Extent of lymph node dissection still remains one of the most controversial issues regarding radical gastrectomy. Knowledge of the pattern and incidence of lymph node metastasis may help to define the optimal extent of lymph node dissection.*
***Material and Method**: The authors analyzed lymph node metastasis and survival rate in 130 consecutive gastric cancer patients who underwent radical gastrectomy with D2 dissection between June 2001 and October, 2008 at the Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.*
***Results**: For N staging, 28.5% of the patients were N0 while N1 was 40% and N2 was 31.5%. 44% of the patients with lymph node positive had metastasis up to group 2 lymph nodes. The patients with node positive had 5 year survival of 39% while the patients with node negative had survival of 73% (p = 0.003). Tumor at the middle part of the stomach had the most widespread lymph node metastasis compared to other regions. Lymph node group 7, 8 and 9 had a high incidence of lymph node metastasis especially for distal cancer while lymph node group 10, 11, 12 had lower incidence of metastasis. No mortality was seen in the present study.*
***Conclusion**: N staging, number of metastatic node > 5 and angiolymphatic invasion were the lymph node related factors contributing to survival. For radical gastrectomy, D2 dissection is required for adequate clearance of metastatic lymph nodes, which can be done without mortality.*

***Keywords:** D2 dissection, Gastric cancer, Gastrectomy*

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In Thailand, gastric cancer presents as one of the most difficult problems for surgeons because the majority of the patients are in the late stage and even when resectable the surgical treatment is radical gastrectomy which is still controversial regarding its extent of lymph node dissection. At present, in Japan, dissection up to group 2 lymph nodes (D2 dissection) is recommended as standard procedure but in Western countries, randomized controlled trials were carried out and D2 dissection was associated with increased mortality without survival benefit[1,2].

Thus, extent of lymph node dissection still remains the most controversial issue regarding radical gastrectomy. The authors believe that knowledge of the pattern and incidence of lymph node metastasis may help to define the optimal extent of lymph node dissection needed to be done.

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Material and Method

In the present study, the authors analyzed lymph node metastasis and survival rate in 130 consecutive gastric cancer patients treated with radical gastrectomy with D2 dissection between June 2001 and October 2008 at the general surgery unit, Department of Surgery, Siriraj Hospital, Mahidol University. To control uniform quality, all were performed systematically by a single surgeon (AM) and the specimens were meticulously dissected for lymph nodes and divided into groups for analysis. Data were prospectively collected in the database for quality control and retrospectively analyzed. D2 dissection was done in patients with no distant metastasis and intraperitoneal dissemination whose functional class

was considered fit for surgery. All patients were staged according to the staging as proposed by the Japanese Gastric Cancer Association[3]. Preoperative esophagogastro-duodenoscopy and CT scan of the abdomen were done for diagnosis and clinical staging.

Numbering of the lymph nodes for grouping and lymph node dissection were done according to the Japanese system (Fig. 1)[3]. The lymph nodes dissection for D2 dissection in subtotal gastrectomy included lymph node group 1, 3, 4, 5, 6, 7, 8a, 9, 11p, 12a and 14v. For total gastrectomy, the authors added lymph node group 2, 10 to the above lymph node groups.

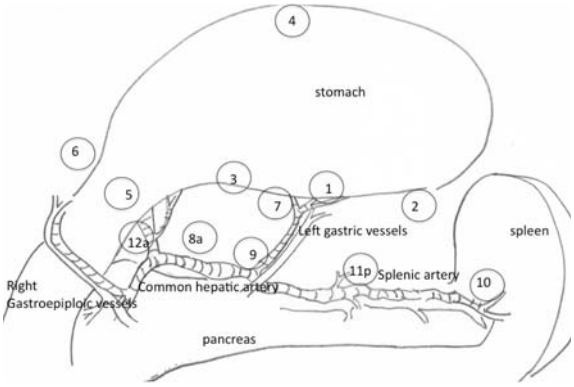

Fig. 1 Number and location of lymph nodes to be dissected in D2 dissection according to the Japanese system. The stomach was disconnected from the transverse colon and rotated anteriorly to expose main vessels along the upper border of the pancreas, which are the locations of most of group 2 lymph nodes

Operative procedure of subtotal gastrectomy (D2 dissection)

After laparotomy, peritoneal wash was done with warm saline 200 ml and sent for cytology. The gastrocolic ligament was divided at the point about 2cm along the border of the transverse colon so that greater omentum was included in the specimen. Dissection of anterior leaf of transverse mesocolon was done. The dissection was continued on the right towards the pylorus and the infrapyloric node (group 6) was dissected. In cases with distal gastric cancer, superior mesenteric vein node (group 14v) was also dissected. Right gastroepiploic vein was divided at its origin from the Henle's trunk and right gastroepiploic artery was divided at its origin from the gastroduodenal artery. Lesser omentum was divided at approximately 1 cm below margin of the liver. The lymph nodes of the anterior region of the hepatoduodenal ligament (group 12a) were dissected and removed en bloc. The right gastric artery was divided and suprapyloric nodes (group 5) was removed.

Duodenum was transected approximately 2 cm distal to the pylorus and duodenal stump was closed with manual suturing or stapler. The lymph nodes dissection was continued along the common hepatic artery (group 8a), celiac axis (group 9), left gastric artery (group 7) and proximal splenic artery (group 11p) respectively. The left gastric vessels were divided. Dissection of the gastrocolic ligament was continued toward the spleen and approximately 2 inframost short gastric vessels were divided. Dissection of lymph nodes groups 1 and 3 were done downwards along the lesser curvature to remove the entire fatty tissue on the lesser curvature.

In subtotal gastrectomy, left cardiac node (group 2) was not dissected because blood supply of the remnant stomach depended on short gastric vessels only. Transection of the stomach was done and anastomosis performed either in Billroth II fashion or Roux-en-Y anastomosis (ante-colic).

In total gastrectomy, all short gastric vessels were removed and lymph node group 2 was dissected. Peritoneum over the esophagogastric junction was opened. Esophagus was transected and reconstruction was done with esophagojejunostomy in Roux-en-Y fashion. No drain was used in the present series. After resection, the lymph nodes were systematically dissected from the specimen and sent for pathological examination in separate groups.

The SSPS 14.0 software package was used for statistical data analysis (SSPS, Chicago, IL, USA). Survival times and curves were established according to the Kaplan-Meier method and compared by the log-rank test. The Chi-square test and log rank test were performed for univariate statistical analysis of each prognostic factor and calculated for hazards ratios, 95% confidence intervals (95% CI) and p-values were calculated using the Chi-square test. All p-values were two-sided in tests and p-values < 0.05 were considered significant. Mean values and survival rates were given with their standard errors.

Results

D2 gastrectomy patients consisted of 72 males and 58 females with a mean age of 61.20 $\pm$ 13.18 years (range 26.00-89.00 years). Characteristics of the patients

Table 1. Demographic data of the D2 gastrectomy patients

Characteristics	n = 130
Age (years)	61.20 ± 13.18
Male/female	72/58
Location	
Upper	20 (15.4%)
Middle	36 (27.7%)
Lower	64 (49.2%)
Entire stomach	10 (7.7%)
Tumor size (cm)	5.49 ± 3.50
Differentiation	
Well differentiated	15 (11.5%)
Moderately differentiated	36 (27.7%)
Poorly differentiated	79 (60.8%)
Surgical margin	
Free	119 (91.5%)
Not free	11 (8.5%)
T category	
T1	18 (13.8%)
T2	15 (11.5%)
T3	91 (70.0%)
T4	6 (4.6%)
N category	
N0	37 (28.5%)
N1	52 (40.0%)
N2	41 (31.5%)
Staging	
Ia	14 (10.8%)
Ib	9 (6.9%)
II	21 (16.2%)
IIIa	48 (36.9%)
IIIb	36 (27.7%)
IV	2 (1.5%)
Harvested lymph nodes	26.53 ± 18.71
Operation time (minutes)	238.60 ± 79.83
Blood loss (ml)	448.06 ± 273.81
Length of stay (days)	15.72 ± 10.10

are shown in Table 1. The tumors were located in the distal stomach in 49.2% of the cases, in the middle part in 27.7% and in the upper part in 15.4%. In 7.7% of cases, the tumor involved the entire stomach. Average size of the tumor was 5.49 ± 3.50 cm. The pathological results were poorly differentiated adenocarcinoma in 60.8% while 27.7% and 11.5% were moderately differentiated adenocarcinoma and well differentiated adenocarcinoma respectively.

For T staging, 70% of the patients were in T3 category, 13.8% in T1, 11.5% in T2 and 4.6% in T4 tumor. For N staging, 28.5% of the patients were N0 while N1 was 40% and N2 was 31.5%. In patients who were lymph node positive, 44% were found to have metastasis to N2 lymph nodes. Average number of lymph node retrieval was 26.53 ± 18.71 nodes. Mean operative time was 238.60 ± 79.83 minutes and average blood loss was 448.06 ± 273.81 ml. Mean length of hospital stay was 15.72 ± 10.10 days. 91.5% of the specimens had free margin.

Subtotal gastrectomy with D2 dissection was performed in 70 cases (54%), total gastrectomy in 43 cases (33%), laparoscopic gastrectomy in 9 cases (7%) and combined resection (total gastrectomy with resection of adjacent organ such as colon or liver) in 8 cases (6%). Complications occurred in 23 cases (17.69%). Wound complication was the most frequent complication occurring in 7 patients, followed by intraabdominal collection (6 cases), which could be treated with percutaneous drainage. Other complications included heart failure (1 case), postoperative ileus (1 case), sepsis (1 case), atelectasis (1 case), pleural effusion (2 cases) and pneumonia (4 cases). No mortality was seen in the present study.

Overall survival in patients received D2 dissection was 47.6%. 5 year survival of the patients with node positive was 39% while the patients with node negative was 73% (p = 0.003) (Fig. 2). The patients with the number of metastatic nodes more than 5 nodes also had poor survival compared to those with less than 5 nodes (26% and 67%, p = 0.001). There was a relationship between T staging and N staging

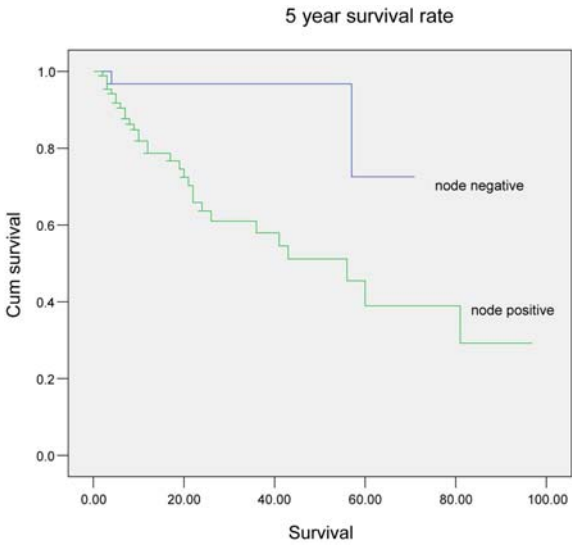

Fig. 2 5-year survival of the patients with node positive compared to those with node negative (p = 0.003)

Table 2. Relationship between T stage and N stage

	N0	N1	N2
T1 (18)	14/18 (77%)	3/18 (16%)	1/18 (5%)
T2 (15)	6/15 (40%)	5/15 (33%)	4/15 (26%)
T3 (91)	15/91 (16%)	42/91 (46%)	34/91 (37%)
T4 (6)	2/6 (33%)	2/6 (33%)	2/6 (33%)
Total (130)	37/130 (28%)	52/130 (40%)	41/130 (32%)

Table 3. Incidence of lymph node metastasis in different lymph node groups according to locations of the tumor

	Upper	Middle	Lower
No.1	31%	38%	27%
No.2	29%	50%	0%
No.3	41%	64%	61%
No.4	11%	63%	39%
No.5	11%	17%	30%
No.6	10%	41%	37%
No.7	11%	36%	30%
No.8a	10%	26%	36%
N0.9	38%	33%	24%
No.10	25%	20%	0%
No.11p	0%	20%	0%
No.12a	0%	20%	5%

(Table 2). N status was positive in 21% of the patients with T1 stage. However, N stage progressed with higher T stage so that 83% of the patients were node positive once the patient was in T3 stage.

The incidence of lymph node metastasis according to location of the tumor is shown in Table 3 and Fig. 3-5. By location, tumor of the upper part of the stomach had a high incidence (> 30%) of lymph node metastasis to lymph node group 1, 3, 9 while tumor of the middle part had a high incidence to group 1, 2, 3, 4, 6, 7, 9 and tumor of the distal stomach had a high incidence to group 3, 4, 5, 6, 7, 8a. Lymph node group 7, 8 and 9 had a high incidence of lymph node metastasis especially for distal cancer while lymph node group 10, 11, 12 had a lower incidence.

By factor analysis, T category, N category, number of metastatic node > 5, staging, postoperative complications, type of operation, presence of linitis plastica, cytology positive by peritoneal wash and angiolymphatic invasion were the factors contributing to survival with statistical significance (Table 4).

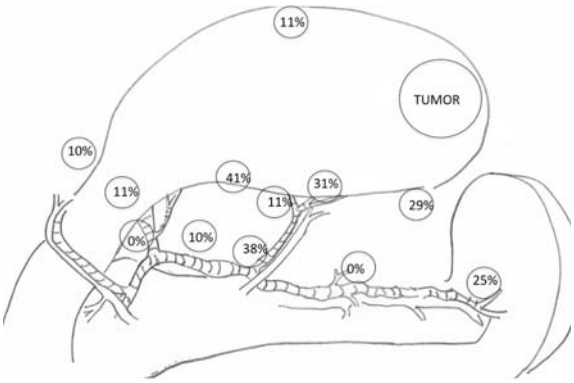

Fig. 3 Incidence of lymph node metastasis when the tumor is in the upper part of the stomach

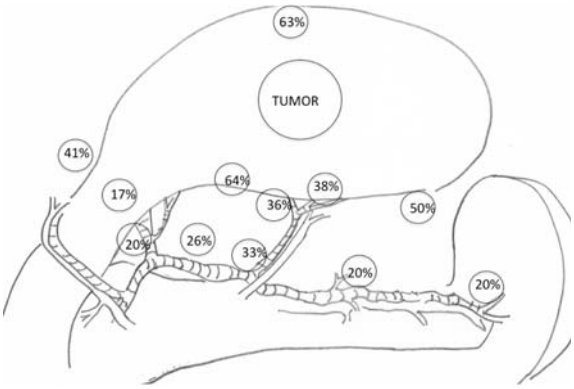

Fig. 4 Incidence of lymph node metastasis when the tumor is in the middle part of the stomach

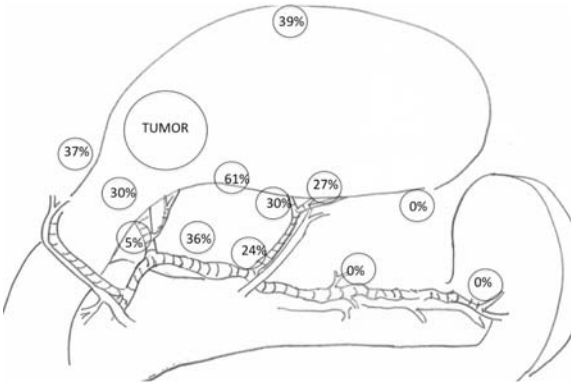

Fig. 5 Incidence of lymph node metastasis when the tumor is in the lower part of the stomach

Table 4. Factor analysis of parameters with relation to 5-year survival

Features	Hazard ratio	95% CI	p-value	5-year survival ± SE	p-value
Staging			0.001		0.008
Ia	1			0.90 ± 0.09	
Ib	1			0.90 ± 0.09	
II	1			0.61 ± 0.25	
IIIa	7.11	2.16-23.44		0.30 ± 0.12	
IIIb	7.11	2.16-23.44		0.46 ± 0.16	
IV	7.11	2.16-23.44		0.00 ± 0.00	
Histology			0.497		0.494
Well and moderately differentiated	-	-		0.50 ± 0.13	
Poorly differentiated	-	-		0.49 ± 0.13	
Tumor size			0.219		0.213
< 5 cm	-	-		0.47 ± 0.12	
> 5 cm	-	-		0.50 ± 0.16	
Margin			0.897		0.900
Free	-	-		0.50 ± 0.09	
Not free	-	-		0.34 ± 0.25	
Angiolymphatic invasion			<0.0001		<0.001
Negative	1			0.71 ± 0.11	
Positive	4.90	2.15-11.24		0.15 ± 0.12	
Complications			0.041		0.040
No	1			0.48 ± 0.10	
Yes	2.25	1.03-4.90		0.47 ± 0.23	
T staging			0.015		0.008
T1/T2	1			0.80 ± 0.11	
T3/T4	4.45	1.34-14.75		0.31 ± 0.12	
N staging			0.010		0.003
N0	1			0.73 ± 0.21	
N1/2	6.54	1.55-27.03		0.39 ± 0.10	
Number of metastatic nodes			0.002		0.001
< 5 nodes	1			0.67 ± 0.11	
> 5 nodes	3.31	1.56-7.04		0.26 ± 0.13	
Peritoneal wash cytology			0.010		0.003
Negative	1			0.81 ± 0.08	
Positive	7.52	1.62-34.48		0.12 ± 0.10	
Tumor location			0.113		0.112
Upper and body	-	-		0.50 ± 0.13	
Distal	-	-		0.43 ± 0.19	
Linitis plastica			0.022		0.016
No	1			0.50 ± 0.10	
Yes	2.92	1.17-7.30		0.15 ± 0.17	

Discussion

Whether dissection of lymph node dissection up to group 2, D2 dissection, should be done routinely in radical gastrectomy is still an issue for debate. In Western countries, only D1 dissection is recommended because D1 is associated with less mortality[4]. On the contrary, for Asian countries, especially Japan, it was shown that lymph node metastasis in gastric cancer is associated with poor survival and to improve survival, adequate lymph node dissection, namely D2 dissection, should be included in radical gastrectomy[5].

The result from factor analysis in the present study strongly supported this concept by showing that lymph node metastasis (N factor), number of metastatic nodes > 5 nodes and presence of angio-lymphatic invasion were related to survival with

statistical significance. Of the 130 patients included in the present study, 32% had lymph node involvement to N2 lymph nodes. Among patients who had lymph node positive, 44% had metastasis to N2 lymph nodes. This result was the same as those reported earlier[6,7]. Therefore, dissection of perigastric nodes only (D1 dissection), which is the standard procedure in Western countries seems inadequate because those lymph nodes with metastasis will be left behind.

However, D2 dissection was reported to be associated with significant morbidity and mortality[8,9]. Randomized controlled trials on D2 dissection also did not result in improved survival[10-14]. Nevertheless, it is still not conclusive at the present since poor results of D2 dissection might be caused by inadequate surgical volume and inexperience on the surgeon side and recent studies increasingly reported D2 dissection to be a safe operation[15,16]. In Japan and Asian countries, mortality of D2 dissection was reported to be less than 1% in specialized centers[17].

Regarding this aspect, the authors had no mortality in the present series of 130 consecutive patients. Complications were found only in 17.69% and these complications included minor events such as wound infections. It could be said that D2 dissection with adequate lymph node clearance (in the present study harvested lymph nodes were 26.53 nodes) could be done safely once the volume of surgery was adequate (the present study surgical volume 19 cases per year). Moreover, lymph node metastasis was as high as 83% in T3 tumors, which was the majority of gastric cancer patients in Thailand. Therefore, D2 dissection should be advised for most of the patients with gastric cancer in Thailand.

The presented 0% mortality may come from the fact that the authors had no apparent leakage in the present study. Six patients had intraabdominal complications but failed to demonstrate leakage on contrast study. Reports from Western countrieees had a high incidence of leakage and fistula in contrast to the result from the present study. Leakage if uncontrolled could lead to sepsis and death. Therefore, effort should be done to prevent this complication. Gentle handling of the tissue, accurate and systematic dissection to mimimize tissue damage and blood loss all play important roles in this regard.

D2 dissection includes perigastric lymph nodes (N1 group) and those along major vessels at the upper border of the pancreas (N2 group: 7, 8a, 9, 10, 11p, 12a, 14v). From the present study, metastasis to N2 group was not uniform among those stations with the highest incidence of metastasis in group 7, 8 and 9 and lower incidence in the remaining groups. From the surgical aspect, meticulous dissection of node 7, 8 and 9 is important and should be done properly en-bloc. This result was the same as reported by Ichikura[18], that lymph nodes group 7, 8, 9 are the most important and advocated that dissection of these groups (D1.5) may be enough. Dissection of the specimen and grouping of the resected lymph node (preferably done by the surgeon) is also important for accurate grouping and pathological examination.

Pattern of lymph node metastasis according to tumor location showed that a tumor of the middle part had the most widespread pattern (to group 1, 2, 3, 4, 6, 7, 9) while a tumor of the upper part had a high incidence of lymph node metastasis to lymph node group 1,3,9. This finding suggests that a tumor of middle part had complex and various routes of lymphatic spread and care has to be taken when the decision is made regarding extent of resection and lymph node dissection for tumor of this area.

Strong relation between angiolymphatic invasion and survival proposed another important aspect. In the present study, angiolymphatic invasion appeared to be the most potent factor to influence prognosis. This finding may reflect the aggressive nature of gastric cancer in Thailand. In this aspect, removal of the lymph nodes along with their associated lymphatic ducts, namely en-bloc dissection may be important to improve its clearance.

Another strong prognostic indicator in the present study was positive peritoneal wash cytology ($p = 0.003$). This finding was also reported in various studies[19-22]. No survival more than 6 months was seen in the presented patients who had cytology positive. Attempt to perform D2 dissection should be withheld in this setting because there was no benefit on survival.

The present study of gastric cancer showed that good survival could be achieved if aggressive surgery with D2 dissection was employed. However, to avoid morbidity and mortality associated with the procedure, understanding of the pattern of lymph node metastasis and systematic dissection as described in the present study is the key to obtain a good result.

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การกระจายไปต่อมน้ำเหลืองในผู้ป่วยมะเร็งกระเพาะอาหารที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองกลุ่มที่ 2 (D2 dissection)

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ในการผ่าตัดมะเร็งกระเพาะอาหาร ขอบเขตที่เหมาะสมในการเลาะต่อมน้ำเหลืองยังไม่มีข้อสรุป ดังนั้น การวิเคราะห์รูปแบบและอุบัติการณ์ของการกระจายไปยังต่อมน้ำเหลืองอาจจะช่วยตอบปัญหานี้ได้ การศึกษานี้ทำการวิเคราะห์การกระจายของมะเร็งไปยังต่อมน้ำเหลือง และอัตราการอยู่รอดของผู้ป่วยมะเร็งกระเพาะอาหาร ที่ได้รับการผ่าตัดกระเพาะอาหารโดยทำการเลาะต่อมน้ำเหลืองถึงกลุ่ม D2 จำนวน 130 คน ซึ่งได้รับการผ่าตัดที่หน่วยศัลยศาสตร์ทั่วไป ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ระหว่างเดือนมิถุนายน พ.ศ. 2544 ถึงเดือนตุลาคม พ.ศ. 2551

การศึกษานี้พบว่ามีผู้ป่วย 40% อยู่ใน stage N1 และ 31.5% อยู่ใน stage N2 ประมาณ 44% ของผู้ป่วยที่มีการกระจายไปต่อมน้ำเหลือง จะมีการกระจายไปยังต่อมน้ำเหลืองกลุ่ม N2 อัตราการอยู่รอดที่ 5 ปี ในผู้ป่วยที่มีการกระจายไปต่อมน้ำเหลืองต่ำกว่ากรณีไม่มีการกระจายอย่างมีนัยสำคัญ (39% และ 73%, p = 0.003) มะเร็งที่อยู่ในส่วนกลางกระเพาะอาหาร มีการกระจายไปยังต่อมน้ำเหลือง ในขอบเขตที่กว้างกว่ามะเร็งในตำแหน่งอื่น ต่อมน้ำเหลืองที่มีการกระจายมากได้แก่กลุ่ม 7,8,9 โดยที่กลุ่ม 10,11,12 มีการกระจายน้อยกว่า ไม่พบอัตราตายในการศึกษานี้การวิเคราะห์ปัจจัยที่มีผลต่อการอยู่รอดพบว่า N staging, การกระจายไปยังต่อมน้ำเหลืองที่มากกว่า 5 ต่อม และการกระจายเข้าสู่ท่อน้ำเหลือง มีผลทำให้การอยู่รอดต่ำลงอย่างมีนัยสำคัญ เพื่อให้การผ่าตัดรักษามะเร็งกระเพาะอาหารได้ผลดี มีความจำเป็น ที่จะต้องเลาะต่อมน้ำเหลืองถึงกลุ่มที่ 2 ออกอย่างเป็นระบบ จึงจะผ่าตัดมะเร็งออกอย่างสมบูรณ์หัตถการนี้สามารถทำได้อย่างปลอดภัย