Role of Neoadjuvant Chemotherapy in Cases of Gastric Cancer

Thesis

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of Master Degree in ***General Surgery***

By

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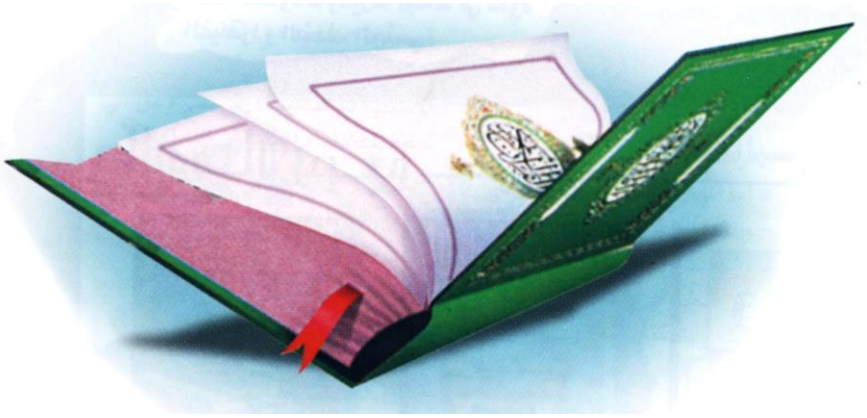
بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ



صدق الله العظيم

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Mohammed Karam Hassan

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List of Abbreviations

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

List of Abbreviations cont...

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

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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 possiblities and reduce the tumor-related symptoms if the choosen 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.