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Alaa Mahfouz Mahmoud Abd Elaziz

Resident doctor at clinical oncology and nuclear medicine, faculty of medicine, al azhar university Cairo, Egypt., alaamahfouzz88@gmail.com

Ahmed Yousry Elagmawi

clinical oncology and nuclear medicine, faculty of medicine, al azhar university Cairo, Egypt.

Sherif Mohamed Azzam

clinical oncology and nuclear medicine, faculty of medicine, al azhar university Cairo, Egypt.

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Treatment Outcome in Non-Metastatic Gastric Cancer: A Retrospective Study

Alaa Mahfouz Mahmoud Abd Elaziz*, Ahmed Yousry Elagmawi, Sherif Mohamed Azzam

Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Al-Azhar University, 11675, Egypt

Abstract

Background: The best surgical therapy technique for elderly patients with stomach cancer must be carefully studied because of their high vulnerability.

Aim and objectives: This study's main objective was to assess our treatment modalities in non-metastatic gastric cancer in terms of disease-free survival, overall survival, and related toxicity. The secondary objective has been to display the clinico-epidemiologic profile of this disease.

Subjects and methods: This retrospective study was conducted in Clinical Oncology and Nuclear Medicine Department at Al-Hussein university Hospital between Jan 2016 and Jun 2021. This study was conducted on 40 patients presented by a pathologically confirmed diagnosis with non-metastatic gastric adenocarcinoma.

Results: Surgery + CCRT (better prognosis with hazard ratio = 0.007, surgery (hazard ratio = 0.021) are statistically significant predictors of overall survival among studied cases; Bad prognosis is detected for cases with partial response (HR = 32) and progressive disease (HR = 17), inadequate LN have bad prognosis (HR = 13.17).

Conclusion: The current study showed that adjuvant concurrent chemoradiotherapy was safe, effective, and practical as a therapy for non-metastatic gastric cancer, and resulted in higher disease-free survival compared to perioperative chemotherapy.

Keywords: Gastric cancer, Gastrectomy, Lymphadenectomy, Toxicity, Non-metastatic

1. Introduction

One of the most frequently reported and most common causes of cancer deaths is stomach cancer.¹

It is the third most common reason for cancer mortality globally and the fifth most commonly diagnosed malignancy overall.² In the United States, about 27,600 new cases of gastric cancer were recorded in 2020, while the number of deaths caused by gastric cancer was about 11,010.

Geographically, stomach cancer mostly affects people in South America, Africa, and Asia. Two-thirds of all new cases of stomach cancer every year occur in Asian nations, including Japan, China, and South Korea.³

The probability of stomach cancer differs depending on the main location: The gastroesophageal junction, cardia, and fundus are the origin of 35% of

tumors. 25% of tumors are body related. 40% of all tumors originate in the antrum and distal stomach.⁴

It is essential to use a multidisciplinary strategy while planning the therapy for stomach cancer. At the very least, a gastroenterologist, surgeon, pathologist, medical oncologist, and radiation oncologist should be members of the multidisciplinary team (MDT).⁵

Postsurgical chemotherapy, chemoradiotherapy, and neoadjuvant chemotherapy have been shown to benefit survival in patients with pathologic T2 or higher and/or node-positive stomach cancer, and chemotherapy must include a doublet or triplet combination of 5-fluorouracil and cisplatin, or its analogues capecitabine and oxaliplatin.

The primary end point was to evaluate the outcomes of gastric cancer treatment modalities regarding event free survival (EFS) (recurrence and/or progression), overall survival (OS), treatment related toxicities, and prognostic factors. The

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* Corresponding author at: Clinical Oncology Department, Faculty of Medicine, Al Azhar University, Egypt.
E-mail address: alaamahfouzz88@gmail.com (A.M.M. Abd Elaziz).

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secondary end point was to study the clinico-epidemiological characteristics of the patients with gastric carcinoma who presented to the Clinical Oncology & Nuclear Medicine Department of Al-Azhar University Hospital from January 2016 to June 2021.

2. Patients and methods

Patients having a pathologically confirmed diagnosis of gastric adenocarcinoma were included in this retrospective study. Patients were referred to the Clinical Oncology and Nuclear Medicine Department at El Hussein University Hospital, Faculty of Medicine, Al-Azhar University, between Jan 2016 and Jun 2021.

Data of patients diagnosed with gastric adenocarcinoma were collected from files of patients in the archive.

2.1. Inclusion criteria

Age more than 18 years and less than 70 of both genders, histo-pathologically proven of gastric adenocarcinoma, Clinically local and locally advanced gastric cancer 'T2- T3 - T4, any T with positive lymph node, received treatment at our department and timing of surgery either initially followed by Adjuvant concurrent chemo-radiotherapy or after neoadjuvant chemotherapy.

2.2. Exclusion criteria

Stage IV disease, patients with synchronous malignancies, pregnancy and prior chemotherapy or radiotherapy treatment.

2.3. Methods

The following data was collected in an excel sheet for all patients: patient related data, Age, gender, performance status and associated co-morbidities. Disease related data: Site of the disease, histopathology, clinical stage at presentation, grade and response rate.

Treatment related data: Radiotherapy (Dose/fractions, site and related toxicity), Chemotherapy (regimen, type and related toxicity), surgery (type, delay interval and related toxicity) and treatment outcomes.

2.4. Statistics

The statistical analysis of overall survival and disease-free survival will be conducted using the one-sided log-rank test of Kaplan-Meier survival

estimates, whereas the univariate analysis of the variables will be conducted using the unpaired T test and one-way ANOVA test.

3. Results

This study was carried out on 40 patients presented by a pathologically confirmed diagnosis with non-metastatic gastric adenocarcinoma, referred to Clinical Oncology and Nuclear Medicine Department, Al-Hussein University Hospital between Jan 2016 and Jun 2021.

The age at time of diagnosis ranged between 25 years and 70 years with mean age was 49.51 (± 14.51) years. Although gastric carcinoma is a disease of elderly, 27/40 patients (67%) were diagnosed at age more than 60 years, while 13/40 patients (32%) were diagnosed at age less than 60 years, about 70% of patients <60 years old with male to female ratio of (1.17:1) (Table 1). Abdominal pain as a main presenting symptom in (52.5%) followed by vomiting (32.5%).

As regard to our clinical data, number of patients not candidate for surgery at presentation were 7 patients (17.5%) these patients received palliative chemotherapy. Patients received adjuvant chemotherapy were 4 patients (10%), the most common protocol is FLOT regimen (fluorouracil, leucovorin, oxaliplatin, Taxotere), and two patients received FLOT. Adjuvant concurrent chemo-radiotherapy were given to 21 patients (52.5%). 4/6 of patients received perioperative chemotherapy by regimen FLOT, Only two patients subjected to surgery and not received neither adjuvant nor neoadjuvant treatment as conditions either preoperative or postoperative no candidate to receive chemotherapy as shown in Table 2.

Overall Survival (OS) is the time from the date of the histological diagnosis to the last follow-up date (for censored observation) or the death date (for uncensored observation). OS for patients at one year was 81.9%, while OS at one and half year was 59.7%, OS at 3 years was 50% as shown in Table 3, Fig. 1.

Studying factors affect OS of non-metastases gastric cancer patients revealed that age, sex, risk factor as smoking, main presentation, pathology, grade, staging had no significant effect on either DFS or OS while site, Treatment options, Performance status (ECOG) and Lymph node Dissection was significantly affect OS, as shown in Table 4.

Table 5: shows that the following are statistically significant predictors of overall survival among studied cases; Surgery followed by concurrent chemoradiotherapy CCRT (better prognosis with hazard ratio = 0.007, surgery (hazard ratio = 0.021).

Table 1. Patients & tumor Characteristics of studied gastric cancer patients.

Patients & tumor characteristics	N = 40 (%)
Age	
<60 years	27 (67.5)
≥60 years	13 (32.5)
Sex	
Male	21 (52.5)
Female	19 (47.5)
Risk factors	
No smoking	27 (67.5)
Smoking	13 (32.5)
ECOG score	
0	1 (2.5)
1	27 (67.5)
2	12 (30.0)
Main presentation	
Vomiting	13 (32.5)
Abdominal pain	21 (52.5)
Weight loss	6 (15.0)
Site	
Proximal	19 (47.5)
Distal	21 (52.5)
Pathology	
Signet ring	12 (30.0)
Adenocarcinoma	24 (60.0)
Mixed	4 (10.0)
Grade	
Well	2 (5.0)
Moderate	15 (37.5)
Poor or UN	23 (57.5)
T	
T1	2 (5.0)
T2	17 (42.5)
T3	14 (35.0)
T4	7 (17.5)
N	
N0	9 (22.5)
N1	31 (77.5)
Stage	
1	11 (27.5)
2	7 (17.5)
3	22 (55.0)
LVI	
-VE	3 (10.0)
+VE	30 (90.0)
SM	
Negative margin	24 (72.5)
Positive margin	9 (27.5)
LN	
Adequate	15 (45.0)
Inadequate	18 (55.0)
Type of surgery	
Subtotal gastrectomy	23 (70%)
Total gastrectomy	10 (30%)

patients with inadequate LN have bad prognosis in comparison to adequate lymph node dissection (HR = 13.17).

At time of analysis as regard 4 patients received adjuvant chemotherapy 3 patients from this group developed locoregional failure (75%) and one

patient developed distant metastasis (25%). Patients from them developed locoregional failure were 2/7 (28.6%), 2/7 (28.6%) patients developed distant metastasis and locoregional, while 3/7 patients (42.9%) developed distant metastasis. The number of patients developed disease free survival during the period of follow up was 8/21 patients (38%) and the patients developed relapse either locoregional failure or distant metastasis were 13/21 patients (62%). The number of patients developed disease free survival 1/2 patients (50%) while patients developed relapse was 1/2 (50%). the number of patients developed disease free survival were 2/6 patients (33%) while patients developed relapse either locoregional failure or distant metastasis were 4/6 patients (67%).

4. Discussion

Randomized clinical trials show that people with nonmetastatic gastric and gastroesophageal adenocarcinoma benefit from combined modality treatment. While postsurgical chemotherapy is an option following an appropriate lymph node dissection, current guidelines identify perioperative chemotherapy or postsurgical chemotherapy plus chemoradiation as preferred approaches.⁶ Large database studies, like the National Cancer Database, show a rise in the use of presurgical treatment, although it seems that one-third to one-fourth of individuals still receive surgery up front.⁷

This retrospective study was conducted in Clinical Oncology and Nuclear Medicine Department at Al-Hussein university Hospital between Jan 2016 and Jun.2021. This study was conducted on 40 patients presented by a pathologically confirmed diagnosis with non-metastatic gastric adenocarcinoma.

Regarding the patients & tumor Characteristics we found that, the age at time of diagnosis ranged between 25 years and 70 years with mean age was 49.51 (\pm 14.51) years. Although gastric carcinoma is a disease of elderly, 27/40 patients (67%) were diagnosed at age more than 60 years. As regard to sex, 19/40 patients (47.5%) were females, while 21/40 patients (52.5%) were males, male to female ratio = 1.2:1.

Smoking is considered as a risk factor for developing cancer, showed that 13/40 patients (32.5%) had the habit of smoking.

Numerous studies have demonstrated the link between cigarette smoking and an increased risk of GC, including both cardiac and noncardiac subtypes.⁸ According to research, smoking increases the risk of GC in men by 60% and in women by 20% when compared with nonsmokers. Former smokers

Table 2. Distribution of the studied patients as Regard to treatment modalities (n = 40).

Type of modality	Number of patients (%)	Type of protocol	Number of cycles	Percentage of patients
Perioperative chemotherapy	6/40 (15%)	Flot	4	4
		Folfox	2	1
		Eox	4	1
Adjuvant chemotherapy	4/40 (10%)	Flot	4	2
		Folfox	4	1
		Degramo	2	1
Adjuvant chemoradiotherapy	21/40 (52.5%)	Mayoclinic	2	15
		Degramo	1	6
		With dose of RTH 54G		
Palliative chemotherapy (not subjected to surgery)	7/40 (17.5%)	Folfox	4	4
		Eox	4	3
Surgery alone	2/40 (5%)	Subtotal gastrectomy	1	1
		Total gastrectomy	1	1

have a decreased risk of GC compared to occasional smokers, while those who smoke more cigarettes per day (more than 20) have a higher risk of GC.⁸

As well, as regard Neurological toxicity related to treatment modalities, we found 5/40 patients (12.5%) were developed neuropathy and 6/40 of patients developed phlebitis (15%).

The treatment related toxicities prevalence varies from study to another depending on the treatment protocol, dose and the patient overall preference, and it was a main reason of treatment discontinuation as reported by Tamaki *et al.*⁹

Table 3. Overall survival distribution among studied cases.

Survival time	Mean	Median	95% CI
Overall survival (OS) (months)	35.17	21	27.37–42.98
1-year	81.9%		
One and half year	59.7%		
3 years	50%		

In the study by Sakuramoto *et al.*,¹⁰ it was shown that chemotherapy had a statistically significant benefit compared to surgery in terms of 3-year survival, with good S-1 tolerability and a reduced

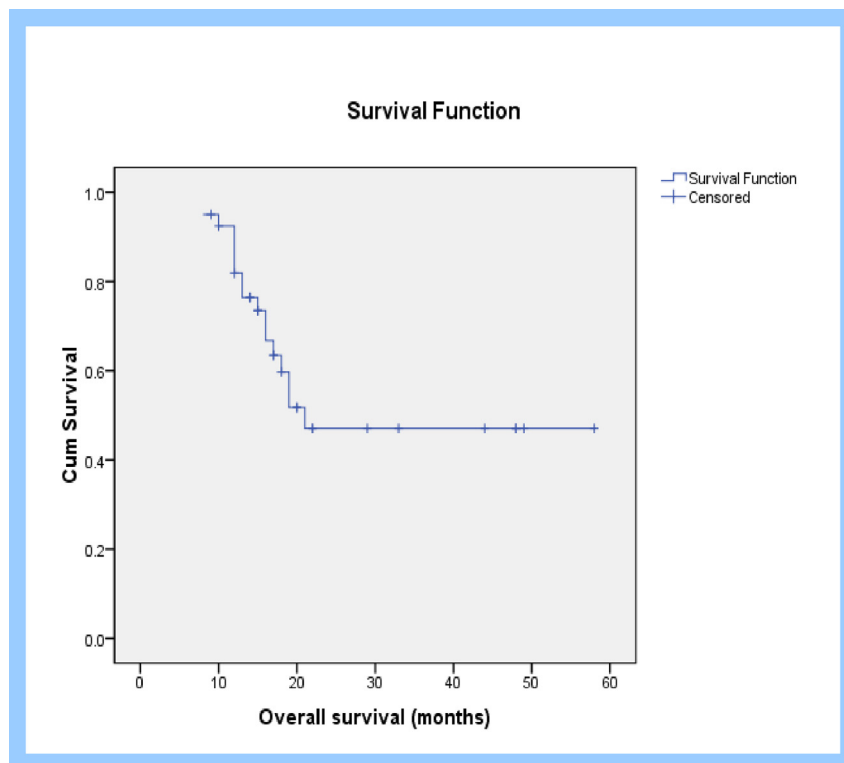


Fig. 1. The Kaplan-Meier curve shows overall survival in patients with gastric cancer.

Table 4. Factors affecting median OS in studied gastric cancer patients (n = 40).

Patient & tumor characteristics	Median OS (95% CI)	log rank χ^2	P value
Age			
<60 years	19.0 (14.6–23.4)	0.499	0.480
≥60 years	41.0 (27.79–54.7)		
Sex			
Male	38 (26–50)	0.091	0.762
Female	28.0 (21.09–36.62)		
Risk factors			
No smoking	21 (16.2–25.7)	1.06	0.304
Smoking	18 (24.91–43.71)		
ECOG score			
0	Not detected	8.82	0.012 ^a
1	44 (35–52)		
2	15 (13–18)		
Main presentation			
Vomiting	35 (24.03–46.29)	0.676	0.713
Abdominal pain	27.0 (19.7–34.92)		
Weight loss	42 (25.67–59.99)		
Site			
Proximal	19 (9.34–28.7)	2.97	0.08
Distal	39 (29–49)		
Pathology			
Signet ring	34.0 (23–45)	0.641	0.726
Adenocarcinoma	33.0 (24–43)		
Mixed	16.0 (14–17)		
Grade			
Well	Not detected	0.975	0.614
Moderate	19 (16–21)		
Poor or UN	21 (20–38)		
T ^a			
T1	Not detected	4.04	0.258
T2	41.0 (29.08–53.21)		
T3	24.55 (15.6–33.48)		
T4	31.48 (17.88–45.09)		
N ^a			
N0	21 (19–31)	0.534	0.465
N1	19 (25–43)		
Stage			
1	21 (19–50)	2.91	0.234
2	42 (31–52)		
3	18 (17–4)		
Treatment options			
Adjuvant chemotherapy	13.75 (10.32–17.18)	16.38	0.003 ^a
Chemotherapy	13.89 (12.96–14.81)		
Surgery + CCRT	44.13 (35.01–53.25)		
Surgery	16 (14–17)		
Peri operative chemotherapy	24 (9.18–39.70)		
LVI			
-VE	28 (19.51–36.49)	0.924	0.336
+VE	19 (15.0–22.9)		
SM			
Negative margin	21 (14–38)	0.035	0.852
Positive margin	19 (15.16–22.8)		
LN			
Adequate (<15)	40 (37.2–56.4)	6.19	0.013 ^a
Inadequate (≥15)	17 (14.22–19.78)		

Not detected as one of the categories have 100% censored cases.

^a Statistically significant.

Table 5. Cox regression of predictors of overall survival duration among studied cases.

Patient & tumor characteristics	B	P value	Hazard ratio (95%CI)
ECOG score			
0	R	0.146	undefined
1	-0.248	0.998	undefined
2	1.85	0.987	
Treatment options			
Adjuvant chemotherapy	R	0.901	1.13 (0.167–7.62)
Chemotherapy	0.121	0.003*	0.007 (0.002–0.174)
Surgery + CCRT	-5.01	0.049*	0.021 (0.002–0.976)
Surgery	-3.86	0.468	5.46 (0.06–50.25)
Peri operative chemotherapy	1.69		
LN			
Adequate(<15)	R	0.008*	13.17 (1.95–25)
Inadequate(≥15)	2.58		

R: reference group.

prevalence of G3-4 toxicity (diarrhea 3.1%, nausea 3.7%, and anorexia 6%).

However, **Bang et al.**,¹¹ revealed that grade 3 or 4 toxicities (anorexia 59.3%, neutropenia 60.5%, and nausea 65.7%) have been reported in 56% of cases in the chemotherapy arm.

The mean Overall Survival for patients at one year was 81.9%, while OS at one and half year was 59.7%, OS at 3 years was 50%, respectively.

The mean disease-free survival for patients at one year was 69.8%, while DFS at one and half year was 54.8%, DFS at 3 years was 50% respectively.

However, **Wang et al.**,¹² enrolled 39 patients treated with neoadjuvant therapy and resection, with a mean follow-up period of 30.4 months (range 2.5–101.6). The rates of overall survival (OS) at 3 and 5 years were 88.9% and 88.9%, respectively. And the rates of disease-free survival (DFS) after three and five years were, respectively, 88.9% and 88.9%.

Also, **Yu et al.**,¹³ reported that the CCRT group had one-, two-, and three-year rates of survival of 85.9, 73.4, and 67.7%, respectively, as opposed to the single chemotherapy group ($P < 0.05$), which had rates of 68.0, 50.0, and 44.1%. In comparison to the single chemotherapy group ($P < 0.05$), the CCRT group had disease-free survival rates of 73.5, 64.7, and 55.8% compared to 61.8, 38.2, and 29.4%.

Regarding the Effect of treatment modalities options on OS and DFS, the current study showed that Median OS and median DFS are 13 months and 6 months in the arm of adjuvant chemotherapy, perioperative chemotherapy 24 months and 21 months, adjuvant chemoradiotherapy 18 months and 16 months, while Palliative chemotherapy OS and EFS were 14 months and 10 months

Table 6. Distribution of treatment failure according to different treatment modalities among studied cases.

Treatment failure	Treatment modalities					Test of significance
	Adjuvant chemotherapy <i>n</i> = 4 (%)	Chemotherapy <i>n</i> = 7 (%)	Chemotherapy + CCRT <i>n</i> = 21 (%)	Surgery <i>n</i> = 2 (%)	Perioperative chemotherapy <i>N</i> = 6 (%)	
No failure	0	0	8 (38.1)	0	2 (33.3)	MC = 16.02
Locoregional failure	3 (75)	2 (28.6)	5 (23.8)	1 (50)	3 (50)	<i>P</i> = 0.190
Distant	0	3 (42.9)	2 (9.5)	1 (50)	0	
Distant + locoregional	1 (25)	2 (28.6)	6 (28.6)	0	1 (16.7)	

MC, Monte Carlo.

respectively, the only two cases who had surgery only then observation reported OS 16 months and DFS 15 months, significantly different treatment modalities affect median OS and DFS (Table 6).

We also found that Surgery + CCRT (better prognosis with hazard ratio = 0.007, surgery (hazard ratio = 0.021) are statistically significant predictors of overall survival among studied cases; Bad prognosis is detected for cases with inadequate LN dissection (HR = 13.17).

In agreement with our results, Tan *et al.*,¹⁴ revealed that treatment modalities were significantly associated with overall survival.

Regarding the Effect of lymph node (LN) dissection on OS, we found that Median OS was 40 months in the arm of adequate LN dissection and 17 months in the arm of inadequate LN dissection. So adequate LN dissection has higher OS rate than inadequate LN dissection.

Invasion and Lymph node Dissection were significant predictors of OS.

This was supported by Chu & Yang,¹⁵ who revealed that as more negative lymph nodes were resected, the rate of overall survival became significantly greater. The rate of overall survival has been significantly higher in the T3-4 group, having greater than 15 lymph nodes removed ($P < 0.001$) amongst the 843 individuals who were in the exact T stage but not in the T1-2 stage individuals ($P = 0.44$). An additional 25 lymph node resections did not result in any further survival advantages.

Regarding the distribution of treatment failure according to different treatment modalities among studied cases, we found that 4 patients received adjuvant chemotherapy 3 patients from this group developed locoregional failure (75%) and one patient developed distant metastasis (25%).

Of patients received palliative chemotherapy there were 2/7 (28.6%), 2/7 (28.6%) patients developed distant metastasis and locoregional, while 3/7 patients (42.9%) developed distant metastasis.

As well, Li *et al.*¹⁶ reported that neoadjuvant CCRT is linked to improved pathologic response

and no increase in complications of serious after surgery.

In Yeh *et al.*, [17] retrospective studies involving patients with gastric cancer, neoadjuvant concurrent chemoradiotherapy (CCRT) resulted in superior progression-free survival and overall survival (OS) compared to neoadjuvant chemotherapy with no significant rise in toxicity.

4.1. Conclusion

The results of the current study showed that adjuvant concurrent chemoradiotherapy was a safe, effective, and practical therapy option for non-metastatic gastric cancer, and that it increased both disease-free survival and overall survival.

According to the most recent guidelines, perioperative chemotherapy and adjuvant CCRT are currently the preferred treatment options.

Treatment options, ECOG and lymph node dissection, significantly affected OS and DFS. We need further comparative research using bigger sample sizes and longer follow-ups to corroborate our findings and identify the risk factors for adverse events.

Consent for publication

I verify that all researchers have agreed to submit a manuscript.

Availability of data & material

Available.

Conflicts of interest

There are no conflicts of interest.

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