



Role of Neoadjuvant Chemotherapy in Cases of Gastric Cancer

Thesis

*Submitted for Partial Fulfillment
of Master Degree in General Surgery*

By

Mohammed Karam Hassan

Under Supervision of

Prof. Dr. Khaled Abudalla El Fiky

*Professor of General Surgery
Faculty of Medicine, Ain Shams University*

Prof. Dr. Ahmed Adel Ain Shoka

*Assistant Professor of General Surgery
Faculty of Medicine, Ain Shams University*

Dr. Mohammed Hisham Said Goda

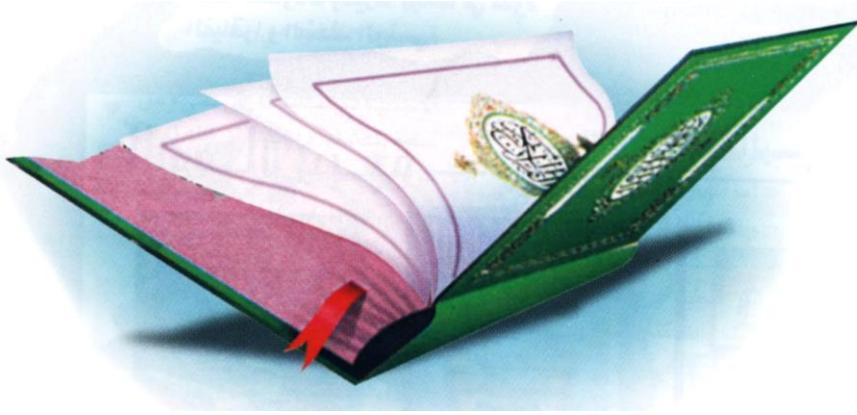
*Lecturer of General Surgery
Faculty of Medicine, Ain Shams University*

Faculty of Medicine - Ain Shams University

2019

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ

وَقُلْ اَعْمَلُوا فِیْ سَبِیْلِ اللّٰهِ
عَمَلَكُمْ وَرَسُوْلَهُ وَالْمُؤْمِنُوْنَ



صدق الله العظيم

[سورة: التوبة - الآية: ١٠٥]

Acknowledgments

*First and foremost, I feel always indebted to **Allah** the Most Beneficent and Merciful.*

*I wish to express my deepest thanks, gratitude and appreciation to **Prof. Dr. Khaled Abudalla El Fiky**, Professor of General Surgery, Faculty of Medicine, Ain Shams University, for his meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Prof. Dr. Ahmed Adel Ain Shoka**, Assistant Professor of General Surgery, Faculty of Medicine, Ain Shams University, for his sincere efforts, fruitful encouragement.*

*I am deeply thankful to **Dr. Mohammed Hisham Said Goda**, Lecturer of General Surgery, Faculty of Medicine, Ain Shams University, for his great help, outstanding support, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Mohammed Karam Hassan

List of Contents

Title	Page No.
List of Abbreviations.....	5
List of Tables.....	7
List of Figures.....	8
Introduction.....	- 1 -
Aim of the Work.....	5
Review of Literature	
▪ Anatomy.....	6
▪ Etiopathogenesis of Gastric Cancer.....	17
▪ Clinical Presentation and Diagnosis of Gastric Cancer.....	37
▪ Neoadjuvant Chemoradiotherapy.....	55
Patients and Methods.....	69
Results.....	74
Discussion.....	90
Summary and Conclusion.....	95
References.....	96
Arabic Summary	

List of Abbreviations

Abb.	Full term
<i>5-FU</i>	<i>5-Fluorouracil</i>
<i>AGC</i>	<i>Advanced Gastric Cancer</i>
<i>AJCC</i>	<i>American Joint Committee on Cancer</i>
<i>ASPDA</i>	<i>Anterior Superior Pancreaticoduodenal Artery</i>
<i>BMI</i>	<i>Body Mass Index</i>
<i>CA</i>	<i>Cancer-related Antigen</i>
<i>CEA</i>	<i>Carcinoembryonic Antigen</i>
<i>CHA</i>	<i>Common Hepatic Artery</i>
<i>CHD1</i>	<i>Chromodomain helicase Dna binding protein</i>
<i>COX</i>	<i>Cyclo oxaginase</i>
<i>CRT</i>	<i>Chemo-radiotherapy</i>
<i>CSC</i>	<i>Cancer Stem Cells</i>
<i>CT</i>	<i>Computed Tomography</i>
<i>ECF</i>	<i>Epirubicin, Cisplatin, 5-Fluorouracil</i>
<i>ECX</i>	<i>Epirubicin, Cisplatin, Capecitabine</i>
<i>EGC</i>	<i>Early Gastric Cancer</i>
<i>EGFR</i>	<i>Epidermal Growth Factor Receptor</i>
<i>EGJ</i>	<i>Esophagogastric Junction</i>
<i>EUS</i>	<i>Endoscopic Ultrasonography</i>
<i>FGFR2</i>	<i>Fibroblastic Growth Factor Receptor 2</i>
<i>GC</i>	<i>Gastric Cancer</i>
<i>GDA</i>	<i>Gastroduodenal Artery</i>
<i>Gist</i>	<i>Gastro intestinal stromal tumor</i>
<i>H.pylori</i>	<i>Helicobacter pylori</i>
<i>HDGC</i>	<i>Hereditary Gastric Cancer</i>
<i>HDGC</i>	<i>Hereditary diffuse gastric cancer</i>
<i>HDL</i>	<i>Hepatoduodenal Ligament</i>

List of Abbreviations cont...

Abb.	Full term
<i>HER2</i>	<i>Human Epidermal Growth Factor Receptor 2</i>
<i>HGF</i>	<i>Hepatocyte Growth Factor</i>
<i>ICC</i>	<i>Indigo Carmine Chromoendoscopy</i>
<i>ICC</i>	<i>Intestinal cell of cajal</i>
<i>IHC</i>	<i>Immunohistochemistry</i>
<i>IL</i>	<i>Interleukin</i>
<i>IM</i>	<i>Intestinal Metaplasia</i>
<i>Kda</i>	<i>Kilo Dalton</i>
<i>LGA</i>	<i>Left Gastric Artery</i>
<i>LGEA</i>	<i>Left Gastro-epiploic Artery</i>
<i>Malt</i>	<i>Mucosa associated lymphoid tissue</i>
<i>MDCT</i>	<i>Multidetector Row Computed Tomography</i>
<i>MRI</i>	<i>Magnetic Resonance Imaging</i>
<i>os</i>	<i>Overall survival</i>
<i>PDD</i>	<i>Photodynamic Diagnostics</i>
<i>RECIST</i>	<i>Response Evaluation Criteria in Solid Tumors</i>
<i>RGA</i>	<i>Right Gastric Artery</i>
<i>RGEA</i>	<i>Right Gastro-epiploic Artery</i>
<i>SEER</i>	<i>Survillence, epidimology,end results</i>
<i>SNP</i>	<i>Single Nucleotide Polymorphisms</i>
<i>SPEM</i>	<i>Spasmolytic Polypeptide-Expressing Metaplasia</i>
<i>TFF2</i>	<i>Trefoil factor 2 gene</i>
<i>TNFA</i>	<i>Tumour Necrosis Factor-Alpha</i>
<i>TNM</i>	<i>Tumor Node Metastasis</i>
<i>VEGF</i>	<i>Vascular Endothelial Growth Factor</i>

List of Tables

Table No.	Title	Page No.
Table (1):	TNM classification of Gastric cancer 7 th edition	53
Table (2):	Staging of Gastric cancer	54
Table (3):	Age and sex and risk factors of gastric cancer for our studied patients.	74
Table (4):	Presentation and methods of diagnosis of gastric cancer for studied patients.....	76
Table (5):	Two types of neoadjuvant chemotherapy tested in this study:.....	79
Table (6):	Surgery intervention	80
Table (7):	Response of the effect of neoadjuvant chemotherapy	81
Table (8):	Comparison between size of mass by CT pre and post treatment.....	82
Table (9):	Comparison between FLOT and ECX groups regarding demographic data	83
Table (10):	Comparison between FLOT and ECX groups regarding clinical presentation and finding bt ct and upper git endoscopy.....	85
Table (11):	Comparison between FLOT and ECX groups regarding LN status and number of cycles and finding of ct post treatment.....	86
Table (12):	Comparison between FLOT and ECX groups regarding surgical intervention and response, finding post surgery.	87
Table (13):	Comparison between FLOT and ECX groups regarding effect of the neoadjuvant on the size of the tumor	88
Table (14):	Comparison between FLOT and ECX groups regarding mean difference of size of the mass by CT.	89

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Stomach Anatomy.....	6
Figure (2):	Muscular layers of stomach.....	8
Figure (3):	Stomach blood supply	11
Figure (4):	Stomach Lymph node stations	13
Figure (5):	Stomach nerve supply.....	14
Figure (6):	Barium meal of normal stomach.....	15
Figure (7):	Endoscopic images of fundus and pylorus	16
Figure (8):	Cells of Gastric pits.....	18
Figure (9):	Multiple genetic and epigenetic alterations during gastric carcinogenesis and lymphomagenesis and the incidence rates in different types of gastric tumors.....	21
Figure (10):	The multi-step molecular pathogenesis of gastric cancer	25
Figure (11):	Scheme for the development of gastric metaplasias in humans after oxyntic atrophy and their relationship to gastric cancer	28
Figure (12):	Stomach cancer risk factors infographics	30
Figure (13):	Endoscopic images of gastric adenocarcinoma	45
Figure (14):	Chromoendoscopy of a differentiated adenocarcinoma	46
Figure (15):	Endoscopic Ultrasound Image from the Proximal Stomach.....	48
Figure (16):	Barium x-ray showing gastric cancer	49

List of Figures cont...

Fig. No.	Title	Page No.
Figure (17):	CT scan image of GC	52
Figure (18):	TN Classification of GC	54
Figure (19):	Proposed treatment algorithm for a multimodality approach to gastric cancer	60
Figure (20):	Pie chart displays percentage of each gender included in the study group.	75
Figure (21):	Graph displays percentage of risk factors of gastric cancer in patients sharing in our study as (family history, habits of medical importance as smoking, comorbidities as DM, HTN).....	75
Figure (22):	Graph displays percentage of clinical presentation in studied patients.	77
Figure (23):	Pie chart displays percentage of upper git endoscopy finding included in the study group.....	77
Figure (24):	Pie chart displays percentage of upper git endoscopy guided biopsy finding as grading of the adenocarcinoma included in the study group.	78
Figure (25):	Pie chart displays percentage of lymph node status for patients included in the study group.	79
Figure (26):	Pie chart displays percentage of type of neoadjuvant chemotherapy used for patients included in the study group.	80
Figure (27):	Comparison between size of mass by CT pre and post treatment.....	82

List of Figures cont...

Fig. No.	Title	Page No.
Figure (28):	Shows Comparison between FLOT and ECX groups regarding age.	84
Figure (29):	Shows Comparison between FLOT and ECX groups regarding sex.....	84
Figure (30):	Shows Comparison between FLOT and ECX groups eas regard effect in downstaging tumor which is higher in FLOT.....	88
Figure (31):	Comparison between FLOT and ECX groups regarding mean difference of size of the mass by ct.	89

INTRODUCTION

Gastric cancer (GC) is a major public health issue, and it is the fourth most common cancer and the second leading cause of cancer-related death. However, its incidence rates in different geographical regions are distinctly varied. Etiologically, gastric cancer is associated with *Helicobacter pylori* (*H. pylori*) infection, dietary and lifestyle factors, and genetics (*Ferlay et al., 2010*).

It is usually diagnosed at an advanced stage, and, consequently, the prognosis is dismal. Although surgery is the definitive therapy, rates of recurrence are high, creating the need for neoadjuvant or adjuvant therapy. These therapies have improved significantly the 5 year survival of these patients but not all patients benefit equally from these treatment options. The ability to predict patient response to specific therapies would be particularly valuable and would allow for the stratification of patients for personalized treatment strategies, likely with less toxicity. Recent advances have improved our understanding of gastric carcinogenesis with an unprecedented opportunity of developing novel therapeutic strategies. Exploring and validating tissue-based biomarkers are ongoing processes, which will certainly open new avenues for treating and improving the prognosis of patients with GC (*Jemal et al., 2010*).

Despite modern advances in diagnostics, surgical techniques, radiation therapy, and chemobiologic therapy, gastric cancer remains a highly fatal disease. Based on SEER data, the 5-year relative survival for gastric cancer (all stages) from 2002–2008 is 27%. The presence of micrometastatic disease, even in apparent early stage disease, contributes to the poor overall survival and the need for improved chemotherapeutics. Most gastric cancers are adenocarcinoma histology (>90%). There has been a migration of gastric cancers over the past century. In the early 1900s most gastric cancers were distal and involved the gastric antrum and body. The incidence of distal gastric cancers has been declining steadily, whereas the incidence of proximal gastric cancers and esophagogastric junction (EGJ) cancers has risen. There has also been a corresponding increase in the number of adenocarcinomas of the distal esophagus. The rate of increase is alarmingly high and should be considered an epidemic. In regards to gastric, EGJ, and distal adenocarcinomas of the esophagus, their natural history, response to treatment, and prognosis are very similar suggesting a shared pathogenesis. Some of the possible causes include infectious pathogens (ie, *Helico bacter pylori*); Barrett esophagus; and obesity. As the world continues to struggle with the obesity epidemic, there will continue to be an increase in these malignancies (*Wijnhoven et al., 1999*).

The 5-year overall survival for resectable GC is approximately 20% to 30% worldwide, but surprisingly it is 70% in Japan and in other eastern countries, where the high incidence of the disease is managed with screening programs to find tumors at an earlier stage, and patients receive adequate surgery, including extended LN dissection (*Hartgrink et al 2004*).

Neo-adjuvant chemotherapy could potentially increase the curative resection rate, improve the tumor downstaging possibilities and reduce the tumor-related symptoms if the chosen drugs have effect on the specific tumor biology (*Cunningham et al., 2010*).

Neo-adjuvant chemotherapy for patients with gastric cancer does not significantly improve the overall outcomes for those with late-stage disease and could be detrimental to survival for those with early-stage disease. However, treatment with Neo-adjuvant chemotherapy resulted in an improved rate of resection (*Schuhmacher et al., 2010*).

Surgical resection is the only curative treatment for GC. Adjuvant and neoadjuvant perioperative approaches, including chemotherapy and/or radiotherapy are now increasingly used in conjunction with surgery for locally advanced disease and early stage disease. Compared with surgery alone, a survival advantage has been demonstrated with adjuvant chemotherapy in Asian trials, adjuvant chemoradiotherapy (CRT) in the

largest North American study, and perioperative chemotherapy in the most cited European trial (*Siegel et al., 2014*).

The publication of two landmark trials in 2001 and 2006 established both post-operative chemo-radiotherapy (CRT) and perioperative chemotherapy (CT) as effective adjuvant treatment options, and both are currently accepted standards of care in the Western world. However, debate continues concerning the applicability of these trials to the Asian population, where there is the highest incidence of gastric cancer (*Cunningham et al., 2010*).

AIM OF THE WORK

The Aim of that study is to detect the importance of Neoadjuvant chemotherapy in cases of stomach cancer as regard:

- a) Increase the curative resection rate.
- b) Decrease tumor size to be easily resectable.