

Retrospective Study

# How does epidemiological and clinicopathological features affect survival after gastrectomy for gastric cancer patients-single Egyptian center experience

Ehab El Hanafy, Ayman El Nakeeb, Helmy Ezzat, Emad Hamdy, Ehab Atif, Tharwat Kandil, Amgad Fouad, Mohamed Abdel Wahab, Ahmed Monier

Ehab El Hanafy, Ayman El Nakeeb, Helmy Ezzat, Emad Hamdy, Ehab Atif, Tharwat Kandil, Amgad Fouad, Mohamed Abdel Wahab, Ahmed Monier, Gastroenterology Surgical Center, Mansoura University, Mansoura 35516, Egypt

**Author contributions:** El Hanafy E and El Nakeeb A conceived and designed this study; El Hanafy E, Hamdy E, Atif E, Kandil T, Fouad A and Wahab MA acquired the data; El Hanafy E, El Nakeeb A, Ezzat H and Monier A analysis and interpretation of data; Atif E, Kandil T and Fouad A drafting of manuscript; El Hanafy E and Wahab MA critical revision of manuscript.

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**Correspondence to:** Ehab El Hanafy, MD, Assistant Professor, Gastroenterology Surgical Center, Mansoura University, Elgomhouria St. Mansoura 35516, Egypt. [dr\\_ahab\\_elhanafy@yahoo.com](mailto:dr_ahab_elhanafy@yahoo.com)  
Telephone: +20-50-2243220

Fax: +20-50-2236868

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## Abstract

**AIM:** To investigate the clinicopathological features and the significance of different prognostic factors which predict surgical overall survival in patients with gastric carcinoma.

**METHODS:** This retrospective study includes 80 patients diagnosed and treated at gastroenterology surgical center, Mansoura University, Egypt between February 2009 to February 2013. Prognostic factors were assessed by cox proportional hazard model.

**RESULTS:** There were 57 male and 23 female. The median age was 57 years (24-83). One, 3 and 5 years survival rates were 71%, 69% and 46% respectively. The median survival was 69.96 mo. During the follow-up period, 13 patients died (16%). Hospital morbidity was reported in 10 patients (12.5%). The median number of lymph nodes removed was 22 (4-41). Lymph node (LN) involvement was found in 91% of cases. After R0 resection, depth of wall invasion, LN involvement and the number (> 15) of retrieved LN, LN ratio and tumor differentiation predict survival. In multivariable analysis, tumor differentiation, curability of resection and a number of resected LN superior to 15 were found to be

independent prognostic factors.

**CONCLUSION:** Surgery remains the cornerstone of treatment. Tumor differentiation, curability of resection and a number of resected LN superior to 15 were found to be independent prognostic factors. Extended LN dissection does not increase the morbidity or mortality rate but markedly improves long term survival.

**Key words:** Cancer stomach; Prognostic factors; Lymph node metastasis; Recurrence after gastrectomy; Lymph node ratio

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**Core tip:** The epidemiology and the surgical outcomes for patients with carcinoma of the stomach vary significantly from one part of the world to another. Surgery remains the cornerstone of treatment. Tumor differentiation, curability of resection and a number of resected lymph node (LN) superior to 15 were found to be independent prognostic factors. Extended LN dissection does not increase the morbidity or mortality rate but markedly improves long term survival.

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## INTRODUCTION

Cancer of the stomach is the fifth most common cancer in the world and it is also the third leading cause of cancer death of both sexes worldwide<sup>[1]</sup>. Prognosis is poor perhaps due to late diagnosis and frequent local-regional recurrences<sup>[2]</sup>. It still one of the common health problems in Egypt. This requires investigation of the possible reasons for the worsening of survival and searching for prognostic factors of better survival.

Whenever possible, complete resection of the tumor with satisfactory safety margins is the standard treatment providing hope for cure<sup>[3,4]</sup>. Many prognostic factors have been investigated to assess their significance in predicting patients' outcome. The number of metastatic lymph nodes (N stage) and the depth of the primary tumor (T stage) are currently considered the most reliable prognostic factors for patients with radically resected gastric cancer<sup>[5-7]</sup>. Lymph node (LN) clearance remains the most challenging part of the operation, the extent of LNs dissection is classically termed D0, D1, and D2<sup>[8,9]</sup>. The UICC/AJCC classification, suggests that at least 15 LNs should be examined for a correct assessment of N stage<sup>[10,11]</sup>.

Therefore, the surgeon experience toward more radical resection with LN removal is the most important non-TNM prognostic factors in gastric cancer. However, prognosis varies among patients with a similar tumor stage; therefore, disease staging alone cannot accurately predict the outcome for individual patients<sup>[12]</sup>.

The aim of this study was to evaluate the Clinico-pathological features and the significance of different prognostic factors in patients undergoing resection for gastric cancer.

## MATERIALS AND METHODS

This is a retrospective study of patients underwent gastrectomy for gastric cancer from February 2009 to February 2013, in gastroenterology surgical center, Mansoura University, Egypt. A total of 80 patients diagnosed with gastric cancer underwent gastrectomy during this period. R0 resection was defined by the complete tumor excision after surgical treatment proved by pathologic examination of the resected margins. Clinicopathological parameters, including gender and age of patients; location of the tumor; depth of invasion; LN metastasis status; operative details; morbidity and mortality; and survival and recurrence were collected. Patients with synchronous malignancies, and those who were diagnosed others than adenocarcinoma was excluded from the study. We did not use endoscopic ultrasound in our center. During the study period, the median survival for patients who did not undergo surgery and only had palliative management was 6 mo. All patients did not receive a preoperative adjuvant or neoadjuvant therapy.

Cancer staging was as described in the seventh edition of the International Union Against Cancer TNM Classification<sup>[9]</sup>.

All of the surgical procedures were performed by experienced gastric surgeons of our single institute with a definitive treatment guideline for gastric cancer. Two types of gastrectomy were performed: Subtotal gastrectomy (STG) or total gastrectomy (TG).

STG was performed for tumors located in the lower and middle third of the stomach when a 3-6 cm tumor proximal free safety margin can be achieved. All the other patients underwent TG. STG includes the removal of the greater and lesser omentum. The first portion of the duodenum was mobilized and divided at least 2 cm distal to the pylorus with at least 2 cm distal safety margin. The left gastric artery was ligated at its origin. A roux-en-Y reconstruction was done for 18 patients who left with small gastric pouches (< 20% of the stomach), while 32 patients had a loop gastrojejunostomy as they had a large remnant gastric pouches. For TG, the resection included removal of the spleen if there was a suspected LN involvement at splenic hilum. Esophagojejunostomy roux-en-Y is the most common type of reconstruction with a Roux limb is at least 45 cm long. In all patients, an extended lymphadenectomy, was used as the standard surgical procedure. All patients

**Table 1 Co-morbidity and possible risk factors**

Symptoms	n (%)
Abdominal pain	80 (100)
Dyspepsia	65 (81)
Heart burn	29 (36)
Dysphagia	17 (21)
Palpable mass	7 (9)
Co-morbidity	
<i>Helicobacter pylori</i>	66 (83)
Smokers	56 (70)
Diabetes mellitus	16 (20)
Hypertension	16 (20)
Total	80 (100)

**Table 2 Preoperative endoscopic evaluation**

Item	n (%)
Site of tumor:	
Antrum	51 (64)
Body	19 (24)
Fundus	10 (12)
Macroscopic feature:	
Exophytic growth	46 (58)
Ulcerative form	34 (42)
Diffuse form	0
Total	80 (100)

did not receive adjuvant or neoadjuvant therapy.

### Statistical analysis

The  $\chi^2$  or Fisher's exact test was used to compare categorical variables. Survival was calculated using the Kaplan Meyer method and groups were compared using the Log-Rank test. Factors that were deemed of potential importance on univariate analysis were included in the multivariate analysis. A probability (*P*) of less than 0.05 (two sided) was considered statistically significant. Overall mortality represented all deaths during follow-up. Cox multivariate proportional hazards regression models were used to assess the overall survival power of these parameters. All analyses were done using SPSS® software program version 21 (Chicago, United States).

## RESULTS

From February 2009 to February 2013, eighty patients with gastric carcinoma were managed in our Gastroenterology Surgical Center. Their age ranged from 24 to 83 years with a mean age  $55.4 \pm 11.8$  years (median age 57 years). Fifty seven were male (71%) and 23 female (29%), with male to female ratio (2.5:1).

Table 1 shows the co-morbidity and possible risk factors in our patients, 66 of patients (83%) had *Helicobacter pylori*, 56 (70%) of them were heavy smokers. Variable symptoms were experienced by our patients; epigastric pain was the main complaint in all patients (100%). The antrum was the most common tumor location within the stomach in 51 patients

**Table 3 Complications after gastrectomy**

	n (%)
Anastomotic leakage	3 (4)
Internal hemorrhage	1 (1)
Splenic bed collection	2 (3)
Pleural effusion	2 (3)
Wound infection	2 (3)
Total	10 (13)

**Table 4 Pattern of recurrence**

Item	n (%)
Local recurrence	9 (11)
Lymph nodes metastasis	2 (3)
Liver metastasis	2 (3)
Total	13 (16)

(64%), and the polypoid growth was the most common macroscopic feature and was found in 46 patients (58%) (Table 2).

### Operative data

Total gastrectomy was performed in 30 patients (38%) and subtotal gastrectomy in 50 patients (62%). The radicality of the operation necessitates extension of the resection to the tail of the pancreas and to the spleen in 5 patients, to the colon in 2 patients and to the left liver lobe in one patient. The mean blood transfusion required for TG and STG was ( $1.29 \pm 0.53$  unit) and ( $0.41 \pm 0.50$  unit).

There is no hospital mortality. Postoperative hospital morbidity was reported in 10 patients (12.5%) (Table 3). Three patients (4%) had anastomotic leakage and were managed conservatively (2 patients after TG and 1 patient after STG). Recurrence was shown in Table 4 whereas local and gastric stump was the commonest site (11%). The median period of hospital stay was 8 d (5 to 36 d).

Table 5 shows the demographic and clinicopathological features predicting overall survival. One, 3 and 5 years survival rates were respectively 71%, 69% and 46%. The median survival was 69.96 mo (Figure 1). During the follow-up period, 13 patients died (16%). The median number of LNs removed was 22 (4-41). LN metastasis was found in 91% of cases. Survival was superior in case of negative LN resected (61 mo vs 31 mo,  $P < 0.0001$ ). Survival also varied according to the number of removed LN. The median survival was 54.48 mo when more than 15 LN were removed vs 14.5 mo when fewer LN were resected ( $P < 0.0001$ ) (Figure 2A). There was no statistical significance between both groups as regard the effect of extended LN dissection on morbidity ( $P = 0.34$ ). The ratio of the number of positive nodes to the total number of nodes retrieved, i.e., the LN ratio, was significantly associated with worse overall survival, it was  $62 \pm 2.5$  mo when LN ratio was  $\leq 0.2$ ,  $62 \pm 2.1$  mo when LN ratio was between 0.2 to

**Table 5** Demographic and clinicopathological features predicting overall survival

Characteristics	Number of patients <i>n</i> (%)	Months after surgery (mean $\pm$ SD)	<i>P</i> value
Sex			
Male	57 (71)	50.2 $\pm$ 3.1	<i>P</i> = 0.830
Female	23 (29)	47.8 $\pm$ 4.6	
Age			
Below 60	49 (61)	47.3 $\pm$ 3.5	<i>P</i> = 0.259
Above 60	31 (39)	53.6 $\pm$ 3.6	
Site			
Antrum	51 (64)	47 $\pm$ 3.5	<i>P</i> = 0.315
Body	19 (24)	57.2 $\pm$ 3.5	
Fundus	10 (12)	40.3 $\pm$ 6	
Type of surgery			
Total gastrectomy	30	65 $\pm$ 7	<i>P</i> = 0.548
Subtotal gastrectomy	50	60	
Tumor differentiation			
Well	37 (46)	65.6 $\pm$ 0.3	<i>P</i> = 0.001
Moderate	20 (25)	50.8 $\pm$ 5.3	
Poor	23 (29)	20.8 $\pm$ 4	
T stage			
T1	10 (13)	60 $\pm$ 3.2	<i>P</i> = 0.001
T2	25 (31)	60 $\pm$ 2.4	
T3	29 (36)	61 $\pm$ 3	
T4	16 (20)	12 $\pm$ 2.3	
LN ratio			
0	7 (9)	61	<i>P</i> < 0.001
$\leq$ 0.2	20 (25)	62 $\pm$ 2.5	
0.2-0.4	26 (32)	62 $\pm$ 2.1	
> 0.4	27 (34)	22 $\pm$ 4.5	
LN status			
Negative	7 (9)	61 $\pm$ 3.5	<i>P</i> = 0.03
Positive	73 (91)	31 $\pm$ 2.3	
Number of examined LN			
> 15	65 (81)	54.48 $\pm$ 2.6	<i>P</i> < 0.001
$\leq$ 15	15 (19)	14.5 $\pm$ 1	
Surgical margin			
Negative	73 (91)	53.8 $\pm$ 2.4	<i>P</i> < 0.001
Positive	7 (9)	9.5 $\pm$ 1	
Recurrence			
No	67 (84)	57.3 $\pm$ 2.3	<i>P</i> < 0.001
Yes	13 (16)	12.3 $\pm$ 1.2	

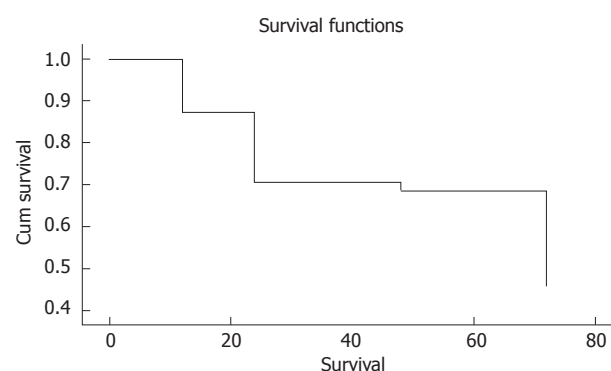
0.4 and 22  $\pm$  4.5 mo when LN ratio was > 0.4; *P* < 0.001 (Figure 2B).

The median survival of T1 and T2 tumors was significantly superior to T4 tumors (60 mo vs 12 mo, *P* = 0.0001) (Figure 2C). Survival was significantly higher in case of well and moderate differentiated tumor to poorly differentiated tumor (65.7 mo vs 20.8 mo, *P* < 0.0001) (Figure 2D). Seventy three patients (91%) had a radical resection which is associated with prolonged survival compared to 7 patients (9%) who had a palliative one (53.8 mo vs 9.5 mo, *P* < 0.0001) (Figure 2E). Patients developed a recurrent tumor (13 patients 16%) had a significant poor survival compared to the others (67 patients 84%) (12.3 mo vs 57.3 mo, *P* < 0.0001).

There is no significant difference in survival rate according to age, gender, tumor location, the type of gastrectomy. On multivariable analysis (Table 6), tumor differentiation, curability of resection and a

**Table 6** Multivariate analysis

Factors	Odds ratio	CI lower-upper	<i>P</i> value
Tumor differentiation	0.142	0.045-1.092	0.044
Radicality of resection	2.57	1.4-5.1	0.001
Number of resected lymph node > 15	2.04	1.3-3.75	0.001

**Figure 1** Overall survival.

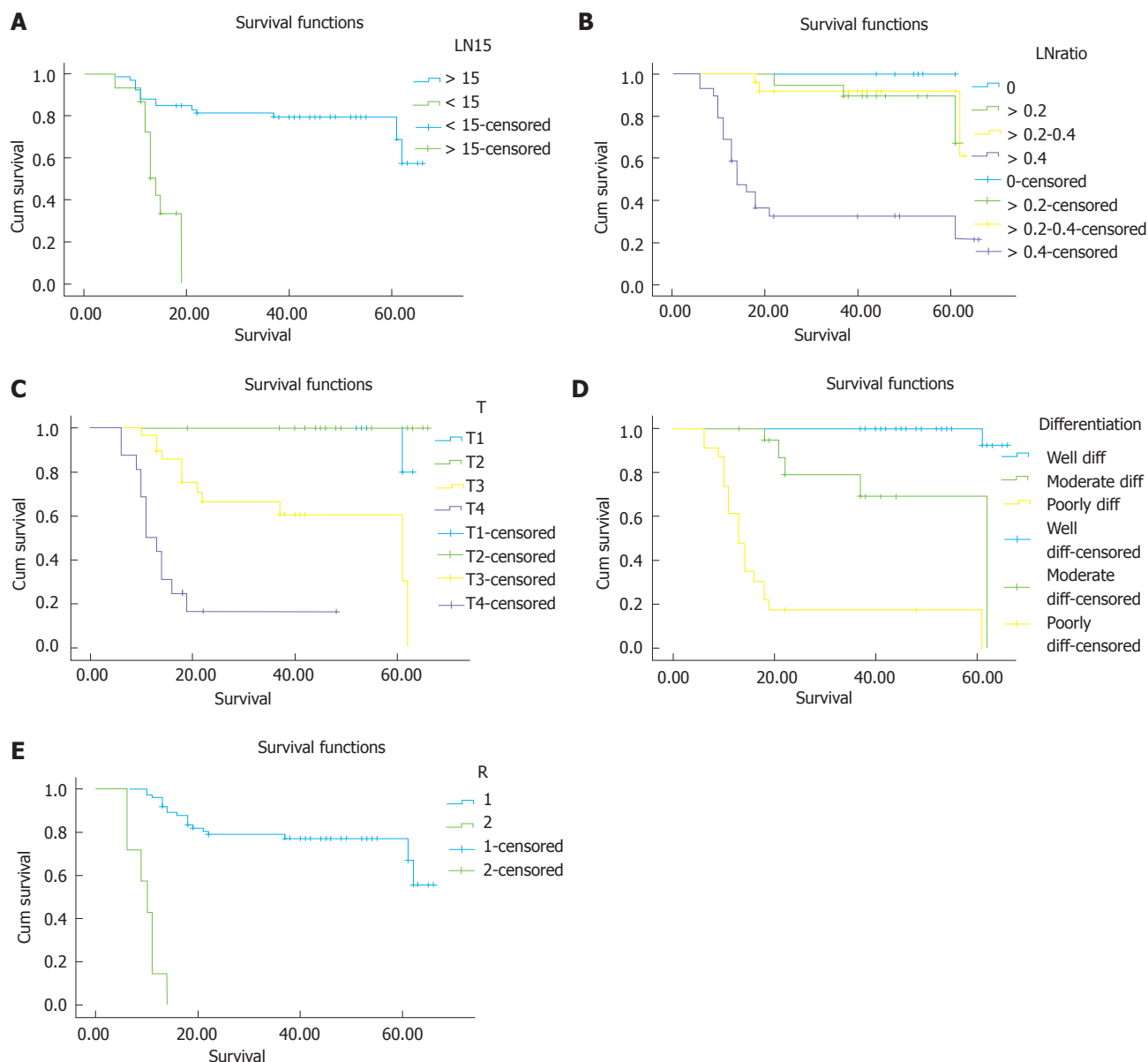
number of resected LN superior to 15 were found to be independent prognostic factors.

## DISCUSSION

The epidemiology, surgical management and outcomes for patients with carcinoma of the stomach differ significantly from one area of the world to another. We have a published data and experience from Western, Eastern and European countries. However, we have a little data from Middle East countries, and here we represent our work from a large gastroenterology and transplantation center in Egypt. Complete tumor excision with satisfactory safety margins (*i.e.*, an R0 resection according to the UICC classification) have been accepted as a major significant factor for reduction of tumor recurrences and improvement of survival time in patients with gastric cancer<sup>[13-19]</sup>. This radical resection is the most important step to have better survival in our patients (53.8 mo vs 9.5 mo, *P* < 0.0001). In our series, after R0 resection and DII lymphadenectomy, depth of wall invasion, LN metastasis, the number of resected LN, LN ratio and tumor differentiation were the independent prognostic factors.

The extent of regional lymphadenectomy required has been a matter of considerable debate. The number of LN metastases has a higher prognostic value compared to their location<sup>[8,20]</sup> and the staging system was updated in the 2010 UICC/TNM 7<sup>th</sup> edition<sup>[21]</sup>. The definition of LN dissections: Has been updated considering the number of removed LN rather than their location, it is as follows: D0 when less than 15 nodes are reported, D1 when 15 to 25 nodes are removed, and D2 when more than 25 nodes are reported in the pathological findings<sup>[8,9]</sup>.

There has been much argument about the mini-



**Figure 2** Actuarial survival (Kaplan Meier analysis) after resection of gastric carcinoma. A: Influence of number of resected LN; B: Influence of LN ratio; C: Influence of tumor stage; D: Influence of tumor grade; E: Influence of radicality of resection. LN: Lymph node.

imum number of LNs removed for proper staging. The Union Internationale Contre Le Cancer (UICC), has standardized the operative management of gastric cancer and propose that for proper staging, at least 15 LNs should be removed and pathologically examined<sup>[22]</sup>. This recommendation highlights the significance of the total number of LNs removed over their relationship to the primary tumor (N1 or N2). Karpeh *et al.*<sup>[8]</sup>, three years later, made a comparison between different staging systems to show their impact on the long term survival (UICC 1988 that used the location of LN vs UICC 1997 that used the number of LN). They reported that, there is superior significant value of the number of metastatic LNs more than their location.

The number of metastatic LNs increases with the depth of tumor invasion through the gastric wall layers and this had a direct relationship to long term

survival<sup>[23-25]</sup>. In our series, the T and N stage had the highest significant prognostic factors especially after R0 resection. Survival was 54.48 mo when more than 15 LN were resected vs 14.5 mo when fewer LN were removed ( $P < 0.0001$ ). In experienced centers, Extended LN dissection does not increase the morbidity or mortality rate but markedly improves long term survival.

The independent prognostic value of LN ratio in our monoinstitutional study was significantly associated with worse overall survival, it was  $62 \pm 2.5$  mo when LN ratio was  $\leq 0.2$ , and  $22 \pm 4.5$  mo when LN ratio was  $> 0.4$ ;  $P < 0.001$ . In various Western series, the LN ratio has been considered as an effective prognostic tool after D2 lymphadenectomy<sup>[26-32]</sup>. Bando *et al.*<sup>[27]</sup> reported that, at multivariate analysis the LN ratio was the only independent prognostic factor when the number



**Table 7** Published series on prognostic factors after resection for gastric carcinoma

Ref.	Period	No.	Gender	Age	Location	No. excised LN	LN ratio	T stage	Histologic type	N stage	Curative resection
Adachi <i>et al</i> <sup>[45]</sup>	1977-1987	479	NS	NS	$P < 0.01$	$P < 0.01$	NR	$P < 0.01$	$P < 0.01$	$P < 0.01$	NR
Bando <i>et al</i> <sup>[27]</sup>	1974-1995	650	NR	NR	NR	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	NR	NR
Yokota <i>et al</i> <sup>[46]</sup>	1985-1995	926	NS	NS	$P < 0.0001$	NR	NR	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	NR
Angelov <i>et al</i> <sup>[47]</sup>	2005-2013	101	NS	NS	NS	NR	NR	NR	NR	$P = 0.003$	$P < 0.001$
			0.347	0.099							
Basaran <i>et al</i> <sup>[48]</sup>	2006-2014	228	NS	$P <$	$P < 0.001$	NR	NR	NS	$P < 0.015$	$P < 0.002$	$P = 0.000$
				0.0001							
Present study	2009-2013	80	NS	NS	NS	$P < 0.001$	$P < 0.001$	$P = 0.001$	$P = 0.001$	NR	$P < 0.001$
			0.83	0.259	0.315						

NS: Non-significant; NR : Not reported; LN: Lymph node.

and the site of metastatic LNs were considered in the analysis. Kunisaki *et al*<sup>[33]</sup> reported the same result and that the LN ratio independently influenced the prognosis of a radically resected 758 patients.

The median survival of T1 and T2 tumors was significantly superior to T4 tumors (60 mo vs 12 mo,  $P = 0.0001$ ) this is also reported by others<sup>[4,34]</sup>. Grade refers to the degree of differentiation of tumor cells and has been shown to correlate with the neoplasm aggressiveness. The prognostic impact in gastric cancer remains to be elucidated, because several retrospective studies have failed to identify grade as an independent prognostic factor<sup>[7]</sup>. In our study, Survival was superior in case of well and moderate differentiated tumor to poorly differentiated tumor (65.7 mo vs 20.8 mo,  $P < 0.0001$ ) others reported the same result<sup>[4,34]</sup>. On multi-variable analysis, tumor differentiation curability of resection and a number of resected LN superior to 15 were found to be independent prognostic factors.

The recurrence after surgical excision of gastric carcinoma shows a different pattern between Eastern and Western countries. However, there are still some disputes. In Eastern countries, the hematogenous recurrence and peritoneal dissemination were the most common recurrence patterns<sup>[35-37]</sup>. Wu *et al*<sup>[38]</sup> reported that the peritoneal recurrence was 38.4% and the hematogenous recurrence was 32.5% of patients. Our results show that local recurrence is the most common one and account for 11%. This result is consistent with an Italian study that showed that the loco-regional recurrence was the most common recurrence pattern and account for 45% of all recurrent cases<sup>[38]</sup>. This difference in recurrence pattern may be explained by that the low incidence of local recurrence in Eastern series is due to a different surgical strategy toward extensive LNs dissection<sup>[39]</sup>.

In this study, the 3 and 5 years survival rates were 69% and 46%, respectively. Our survival rates are similarly to those reported in Memorial Sloan-Kettering cancer center in New York<sup>[23]</sup> and the German gastric cancer study<sup>[3]</sup> and some other western centers<sup>[29,34,40,41]</sup>. However, our survival results are better than a reported

study from Poland<sup>[42]</sup>. We have a lower survival rates than those reported in Japan<sup>[43,44]</sup>. Table 7 shows some published series on prognostic factors after resection for gastric carcinoma. Epidemiology, late discovery of the disease, differences in the staging systems and the operative strategy with extensive lymphadenectomy in Japan may explain these differences.

In conclusion, the epidemiology, surgical management and outcomes differ significantly from one area of the world to another. Surgery stills the gold-stander line of management. There might be a correlation between time to discover the disease, radicality and survival. Our study showed that after R0 resection, depth of wall invasion, LNs involvement and the number ( $> 15$ ) of resected LN, In ratio and tumor differentiation predict survival. On multivariable analysis, tumor differentiation, curability of resection and a number of removed LN more than 15 were found to be independent prognostic factors. In order to have a better survival in our patients, we recommend frequent use of upper endoscopy for gastrointestinal symptoms for early detection of gastric cancer.

## COMMENTS

### Background

The epidemiology and the surgical outcomes for patients with carcinoma of the stomach vary significantly from one part of the world to another. However, prognosis varies among patients with a similar tumor stage; therefore, disease staging alone cannot accurately predict the outcome for individual patients. There might be a correlation between time to discover the disease, radicality of resection and survival. The experience of the surgeons toward more radical resection with lymph node (LN) removal is the most important non-TNM prognostic factors in gastric cancer.

### Research frontiers

Prognosis is poor perhaps due to late diagnosis and frequent local-regional recurrences. This requires investigation of the possible reasons for the worsening of survival and searching for prognostic factors of better survival. Complete resection of the tumor with satisfactory safety margins is the standard treatment. Many prognostic factors have been investigated to assess their significance in predicting patients' outcome. The number of metastatic LNs (N stage) and the depth of the primary tumor (T stage) are currently considered the most reliable prognostic factors for patients with radically resected gastric cancer. LN clearance remains the most challenging part of the operation, the UICC/AJCC classification,

suggests that at least 15 LNs should be examined for a correct assessment of N stage.

### Innovations and breakthroughs

The authors have a published data and experience from Western, Eastern and European countries. However, we have a little data from Middle East countries, and here we represent the authors' work from a large gastroenterology and transplantation center in Egypt. The aim of this study was to evaluate the Clinicopathological features and the significance of different prognostic factors in patients undergoing resection for gastric cancer. Clinicopathological parameters, including gender and age of patients; location of the tumor; depth of invasion; LN metastasis status; operative details; morbidity and mortality; and survival and recurrence were collected. All of the surgical procedures were performed by experienced gastric surgeons of the single institute with a definitive treatment guideline for gastric cancer. In all patients, an extended lymphadenectomy, was used as the standard surgical procedure.

### Applications

Epidemiology, late discovery of the disease, differences in the staging systems and the operative strategy with extensive lymphadenectomy may explain the difference between prognostic factors between different parts of the world. The center is a referral tertiary center, most of their patients comes with a relatively advanced tumor stage. Intra-operatively there was much LN involvement. So their policy is to remove of all suspected LN involved with the disease to reach satisfactory radical resections. In order to have a better survival in their patients, they recommend frequent use of upper endoscopy for gastrointestinal symptoms for early detection of gastric cancer.

### Terminology

The extent of LNs dissection is classically termed D0, D1, and D2 LN dissection was initially classified as D1 to D4, depending on the extent and removal of each LN station according to the primary tumor location. In distal subtotal gastrectomy, D1 included removal of only LN stations 1, 3, 4, 5, 6 and 7 surrounding the stomach, whereas D2 included D1 LN dissection and station 8a, 12a, 9 and 11. D3 and D4 LN dissections occur when the other LN stations are removed. This system has been revised and now reflects the number of retrieved LNs rather than their location. Hence, it is as follows: D0 when less than 15 nodes are reported, D1 when 15 to 25 nodes are removed, and D2 when more than 25 nodes are reported in the pathological findings.

### Peer-review

The authors present their surgical experience in the treatment of gastric cancer in one the Middle East centers. Their study included 80 patients with different clinicopathological characteristics in an attempt to investigate the impact of in study mentioned variables on the patients' survival following surgical management.

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