

# Survival Rate in Curative Resection of Gastric Cancer Patients at Maharat Nakhon Ratchasima Hospital

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## Abstract

**Background:** Gastric cancer still remains an important cancer because of the mortality rate of this lethal disease is high, this cancer has rapid progression and it is difficult to detect early stage. Survival rate is variety between geographically and accurate prognostic factors for gastric cancer are still limited.

**Objective:** The aim of this study was to evaluate survival rate and the clinicopathological factors associated with survival of gastric cancer patients.

**Methods:** Data of gastric cancer patients who underwent resection were collected from medical records between January 1, 2012 to December 31, 2016 (5 years). The primary outcome was overall survival by Kaplan-Meier method. Univariable and multivariable Cox proportional hazard regression analysis were performed to determine independent prognostic factors.

**Results:** Of 96 patients, mean age was 62.4 years, lower third was the most common tumor location, total gastrectomy was the most common procedure. The study demonstrated median survival time was 12.4 months and 1-year, 3-year, 5-year survival rates were 53%, 18%, and 12% respectively. Univariable Cox regression found that lymph node ratio (LNR)  $> 0.4$  (HR 3.96, 95% CI 1.81-8.67,  $p = 0.001$ ) and stage IV (HR 8.41, 95% CI 1.88-37.57,  $p = 0.005$ ) were associated with poor survival. Multivariable Cox regression analyses showed that only staging IV (HR 9.02, 95% CI 1.35-60.20,  $p = 0.024$ ) was significantly associated with survival.

**Conclusion:** Our study demonstrates that clinical stage IV is the independent prognostic factor associated with poor survival outcome.

**Keywords:** Gastric cancer, Survival rate, Prognostic factors

## INTRODUCTION

Gastric cancer remains an important cancer worldwide because of the mortality rate of this lethal disease is high, this cancer has rapid progression and it is difficult to detect early stage. Despite the steady decline in its incidence rate and mortality in recent years, survival rate of gastric cancer still is dismal. In 2020, estimated

1,089,103 new cases and 768,793 deaths, ranking fifth for incidence and fourth for mortality globally.<sup>1</sup> National Cancer Institute of Thailand reported the age-standardized incidence rate of gastric cancer was 4.1 per 100,000 per year in Thai males and 2.6 per 100,000 per year in Thai females and it is the eighth leading cancer in males and the ninth in females.<sup>2</sup> 5-year survival rate is variety

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in range which high in Japan (60-70.5%) compare to western (10-25%).<sup>3-6</sup> Report from Thailand showed 5-year survival rate was high (59%).<sup>7</sup> Many clinicopathologic factors associated with gastric cancer survival including tumor size, surgical margin, depth invasion, lymph node metastasis, lymph node ratio (LNR), blood loss, and body mass index (BMI).<sup>8-12</sup> This study aims to evaluate survival rate and the clinicopathological factors associated with survival of gastric cancer patients.

## MATERIALS AND METHODS

### Study population

Data were collected retrospectively from medical records at Maharat Nakhon Ratchasima Hospital between January 1, 2012 to December 31, 2016 (5 years) of patients with gastric cancer codes ICD10 (C161, C162, C163, C164, C165, C166, C167, C168, C169). All elective patients underwent gastric resection and had pathological report confirmed gastric adenocarcinoma. We excluded patients with adenocarcinoma of cardia, metastatic other cancers to stomach and recurrent gastric cancer. After that, patients were followed until December 31, 2021. Clinicopathological factors were collected including gender, age, tumor size ( $< 5$  cm,  $> 5$  cm),<sup>8</sup> body mass index (BMI) ( $< 18.5$  kg/m<sup>2</sup>,  $18.5 - < 23$  kg/m<sup>2</sup>,  $> 23$  kg/m<sup>2</sup>),<sup>9</sup> surgical margin (negative, positive), lymphovascular invasion (LVI) (negative, positive), intraoperative blood loss (IBL) ( $< 400$  ml,  $> 400$  ml),<sup>10</sup> lymph node ratio (LNR) ( $0, < 0.13, > 0.13 - < 0.4, > 0.4$ ),<sup>12</sup> and staging base on American Joint Committee on Cancer 7<sup>th</sup> edition (AJCC7<sup>th</sup>) (4 major subgroups).<sup>13</sup>

### Statistical analysis

Histograms, boxplots, and descriptive methods were used to examine data for errors, outliers, and missing values. All statistical analyses were performed with STATA, version 11.0, software (StataCorp LP, College Station, Texas). The survival analysis was calculated using the Kaplan–Meier method. The independent prognostic factors including gender, age, BMI, tumor size, LVI, LNR, surgical margin, IBL, and staging AJCC7<sup>th</sup> (4 major subgroups) were examined by Univariable Cox proportional hazard regression analysis. All interested variables included, age, BMI, tumor size, LNR, surgical margin, and staging AJCC7<sup>th</sup> (4 major subgroups) were forced in final model. The results were expressed as hazard ratios

with p-values and 95% confidence intervals. A p-value of  $< 0.05$  was considered statistically significant. The local Ethical Committee of our hospital approved the study as Declaration of Helsinki (Document No 054/2022).

## RESULTS

### Demographic data

Of 96 patients, demographic data are presented in Table 1. Mean age was 62.4 years (ranged 39 to 86). There were more males (68.7%) than females (31.3%). The most common tumor location was lower third (68.7%) and middle third (21.9) was the second most common. Total gastrectomy (40.3%) was the most common operation, and subtotal gastrectomy (33.3%) was the second most common. Only 12 patients (12.5%) were performed D<sub>2</sub> lymphadenectomy. The average number of lymph nodes yield was 16.5 (ranged 0-45). According to the 7<sup>th</sup> edition American Joint Committee on Cancer (AJCC) staging system for gastric cancer, most patients in this study were in stage III (60.4%) which in IIIC, IIIB, IIIA were 28.1%, 18.8%, and 13.5% respectively and stage IV was 17.8%. Of all patients, only 40.6% were received adjuvant chemotherapy. The mean tumor size was 6.0 cm (ranged 1.5- 15). The average BMI was 19.2 kg/m<sup>2</sup> (ranged 11.4- 33.8). Median intraoperative blood loss (OBL) was 225 ml (IQR 137-500). Approximately 31.30% of patients had comorbidities, the most common was hypertension (19.8%) and the second common was diabetes mellitus (7.3%). In Table 2 demonstrated that the most common metastatic site was peritoneal metastasis (9.4%) and the second most common was liver metastasis (5.2%). In present study, we performed peritoneal washing for cytology only 7.2% and 2.1% had positive result. Postoperative morbidities and postoperative mortality are demonstrated in Table 3. Postoperative complication was 22.9% and there were esophagojejunal anastomosis leakage (2.1%), gastrojejunal anastomosis leakage (1%), and pancreatic leakage (1%). There were 2 subdiaphragmatic collection patients which need percutaneous drainage. Reoperation was performed in a patient with gastrojejunal anastomosis leakage. The rest of other anastomosis leakage patients were successfully managed with non-operative treatment. There were 4 postoperative deaths (4.2%) The cause of death were postoperative myocardial infarction and hospital acquire pneumonia with sepsis.

**Table 1** Demographic data (N = 96)

Character	n (%)
<b>Age year mean (SD, range)</b>	64.4 (12.5, 31 - 86)
< 60	37 (38.5)
≥ 60	59 (61.5)
<b>Gender</b>	
Male	66 (68.7)
Female	30 (31.3)
<b>Location</b>	
Upper third	6 (6.3)
Middle third	21 (21.9)
Lower third	66 (68.7)
Entire	3 (3.1)
<b>Operation</b>	
Total gastrectomy	39 (40.3)
Subtotal gastrectomy	32 (33.3)
Hemigastrectomy	19 (19.8)
Distal gastrectomy	6 (6.3)
<b>Lymph dissection</b>	
< D <sub>2</sub>	84 (87.5)
≥ D <sub>2</sub>	12 (12.5)
<b>Lymph nodes yield mean (SD, range)</b>	16.5 (11.5, 0 - 45)
<b>Lymph node ratio (LNR)</b>	
0	12 (13.2)
< 0.13	14 (15.4)
≥ 0.13 - < 0.4	18 (19.8)
≥ 0.4	47 (51.7)
<b>Lymphovascular invasion, n = 70</b>	60 (85.7)
<b>American Joint Committee on Cancer 7<sup>th</sup> stage</b>	
IA	1 (1.0)
IB	3 (3.1)
IIA	8 (8.3)
IIB	9 (9.4)
IIIA	13 (13.5)
IIIB	18 (18.8)
IIIC	27 (28.1)
IV	17 (17.8)
<b>BMI (kg/m<sup>2</sup>) mean (SD, range)</b>	19.2 (4.0, 11.4 - 33.8)
< 18.5	39 (50.0)
18.5 - < 23	26 (33.3)
≥ 23	13 (16.7)
<b>Adjuvant chemotherapy</b>	
Yes	39 (40.6)
No	57 (59.4)
<b>Comorbidity</b>	30 (31.3)
<b>Tumor size (cm) mean (SD, range)</b>	6.0 (2.5, 1.5 - 15)
≤ 5 cm	41 (42.7)
> 5 cm	55 (57.3)
<b>Blood loss (ml) median (IQR Q1-Q3)</b>	225 (137 - 500)

**Table 2** Organs metastasis in stage IV (N = 96)

Organ	n (%)
<b>Gross peritoneal metastasis</b>	9 (9.4)
<b>Liver metastasis</b>	5 (5.2)
<b>Ovary</b>	1 (1)
<b>Peritoneal washing cytology</b>	7 (7.3)
Positive	2 (2.1)
Negative	5 (5.2)

**Table 3** Postoperative complication and postoperative death (N = 96)

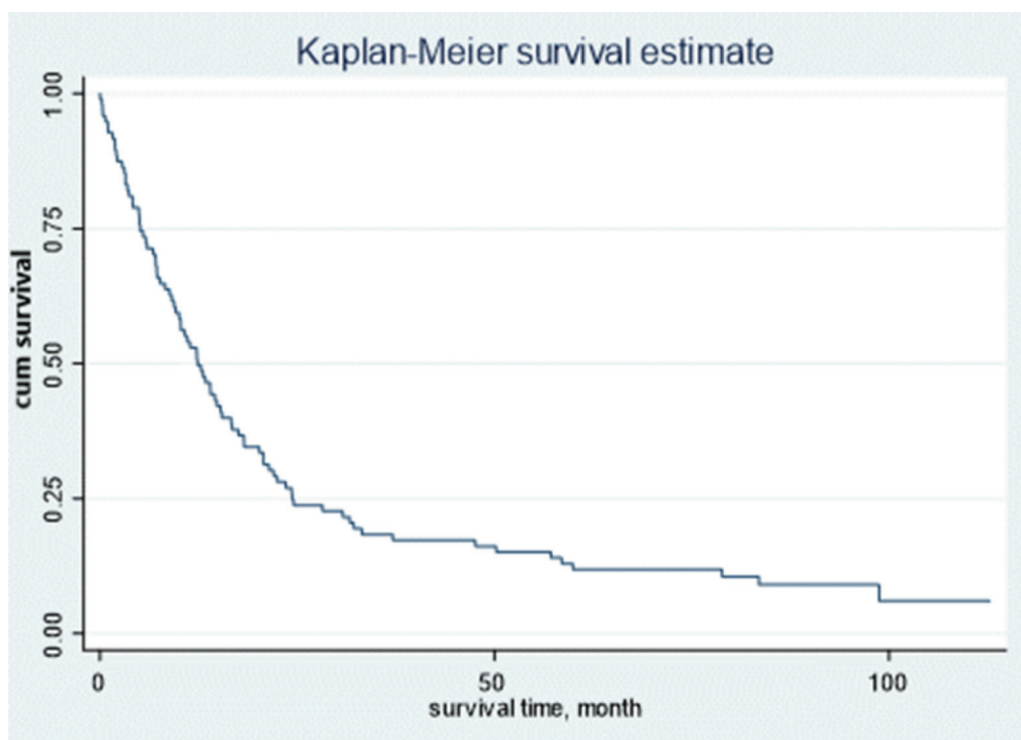
Postoperative complication	n (%)
Postoperative myocardial infarction	2 (2.1)
Hospital acquire pneumonia	3 (3.1)
Wound infection	3 (3.1)
Pancreatic leakage	1 (1)
Esophagojejunal anastomosis leakage	2 (2.1)
Gastrojejunal anastomosis leakage	1 (1)
Subdiaphragmatic collection	2 (2.1)
Prolonged drainage	8 (8.3)
Postoperative deaths	4 (4.2)
Postoperative myocardial infarction	2 (2.1)
Hospital acquire pneumonia with sepsis	2 (2.1)

### Survival analysis

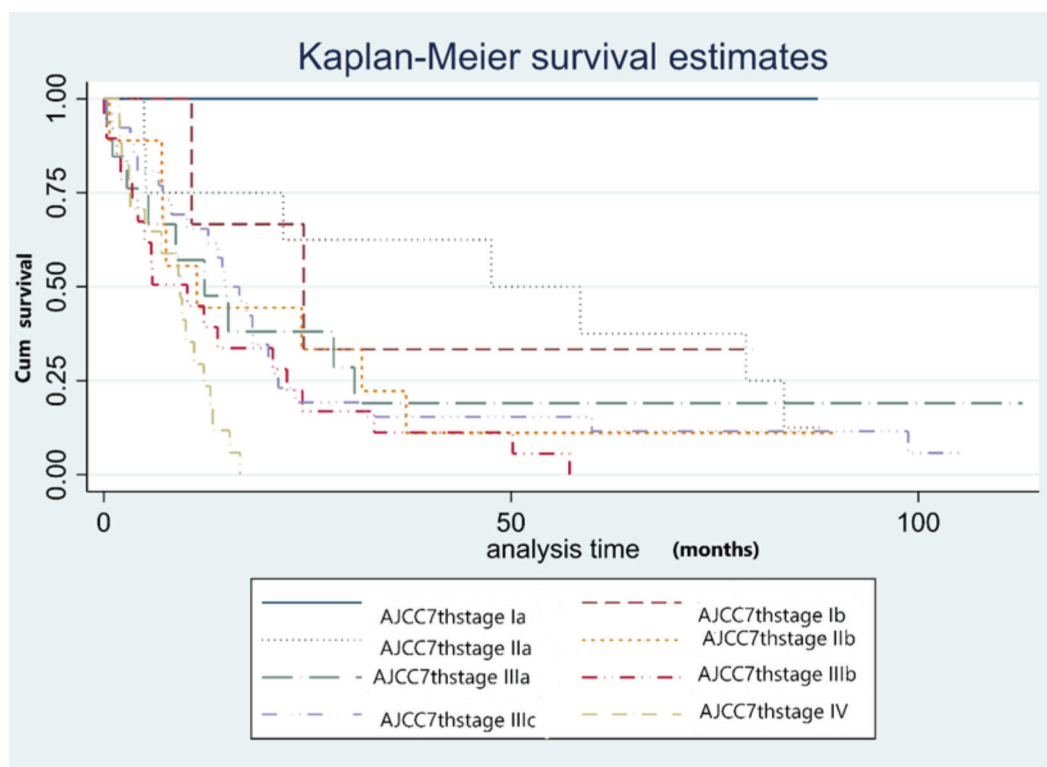
Overall survival is demonstrated in **Figure 1**. Median survival time was 12.4 months (95% CI 9.4-15.4) and 1-year, 3-year, 5-year survival rates were 53% (95% CI 42%-62%), 18% (95% CI 11%-27%), 12% (95% CI 6%-19%) respectively. **Figure 2** staging describe AJCC7<sup>th</sup> showed that 5-year survival rate was 100% in patients with stage IA, 33% for IB, 37% for IIA, 11% for IIB, 19% for IIIA, 11% for IIIB, 11% for IIIC, and 0% for IV.

### Clinicopathologic factors analysis

In **Table 4** demonstrate that the longest median survival was 33 months for patients with lymph node ratio < 0.13. The mortality rate was highest in stage (subgroups AJCC7<sup>th</sup>) IV (12 per 100 person-months). The person-months at risk more than 1,500 person-months in patients with negative surgical margin, male gender, and patients with blood loss < 400 ml.



**Figure 1** Overall survival gastric cancer patients  
Y-axis name: cum survival and X-axis name: time (months)



**Figure 2** Survival gastric cancer patients by staging AJCC7<sup>th</sup>  
Y-axis name: cum survival and X-axis name: time (months)

The clinicopathologic factors (Table 4) were analyzed in univariable Cox regression found that lymph node ratio (LNR) and staging (subgroups of AJCC7<sup>th</sup>) were associated with poor survival. The mortality risk was increased for patients with LNR  $\geq 0.4$  (HR 3.96, 95% CI 1.81-8.67,  $p = 0.001$ ). In addition, the mortality risk was 8-fold higher in patients with stage IV (HR 8.41, 95% CI 1.88-37.57,  $p = 0.005$ ) compared to stage I (IA,

IB). Other factors, such as age, gender, body mass index (BMI), tumor size, surgical margin, lymphovascular invasion, and intraoperative blood loss had no association with patient survival ( $p > 0.05$ ). Multivariable Cox regression analyses (Table 5) showed that only staging IV (aHR 9.02, 95% CI 1.35-60.20,  $p = 0.024$ ) was significantly associated with survival.

**Table 4** Cox univariable regression analysis of clinicopathologic factors

Character	n	Median survival (months)	Time at risk	Incidence rate/100	Crude HR (95% CI)	p-value
Gender						
Male	66	14.6	1,517.3	3.76	1	0.421
Female	30	9.1	635.3	4.41	1.21 (0.76 - 1.90)	
Age						
> 60	40	12.4	1,050.4	3.52	1	0.520
≤ 60	56	11.4	1,102.2	4.35	0.87 (0.56 - 1.34)	
BMI (kg/m²)						
< 18.5	39	10.3	782.6	4.60	1.29 (0.76 - 2.21)	0.344
18.5 - < 23	26	15.4	649.1	3.54	1	
> 23	13	15.3	355.8	3.09	0.92 (0.44 - 1.89)	0.813
Tumor size cm						
≤ 5	41	10.8	896.6	4.13	1	0.708
> 5	55	14.0	1,256.0	3.82	1.17 (0.71 - 1.92)	
Surgical margin						
Positive	13	11.4	150.2	7.99	1	0.125
Negative	83	13.1	2,002.4	3.65	0.62 (0.33 - 1.14)	
Lymphovascular invasion, n = 70						
No	10	14.0	323.5	2.47	1	0.294
Yes	60	12.3	1,284.5	4.13	1.49 (0.71 - 3.15)	
Blood loss, cc.						
< 400	64	12.3	1,649.3	3.33	1	0.156
≥ 400	32	14.6	503.3	5.96	1.39 (0.88 - 2.18)	
LNR						
0	12	24.3	515.4	1.55	1	0.519
< 0.13	14	33.2	516.7	2.13	1.35 (0.54 - 3.36)	
≥ 0.13 - < 0.4	18	13.4	435.0	3.68	2.04 (0.86 - 4.81)	0.104
≥ 0.4	47	9.6	577.0	7.80	3.96 (1.81 - 8.67)	
Staging AJCC7 <sup>th</sup> (4major subgroups)						
I (IA, IB)	4	24.5	202.6	0.99	1	0.258
II (IIA, IIB)	17	24.3	605.3	2.48	2.34 (0.54 - 10.26)	
III (IIIA, IIIB, IIIC)	58	14.0	1,200.1	4.25	3.64 (0.88 - 15.04)	0.074
IV (IV)	17	9.4	144.6	11.76	8.41 (1.88 - 37.57)	

BMI, body mass index (kg/m<sup>2</sup>); LNR, lymph node ratio; AJCC7<sup>th</sup>, American Joint Committee on Cancer 7<sup>th</sup> edition

**Table 5** Cox multivariable regression analysis of clinicopathologic factors

Character	Crude HR (95% CI)	Adjusted HR (95% CI)	p-value
<b>Age</b>			0.296
≥ 60	1	Ref.	
< 60	0.87 (0.56 - 1.34)	1.37 (0.76 - 2.47)	
<b>BMI (kg/m<sup>2</sup>)</b>			0.284
< 18.5	1.29 (0.76 - 2.21)	1.57 (0.85 - 2.92)	
18.5 - < 23	1	Ref.	
≥ 23	0.92 (0.44 - 1.89)	1.59 (0.71 - 3.53)	
<b>Tumor size, cm.</b>			0.772
≤ 5	1	Ref.	
> 5	1.17 (0.71 - 1.92)	0.92 (0.51 - 1.64)	
<b>Surgical margin</b>			0.212
2 = positive = < 1 mm	1	Ref.	
1 = negative = > 1 mm	0.62 (0.33 - 1.14)	0.61 (0.29 - 1.29)	
<b>LNR</b>			0.122
1 = 0	1	Ref.	
2 = < 0.13	1.35 (0.54 - 3.36)	1.06 (0.22 - 5.09)	
3 = > 0.13 - < 0.4	2.04 (0.86 - 4.81)	1.91 (0.45 - 8.05)	
4 = > 0.4	3.96 (1.81 - 8.67)	2.48 (0.56 - 10.85)	
<b>Staging (AJCC7<sup>th</sup>) subgroup</b>			0.024
1	1	Ref.	
2	2.34 (0.54 - 10.26)	1.64 (0.33 - 8.19)	
3	3.64 (0.88 - 15.04)	3.95 (0.64 - 24.25)	
4	8.41 (1.88 - 37.57)	9.02 (1.35 - 60.20)	

BMI, body mass index (kg/m<sup>2</sup>); LNR, lymph node ratio; AJCC7<sup>th</sup>, American Joint Committee on Cancer 7<sup>th</sup> edition

## DISCUSSION

5-year survival rate was highest in Japan (60-70.5%),<sup>3-4</sup> while western reported 10%-25%.<sup>5-6</sup> The present study demonstrated that 5-year survival rate (12%). There was study reported that early stage gastric cancer detection had 5-year survival rate over 90%.<sup>14</sup> In our study nearly 80% of patients were in stage III, and IV. A study in university institution from Thailand showed that 5-year survival rate was high (59%) benefit clearly in stage II, IIIA (75%, 78% respectively), even though had 66% of patients in stage III, and IV.<sup>7</sup> We found that all patients (100%) in Thai study had D2 gastrectomy compared to present study had only 12.5%. The number of lymph node yield is important in survival. A study reported at least 40 lymph nodes yield from lymph node dissection in gastrectomy improved survival 7.6% (for T1/2N0), 5.7% (for T1/2N1), 11% (for T3N0), and 7% (for T3N1).<sup>11</sup> Also,

for accurate staging at least 16 retrieved lymph nodes needed and at least 24 nodes yield reduced the risk of locoregional recurrence.<sup>15-16</sup> In our study average lymph node yield was 16.5 nodes. In western, postoperative morbidity was high in D2 gastrectomy patients compared to D1 gastrectomy (43 vs 25%,  $p < 0.001$ ) and hospital mortality in D2 gastrectomy group also higher than D1 gastrectomy (10 vs 4%,  $p = 0.004$ ) which contrast to Japan studies reported mortality rate of 2-3%.<sup>17-19</sup> A study from Thailand also reported low hospital morbidity (17%) and no mortality compared to western.<sup>7</sup> In present study showed postoperative complication was 22.9% higher than Japanese report and lower than western reports. We found explanation that only 12.5% of D2 gastrectomy was performed in our study, and the BMI in Thai patients is low compare to Western patients. In our study showed pulmonary infection, anastomosis leakage, and wound



infection were common report, but cardiovascular and pulmonary complication can lead to hospital mortality. In current study, univariable Cox regression showed lymph node ratio ( $\text{LNR} \geq 0.4$ ) and stage IV (subgroups of AJCC7<sup>th</sup>) were independent prognostic factor. A study demonstrated that the number of retrieved lymph node was an independent prognostic factor and a larger number of lymph nodes can increase 5-year overall survival rate.<sup>11</sup> In the 7<sup>th</sup> Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) tumor, lymph node, metastasis (TNM) staging system published in 2010, requires that at least 15 lymph nodes be examined to get accurate staging. The phenomenon of stage migration is happened by an insufficient number of lymph nodes examined.<sup>20</sup> LNR was used to reduce stage migration, even in the case of limited lymph node dissection and also showed that LNR was an independent prognostic factor.<sup>20-23</sup> Cox multivariable regression analysis in the present study demonstrated only stage IV (subgroups of AJCC7<sup>th</sup>) was clearly independent prognostic factor. In present study showed that gross peritoneal metastasis was the most common found. A study showed peritoneal metastasis, vascular invasion, lymphatic invasion were independent prognostic factors for survival in stage IV and positive peritoneal washing cytology is predictor of peritoneal recurrence.<sup>6-7,24-25</sup> There are several modalities for liver metastasis treatment to improve survival rate such as hepatectomy if possible or inoperable patients, transcatheter arterial chemoembolization (TACE), systemic chemotherapy, microwave coagulation therapy (MCT), or immunotherapy were introduced. The prognosis is still poor because single liver metastasis is infrequent.<sup>24</sup> A study showed patients with peritoneal metastasis and liver metastasis had 5-year survival rate 16.2%, 0.0% respectively.<sup>24</sup> In present study, there was no 5-year survival rate in both groups. There was study showed BMI (underweight and overweight/obese patients) was associated with poor survival rate contrast to the present study found that no association with survival.<sup>9</sup> However, nutritional status should be optimized in high-risk patients for better outcome.<sup>9</sup> A Japanese study reported that lymphovascular invasion (LVI) was an independent prognostic factor in advanced gastric cancer with lymph node metastasis.<sup>26</sup> The explanation from study, lymph nodes had much blood flow through the import and export lymph vessels, believed that metastases to the lymph nodes may be derived through routes other than the lymph flow.<sup>26</sup> In present study showed 85.7%

of patients had LVI, and had no association between LVI and survival. The present study has a clinical limitation. It was a retrospective study with a relatively small sample size, larger population study is needed.

## CONCLUSION

The present study demonstrates 5-year survival rates was 12% and clinical stage IV is the independent prognostic factor associated with poor survival outcome. Improving therapeutic outcomes requires early diagnosis and careful surgery.

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## บทคัดย่อ อัตราการรอดชีวิตของผู้ป่วยมะเร็งกระเพาะอาหารที่ได้รับการผ่าตัดหวังผลหายขาดของโรงพยาบาลมหาราชนครราชสีมา

กิริศักดิ์ จัตววัฒนกุล, พบ.

หน่วยศัลยกรรมทั่วไป กลุ่มงานศัลยกรรม โรงพยาบาลมหาราชนครราชสีมา

**ความเป็นมา:** ถึงแม้อุบัติการณ์การเกิดมะเร็งกระเพาะอาหารจะลดลงแต่ก็เป็นมะเร็งที่มีอัตราการเสียชีวิตของผู้ป่วยที่อยู่อันดับต้นๆ อัตราการรอดชีวิตยังคงมีความแตกต่างระหว่างภูมิภาคโดยพบว่าอัตราการรอดชีวิตที่สูงในเอเชียตะวันออกและรองลงมาในตะวันตกและพบว่ามีหลายปัจจัยเสี่ยงที่ผลต่ออัตราการรอดชีพ

**วัตถุประสงค์:** เพื่อศึกษาอัตราการรอดชีวิต ของผู้ป่วยมะเร็งกระเพาะอาหารที่ได้รับการผ่าตัดหวังผลหายขาด และปัจจัยเสี่ยงที่มีผลต่ออัตราการรอดชีวิตของมะเร็งกระเพาะอาหาร

**วิธีการศึกษา:** ศึกษาข้อมูลจากเวชระเบียนย้อนหลังผู้ป่วยมะเร็งกระเพาะอาหารที่ได้รับการผ่าตัดหวังผลหายขาดที่โรงพยาบาลมหาราชนครราชสีมาในช่วงเวลา 1 มกราคม 2555 ถึง 31 ธันวาคม 2559 อัตราการรอดชีวิต (survival rate) วิเคราะห์โดย Kaplan-Meier curve และวิเคราะห์ปัจจัยที่มีผลต่อการรอดชีวิตโดย Cox proportional hazard regression แสดงผลลัพธ์ hazard ratios ค่า  $p$ -values และ 95% confidence intervals กำหนดระดับนัยสำคัญ 0.05

**ผลการศึกษา:** ในการศึกษานี้มีผู้ป่วยทั้งหมด 96 ราย เพศชายร้อยละ 68.7 อายุเฉลี่ยเท่ากับ 64 ปี (SD = 12.5) มะเร็งพบมากบริเวณ 1 ส่วน 3 ล่างของกระเพาะอาหารร้อยละ 68.7 และมีผู้ป่วยอยู่ในระยะ 3 มากสุุ่ร้อยละ 60.4 พบการผ่าตัดแบบ total gastrectomy มากสุุ่ร้อยละ 40.3 มีอัตราแทรกซ้อนหลังการผ่าตัดร้อยละ 22.9 และมีอัตราเสียชีวิตหลังผ่าตัดร้อยละ 4.2 ในการศึกษาพบว่ค่ามัธยฐานเวลาการรอดชีวิต (Median survival time) เท่ากับ 12.4 เดือน และอัตราการรอดชีวิตที่ 1, 3, 5 ปีเท่ากับร้อยละ 53% (95% CI 42% - 62%), 18% (95% CI 11% - 27%), 12% (95% CI 6% - 19%) ตามลำดับ ปัจจัยเสี่ยงที่สัมพันธ์กับการรอดชีวิต (Independent factors) คือ มะเร็งระยะที่ 4 (Stage IV) (aHR 9.02, 95% CI 1.35 - 60.20,  $p = 0.024$ )

**สรุปผลการศึกษา:** ในการศึกษาพบว่พบว่มะเร็งระยะที่ 4 ผลต่อการรอดชีวิตโดยรวมอย่างมีนัยสำคัญ