

The significance of gastrectomy in advanced gastric cancer patients with hepatic metastasis

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This study was designed to investigate the role of palliative gastrectomy in advanced gastric adenocarcinoma patients having hepatic metastasis without extra-abdominal disease at diagnosis.

Patients and methods: *This study was performed in General Surgery Department, Tanta University Hospitals, Egypt on 29 patients with advanced gastric cancer having hepatic metastasis. Patients were selected with histopathologically proven gastric adenocarcinoma; presence of hepatic metastasis at the time of diagnosis; absence of extra-abdominal disease and having a performance status of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale. None had received prior chemotherapy or radiation therapy. Patients were categorized into the two groups; Group I, 8 males and 3 females underwent gastrectomy with subsequent chemotherapy. Eighteen patients in group II, 11 males and 7 females received chemotherapy alone without gastrectomy. All patients were treated with systemic 5-fluorouracil based regimens.*

Results: *The mean follow-up time was 258 ± 122 days. The mean survival of GI and GII patients were 397 ± 59.7 and 173 ± 46.8 days ($p > 0.0001$). The mean metastatic progression-free survival was 329 ± 54.7 and 141 ± 49.4 days ($p > 0.001$). In 11 (38%) of 29 patients the primary tumor was removed (total gastrectomy in 7 and distal gastrectomy 4 patients). No patient underwent liver resection. Wound infection developed in one of the patients of the resection group. He were conservatively treated. One of the patients was reoperated for minor leakage from the anastomosis leading to intraabdominal collection. The mean hospital stay of the first admission for GI and GII patients was 13.9 ± 6.41 and 4.28 ± 1.41 days respectively ($p > 0.0001$). The Hospitalization index was not different between the two groups. The Ingestion index was significantly higher in GI than in GII. Gastrectomy increased the survival of the patients regardless to their number and localization of hepatic metastasis. Related risk factors based on the univariate analysis were serum tumor marker levels ($p 0.036$), number of hepatic metastasis ($p 0.0045$), resection of primary tumor ($p > 0.0001$) and the absence of extra hepatic spread ($p 0.027$).*

Conclusion: *Despite stage IV patients have poor prognosis, removal of the intact primary tumor for gastric cancer with synchronous hepatic metastasis at diagnosis is associated with improvement in overall survival and metastatic progression-free survival.*

Key words: *Gastrectomy, advanced gastric cancer, hepatic metastasis.*

Introduction:

Gastric cancer has been described as early as 3000 BC in hieroglyphic inscriptions and papyri manuscripts from ancient Egypt. The first major statistical analysis of cancer incidence and mortality (using data gathered in Verona, Italy from 1760 to 1839) showed

that gastric cancer was the most common and lethal cancer. It has remained one of the most important malignant diseases with significant geographical, ethnic, and socioeconomic differences in distribution with approximately 989,600 new cases and 738,000 deaths per year, accounting for about 8 percent of new

cancers.¹ Approximately 21,320 patients are diagnosed annually in the United States, of whom 10,540 are expected to die.²

Despite some recent advances in neoadjuvant therapy, studies generally have failed to show any improvement in overall or relapse-free survival. Surgical treatment remains as the most effective modality in treating gastric cancer³. In the Western world, a potential curative resection is undertaken in less than 40-60% of patients^{4,5} as compared to 70-85% of patients in Japan⁶. Palliative surgery has traditionally been offered to most remaining patients to relieve symptoms and maintains survival. The benefit of palliative surgery for stomach carcinoma is controversial.^{7,8} Questions are commonly raised whether resection should be performed whenever possible and about the survival advantages of this resection.

Several studies indicate the importance of palliative gastrectomy in Stage IV gastric cancer.⁹⁻¹⁴ Stage IV gastric cancer is defined according to the American Joint Committee on Cancer, as M1 with any T or any N,¹⁵ in this heterogeneous variety of patients, subgroup analyses are necessary to determine patients who can benefit from surgery.

This study was designed to investigate the role of palliative gastrectomy in advanced gastric adenocarcinoma patients having hepatic metastasis without extra-abdominal disease at diagnosis.

Patients and methods:

This study was performed in General Surgery Department, Tanta University Hospitals, Egypt during the period from April 2007 to September 2012 on 29 patients diagnosed with advanced gastric cancer having hepatic metastasis.

Patients were selected according to following criteria: histopathologically proven gastric adenocarcinoma; presence of hepatic metastasis at the time of diagnosis; absence of extra-abdominal disease, having a performance status of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale¹⁶ at initial diagnosis and none had received prior chemotherapy or radiation

therapy.

Full explanation of procedures; possible complications and patient consent were assured before inclusion in the research. The study protocol was approved by the Ethics Committee of General Surgery Department, Tanta University Hospitals. Palliative gastrectomy was decided according to the patient's symptoms and general health, performance status, extent of the disease, and feasibility of resection. Patients were categorized into the two groups. Group I, 8 males and 3 females underwent gastrectomy with subsequent chemotherapy. Eighteen patients in group II, 11 males and 7 females received chemotherapy alone without gastrectomy. None of the patients received postoperative adjuvant radiotherapy. All patients were treated with systemic 5-fluorouracil based regimens.

Follow-up examinations were performed in 3-week intervals during the chemotherapy schedules and in every three months thereafter. The follow-up program included clinical examination, hematological analyses, liver function tests, and tumor marker assay (carcinoembryonic antigen (CEA) and CA19-9), abdominal ultrasound and chest x-ray. Upper digestive tract endoscopy was planned once a year. Abdominal and/or thoracic computed tomography was performed in cases of suspected recurrence.

Statistical analysis:

Statistical Analysis Quantitative variables were expressed as mean \pm Standard Deviation. Qualitative variables were expressed as frequency and percent. Quantitative parametric variables were compared between the two groups using unpaired student t-test, quantitative non-parametric variables were compared using Mann-Whitney test. Qualitative variables were compared using Chi-square test or Fisher exact test (when the criteria for using Chi-square were not sufficient. The power used was 0.80 while the level of significance was 5%.

Results:

Demographics and tumor characteristics

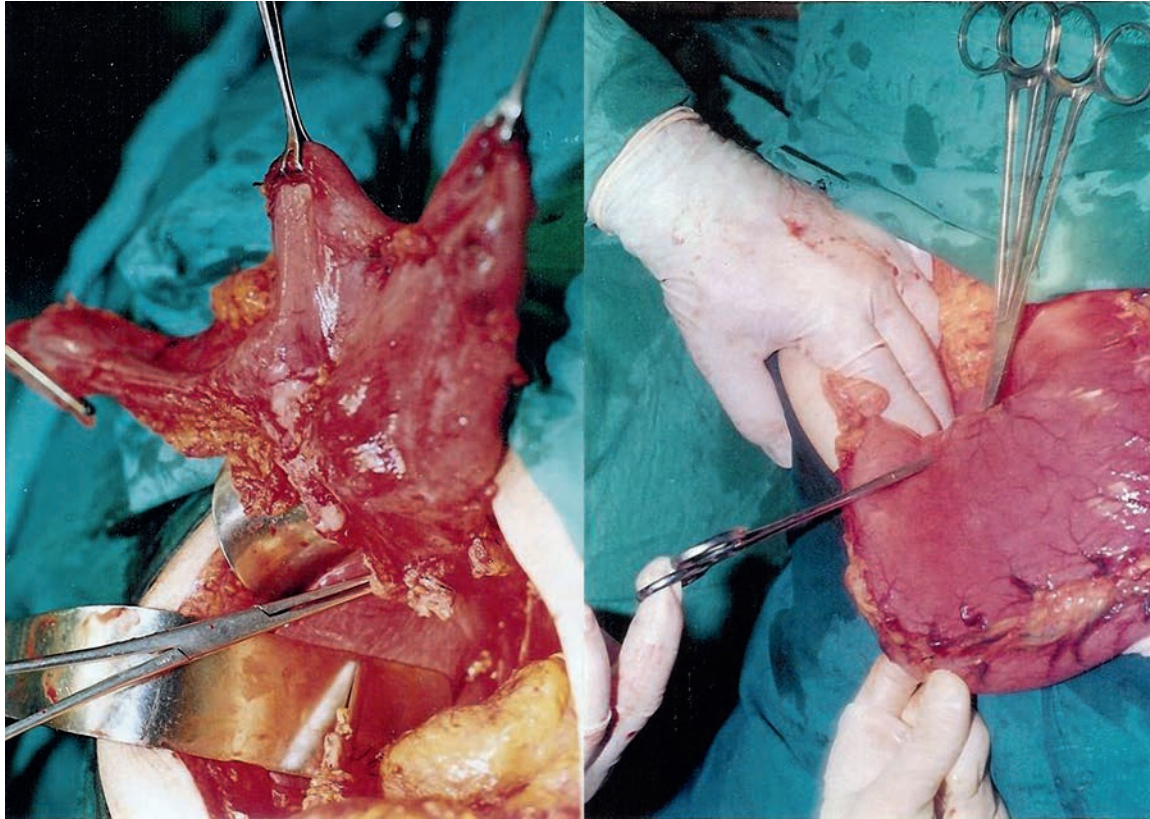


Figure (1): Resection of the stomach.

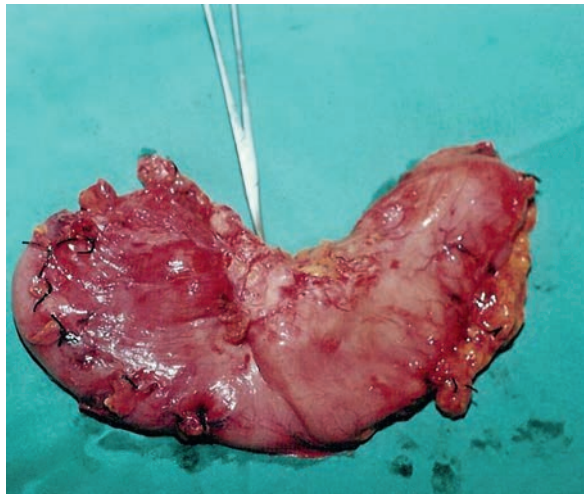


Figure (2): After complete Resection.

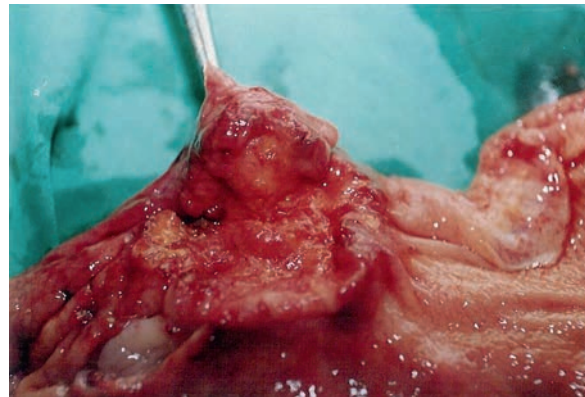


Figure (3): The specimen showing the tumor.

of patients for the GI and GII are showed in **Table (1)**. Vomiting, fatigue and weight loss were the main symptoms of all the patients in this study. Histologically, 10 patients had intestinal-type adenocarcinoma and 19 had diffuse-type adenocarcinoma.

In 11 (37.93%) of 29 patients the primary tumor was removed (total gastrectomy in 7 and distal gastrectomy 4 patients). Laparotomy showed resection to be impossible due to local infiltration of nearby

organs in another 2 patients. They were excluded from this study. No patient had undergone liver resection. Wound infection developed in one of the patients of the resection group. He was conservatively treated. One of the patients was reoperated for minor leakage from the anastomosis leading to intraabdominal collection. All patients were examined by a medical oncologist after their histopathological investigation and were discharged from hospital after their

Table 1: Demographics and tumor characteristics of patients for the GI and GII.

	GI	GII	P
Age	54.9±13.8	60.3±13.4	0.31
< 60 years	5 (17.24%)	6 (20.69%)	
≥ 60 years	6 (20.69%)	12 (41.38%)	
Gender			0.67
Males	8 (27.59%)	11 (37.93%)	
Females	3 (10.34%)	7 (24.14%)	
Level of CEA and CA 19.9			0.51
Normal	3 (10.34%)	3 (10.34%)	
High	8 (27.59%)	15 (51.72%)	
Primary tumor Localization			
Upper third	3 (10.34%)	4 (13.79%)	
Middle third	4 (13.79%)	6 (20.69%)	
Lower third	4 (13.79%)	8 (27.59%)	
Histopathology of primary tumor			
Intestinal-type adenocarcinoma	4 (13.79%)	6 (20.69%)	
Diffuse-type adenocarcinoma	7 (24.14%)	12 (41.38%)	
Hepatic metastasis			
Solitary	8 (27.59%)	8 (27.59%)	
Multiple	3 (10.34%)	10 (34.48%)	
Unilobar	2 (6.90%)	6 (20.69%)	
Bilobar	1 (3.45%)	4 (13.79%)	
With extra hepatic spread	0	3 (10.34%)	

Table 2 .Hospitalization index and ingestion index.

	G I	G II	p
Hospitalization index	0.391± 5.449E-02	0.377 ±4.959E-02	0.48
Ingestion index	0.886 ±9.729E-02	0.696 ±0.172	0.0025

Table 3: Study of survival according to liver tumors in group I

14 Hepatic metastasis	Number of Patients	Mean survival (days)	p
Solitary hepatic metastasis	8 (27.59%)	419 ±54.6	0.034 (solitary versus multiple)
Multiple hepatic metastasis	3 (10.34%)	338 ±11.6	
Unilobar	2 (6.90%)	359	
Bilobar	1 (3.45%)	296	
Hepatic metastasis with extra hepatic spread	0		

chemotherapy schedule was determined. The mean hospital stay of the first admission for GI and GII patients was 13.9 ±6.41 and 4.28±1.41 days respectively (p >0.0001). The Hospitalization index (the duration of

hospital stay relative to the overall survival period)⁶ was not different between the two groups. On the other hand, the Ingestion index (the duration of the period in which oral intake was maintained relative to the overall

Table 4: Study of survival according to liver tumors in group II.

31 Hepatic metastasis	Number of Patients	Mean survival (days)	p
Solitary Hepatic metastasis	8 (27.59%)	208 ±42.3	0.0022 (solitary versus multiple)
Multiple Hepatic metastasis	10 (34.48%)	146 ±29.5	0.060 (unilobar versus bilobar)
Unilobar	6 (20.69%)	160± 24.5	
Bilobar	4 (13.79%)	125 ±25.2	
Hepatic metastasis with extra hepatic spread	3 (10.34%)	113 ± 11.5	

Table 5: Study of effect of resection of primary tumor on survival in both groups.

	GI		GII		P
	Number	Mean survival	Number	Mean survival	
Age					
< 60 years	5 (17.24%)	411 ± 72.0	6 (20.69%)	187 ±66.2	0.0004
≥ 60 years	6 (20.69%)	386 ±51.4	12 (41.38%)	167 ±35.2	>0.0001
Gender					
Males	8 (27.59%)	408 ± 61.4	11 (37.93%)	163 ± 35.8	>0.0001
Females	3 (10.34%)	369 ± 54.5	7 (24.14%)	190 ± 59.4	0.0022
Level of CEA and CA 19.9					
Normal	3 (10.34%)	460 ±36.1	3 (10.34%)	230 ±70.0	0.0072
High	8 (27.59%)	374 ±48.9	15 (51.72%)	162 ±33.6	>0.0001
Primary tumor Localization					
Upper third	3 (10.34%)	460 ±36.1	4 (13.79%)	212± 67.0	0.0023
Middle third	4 (13.79%)	359 ±48.1	6 (20.69%)	167± 29.4	>0.0001
Lower third	4 (13.79%)	387 ±52.4	8 (27.59%)	159± 40.2	>0.0001
Histopathology of primary tumor					
Intestinal-type adenocarcinoma	4 (13.79%)	431 ±64.6	6 (20.69%)	187± 66.2	0.0004
Diffuse-type adenocarcinoma	7 (24.14%)	378± 51.4	12 (41.38%)	167 ±35.2	>0.0001
Liver metastasis					
Solitary	8 (27.59%)	419 ±54.6	8 (27.59%)	208 ±42.3	>0.0001
Multiple	3 (10.34%)	338 ±11.6	10 (34.48%)	146 ±29.5	>0.0001
Extra hepatic spread	0		3 (10.34%)	113 ± 11.5	
Resection of primary tumor	11(37.93%)	397±59.7	18 (62.07%)	173±46.8	>0.0001

survival period)⁶ was significantly higher in GI than in GII **Table (2)**. It was observed that resection increased the survival of the patients regardless to their number and localization of hepatic metastasis **Tables (3,4)**.

The mean follow-up time was 258 ±122 days. The mean survival of GI and GII

patients were 397 ±59.7 and 173 ±46.8 days (p >0.0001). The mean metastatic progression-free survival of the GI and GII groups were 329 ±54.7 and 141 ±49.4 days (p >0.001). The difference in survival was statistically significant.

The factors affecting overall survival

Table 6: Univariate analysis of factors affecting survival in both groups

	Number	Mean survival	p
Age			
< 60 years	11 (37.93%)	289 ±134	0.30
≥ 60 years	18 (62.07%)	240 ±113	
Gender			
Males	19 (65.52%)	280 ±125	0.19
Females	10 (34.48%)	217 ±110	
Level of CEA and CA 19.9			
Normal	6 (20.69%)	345 ±135	0.036
High	23 (79.31%)	235 ±105	
Primary tumor Localization			
Upper third	7 (24.14%)	319 ±142	0.329
Middle third	10 (34.48%)	244± 106	
Lower third	12 (41.38%)	235 ±120	
Histopathology of primary tumor			
Intestinal-type adenocarcinoma	10 (34.48%)	284 ±141	0.41
Diffuse-type adenocarcinoma	19 (65.52%)	244 ±112	
Liver metastasis			
Solitary	16 (55.17%)	313 ±119	0.0045
Multiple	13 (44.83%)	190± 88	
Unilobar	8 (27.59%)	205 ±86.7	0.46
Bilobar	5 (17.24%)	166 ±94.2	
Extra hepatic spread	3(10.34%)	113 ± 11.5	0.027
Resection of primary tumor	11 (37.93%)	397±59.7	>0.0001
No resection	18 (62.07%)	173±46.8	

in gastric cancer patients who had hepatic metastasis are compared between both groups in **Table (5)**. Related risk factors based on the univariate analysis were serum tumor marker levels (p 0.036), number of hepatic metastasis (p 0.0045), resection of primary tumor (p >0.0001) and the absence of extra hepatic spread (p 0.027) . These factors were analyzed with Cox regression analysis and results are showed in **Table (6)**.

Discussion:

In the stage IV gastric carcinomas primary tumor can result in gastric obstruction, perforation, bleeding, or excessive ascites. The aim of the palliative procedures is to manage those complications. Increased survival may be a secondary goal for a palliative procedure. The benefits of palliative

surgery in the survival of the patients having stage IV metastasis were indicated in several studies.⁹⁻¹² The effect was not identified in other studies.¹⁷⁻¹⁹ The reason of the different results in the series is poor prognosis in the stage IV gastric carcinomas. The estimated survival time is too short and performing resection or not may have different clinical features. However, performing the same conditions is clinically impossible. This study was carried out to determine whether surgical removal of the primary tumor provides a better survival and disease progression. Tumor load reduction diminishes the metabolic demand by the tumor. In addition, because the tumor itself can produce immunosuppressive cytokines, reducing the tumor load may also have an immunologic benefit.²⁰ However, if a significant proportion of the tumor load is

removed perhaps the disease may be more responsive to adjuvant treatment.²¹ It can also be seen that gastrectomy was useful for maintaining a longer period of oral intake.

No hepatic resection was done and all the patients received chemotherapy. The mean metastatic progression-free survival of the GI and GII groups were 329 ± 54.7 and 141 ± 49.4 days ($p > 0.001$). Analyses were done based on both the number and the localization of the hepatic metastasis. The effect of the presence of solitary or multiple metastases on the survival was significantly different. However, bilobar metastasis was not determined as an important factor that statistically affected survival. In literature there were studies supporting^{10,22} and contradicting^{7,12} these findings.

Four signs of incurability were noted: irresectable tumor, hepatic metastasis, peritoneal metastasis, and distant lymph node metastasis. The resectability rate decreases as the number of sites of tumor spread increases. Survival advantage of resection procedure disappeared when more than two sites of tumor spread were present.^{9,23,24} In the study of Kikuchi et al.,²⁵ the benefit of resection in the survival was not presented in the patients who have both hepatic metastasis and peritoneal spread. In the present study, all the patients had hepatic metastasis. Extra hepatic spread was observed only in 3 patients and resection was not applied to such patients. When their survival was examined according to overall survival, univariate analysis revealed extra hepatic spread as a negative factor.

Neither in this study nor in the others, the age of the patient was determined as a factor that significantly affects survival.^{10,11,22} Hartgrink et al.⁹ indicated that resection was not effective in patients older than 70 years with multiple metastases.

Increased tumor marker levels at the time of diagnosis negatively affect the prognosis.²⁶ Results of the present study supported this finding. However, there was an opposing study.¹²

Localization of the tumor in the stomach did not affect the survival.^{10,11} Although the

site of the tumor is considered as an important parameter in the study of Kunisaki et al.,¹⁰ neither present study nor the study of Kim et al.²² supports this finding.

The strictest argument about palliative resection versus other conservative palliative procedures is the increased ratio of postoperative mortality, morbidity, and time of hospitalization.^{9,10,24} We didn't encounter surgery related mortality in this study. Complication was observed in two patients in GI. One of these was wound sepsis and the other was anastomotic leakage and localized peritonitis. The first hospital stay in the GI, was significantly longer than the other group but without significant effect on hospitalization index. There were studies indicating that palliative resection did not have a negative effect on the mortality and morbidity.¹⁷

In conclusion, despite that stage IV patients have poor prognosis, removal of the intact primary tumor for gastric cancer with synchronous hepatic metastasis at diagnosis is associated with improvement in overall survival and metastatic progression-free survival.

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