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Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction

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***Abstract*---**Background: Adenocarcinomas of the gastro-esophageal junction (GEJ) are often lumped in therapeutic trials and analyzed with either esophageal cancer or gastric cancer. Aim: We investigated the effect of surgery plus postoperative (adjuvant) chemoradiotherapy on the survival of patients with resectable adenocarcinoma of the stomach or gastroesophageal junction. Patients and methods: This study was conducted at Ali bn Ali hospital in corporation with Soliman Fakeeh Hospital. This study was conducted on 505 patients with resected adenocarcinoma of the stomach or GEJ were randomly assigned to surgery plus postoperative chemoradiotherapy or surgery alone, those were divided into two groups: Surgery only group (N=247), and Chemoradiotherapy group (N=258). Results: There was highly statistically significant difference between the studied groups regarding overall survival among all eligible patients with majority of dead rate in surgery only group (70.4%). And Relapse-free Survival among All Eligible Patients with majority of dead rate in Surgery only group (74.9%). While, there was no statistically significant difference regarding age sex, T stage, No. of positive nodes and location of primary tumor. Reason for cessation, 165 patients 63.9% had Protocol treatment completed, 43 patients 16.7% had Toxic effects, 22 patients 8.5% declined further treatment, 13 patients 5.1% had Progression of disease, 3 patients (1.2%) died and 12 patients 4.6% had other causes. Conclusion: we conclude that postoperative chemoradiotherapy treatment significantly improves overall and relapse-free survival compared to surgery alone among patients with adenocarcinoma of the stomach, lower esophagus, or gastroesophageal junction.

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***Keywords*---**Gastric adenocarcinoma, Chemoradiotherapy, Gastro-esophageal junction, Relapse-free Survival.

Introduction

Adenocarcinomas affecting the gastro-esophageal junction (GEJ) are frequently grouped together for analysis in clinical trials alongside gastric or esophageal cancer (1). Gastric resection is considered the definitive therapeutic approach for stomach cancer. However, the majority of patients do not recover from this operation (2).

The principal therapeutic approach for adenocarcinoma located at GEJ is surgical resection. Unresected microscopic metastases that were present during surgery will cause at least 50 % of the patients to relapse with their cancer (3). The high incidence of local and regional relapses subsequent to gastric cancer resection in patients with adenocarcinoma of the GEJ or stomach prompted us to investigate the effectiveness of a combined therapy involving radiation and chemotherapy (4). Numerous prospective studies have examined preoperative and postoperative therapy strategies in an effort to improve survival rates and prevent relapse (5).

Response rates for locally advanced gastric cancer treated with the epirubicin, cisplatin, and infused fluorouracil (ECF) regimen, which was developed in the late 1980s, have varied between 49% and 56% according to randomized trials (6). When compared to a regimen consisting of fluorouracil, doxorubicin, and methotrexate (FAMTX), the ECF regimen exhibits favorable side-effect profile and enhances survival and response rates in patients diagnosed with advanced esophagogastric cancer (7).

The aim of this study was to assess the effect of postoperative adjuvant chemoradiotherapy and surgical intervention combined on the survival rate of patients who have been diagnosed with resectable gastric or GEJ adenocarcinoma.

Patients and Methods

This study was conducted at Ali bn Ali hospital in corporation with Soliman Fakeeh Hospital. This study was conducted on 505 patients who had stomach or GEJ adenocarcinoma resected were randomly assigned to receive either surgery alone or surgery plus postoperative chemoradiotherapy, those were categorized into two groups: Surgery only group (N=247), and Chemoradiotherapy group (N=258)

Inclusion criteria were the following: Patients diagnosed with gastric adenocarcinoma confirmed through histopathological examination, patients of any age and gender with a primary or recurrent diagnosis of gastric adenocarcinoma, patients who have received or are eligible for various treatment modalities, including surgery, chemotherapy, and patients who have undergone neoadjuvant or adjuvant therapy as part of their treatment regimen.

Exclusion criteria were the following: Patients with histologically confirmed gastric cancers other than adenocarcinoma (e.g., gastric lymphoma, gastrointestinal stromal tumors), patients with secondary malignancies or metastatic tumors originating from sites other than the stomach. Patients with incomplete medical records or insufficient data regarding diagnosis, treatment, or outcomes, and patients who have received treatment outside the scope of recent advances in gastric adenocarcinoma management (e.g., traditional chemotherapy regimens without novel agents or approaches).

Ethical Consideration: Approval and Ethics Committee was taken before preceding the study. The informed consent was obtained.

Sample size calculation

This study base on study carried out by Macdonald et al., (8) Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: - 95% two-sided confidence level, with a power of 80%. & α error of 5%. Main outcome was relapse-free Survival among all eligible patients which occurred at a ratio of 24.9% and 37% after Surgery only and chemo radiotherapy after surgery, respectively. The final maximum sample size taken from the Epi- Info output was 456. Thus, the sample size was increased to 505 subjects to assume any drop out cases during follow up.

Each individual patient subsequently underwent the following: Complete history taking: (Personal history, medical history and history of previous abdominal surgeries), **Physical examination and investigational studies:** including routine laboratory investigations and Radiological investigations.

Treatment Plan

A random assignment was made among patients who underwent gastrectomy to be treated with either surgery only or a postoperative combination of local–regional radiation, leucovorin and fluorouracil. 20 to 40 days after surgery, randomization was performed using a dynamic balancing procedure; stratification was according to tumor stage (T1 to T4, T3, or T4) and nodal status (no positive nodes, one to three positive nodes, or four or more positive nodes).

The North Central Cancer Treatment Group established the regimen containing leucovorin and fluorouracil (9) administered during the pre-radiation and post-radiation phases. Following the initiation of chemotherapy (Daily leucovorin application of 20 mg per square meter and daily administration of 425 mg fluorouracil per square meter of body surface area for 5 days), chemoradiotherapy was initiated 28 days after the initial chemotherapy cycle was initiated. For five weeks, chemotherapy was administered five days per week, 4500 cGy of radiation at 180 cGy per day, in conjunction with leucovorin (20 mg per square meter per day) and fluorouracil (400 mg per square meter per day) on the final three days of radiotherapy and the first four days of radiotherapy, respectively. Two five-day cycles of leucovorin (20 mg per square meter per day) and fluorouracil (425 mg per square meter per day) were administered one month subsequent to the

conclusion of radiotherapy. In patients with toxic effects of grades 3 or 4, the dosage of fluorouracil was decreased.

A total of 4500 cGy of radiation was administered in 25 fractions over the course of five days per week to the tumor bed, regional nodes, and an extra 2 cm beyond the proximal and distal margins of resection. The tumor bed was identified through the utilization of preoperative computed tomographic (CT), barium roentgenographic, and, in specific instances, surgical clip imaging techniques. The necessity for medial left hemidiaphragmatic treatment originated from the existence of proximal T3 lesions. The regional lymph node areas were delineated using the definitions that were supplied by the Japanese Research Society for Gastric Cancer**. (10, 11).** The radiation fields included lymph nodes located in the periaortix, local para-aortic, celiac, splenic, hepatic-portal or hepatoduodenal, and pancreaticoduodenal regions. Radiation fields were expanded to include paracardial and paraoesophageal lymph nodes in patients with GEJ tumors; however, radiation to the pancreasoduodenum was not necessary. In order to preserve the integrity of the left kidney, exclusion of the splenic nodes was permissible in patients presenting with antral lesions. The radiation was transmitted using photons of a minimum 4MV. A maximum dose of 3000 cGy of radiation was administered to less than 60% of the hepatic volume. A minimum of two-thirds of a kidney was kept away from the radiation field, and no segment comprising 30 percent of the cardiac volume was exposed to an excess of 4000 cGy of radiation. A bolus of fluorouracil (400 mg per square meter) and leucovorin (20 mg per square meter) was administered intravenously on the final three days of irradiation and each of the initial four days. The tolerability of this regimen was established in a prior clinical trial (12).

Quality Assurance for Radiotherapy

Prior approval was required from the radiation-oncology coordinator prior to the commencement of the radiotherapy treatment plan. Prior to initiating treatment, preoperative reports on tumor imaging, treatment fields, dosimetry, surgery, and pathology were submitted for evaluation. Prior to the initiation of therapy, modifications were made to plans that were declined for approval on account of the potential for toxic effects on vital organs or the inability to treat the designated target volumes. During these evaluations, it was discovered that 35% of the treatment plans contained significant or minor protocol deviations, the majority of which were rectified prior to the commencement of radiotherapy. The final assessment of radiotherapy quality assurance unveiled significant changes in 6.5% of the treatment plans following radiation administration.

Follow-Up of Patients

Two years of monitoring were conducted at three-month intervals for both groups, followed by three years of monitoring at six-month intervals, and finally an annual follow-up. During the follow-up investigation, clinically indicated procedures including complete blood count, liver function testing, chest radiography, CT scanning and physical examination were carried out. The patient's date of death, if applicable, and the location and time of their initial relapse were documented.

Statistical Analysis

Analysis of data was performed using Statistical Package for Scientific Studies (SPSS) version 23 for Windows (IBM SPSS, Inc., Chicago, IL). The description of quantitative variables was in the form of mean, standard deviation (SD) and range for parametric data, and median and interquartile range for non- parametric data. The Kolmogrov-Simrnov test for detection of normality distribution was used. The description of qualitative variables was in the form of numbers (No.) and percent (%). Chi-square test was used to compare categorical variables while independent samples t-student test was used to compare the continuous variables between the two groups. The significance of the results was assessed in the form of P-value that was differentiated into: Nonsignificant when P-value > 0.05.

Results

Table (1): Distribution of demographic data between the studied groups

	Surgery only group N=247	Chemoradiotherapy group N=258	Test	P value
Age (year)				
Mean± SD	51.5±13.1	56±12.5	**t=** 1.38	0.166
Sex				
Male	175 (70.8%)	182 (70.6%)	**X^2=** 0.006	0.938
Female	72 (29.2%)	76 (29.4%)		

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant, SD: standard deviation, t: T test, x2: qui square test.

Age and sex did not differ between the groups under study in a statistically significant manner, as shown in the table.

Table (2): Distribution of tumor characteristics between the studied groups

	Surgery only group N=247	Chemoradiotherapy group N=258	Test	P value
T stage (%)				
T1 or T2	77 (31.2%)	79 (30.6%)	**X^2=** 0.599	0.741
T3	150 (60.7%)	153 (59.3%)		
T4	20 (8.1%)	26 (10.1%)		
No. of positive nodes (%)				
0	39 (15.8%)	38 (14.7%)	**X^2=** 0.118	0.942
1-3	103 (41.7%)	108 (41.8%)		
≥4	105 (42.5%)	112 (43.5%)		
Location of primary tumor (%)				
Antrum	138 (55.9%)	137 (53.2%)	**X^2=** 1.285	0.732
Corpus	62 (25.1%)	62 (24%)		
Cardia	44 (17.8%)	54 (20.9%)		
Multicentric	3 (1.2%)	5 (1.9%)		

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant, x2: qui square test.

As shown in this table, no statistically significant difference existed among the groups under study with regard to T stage, No. of positive nodes and location of primary tumor.

Table (3): Distribution of reason for cessation in Chemoradiotherapy group

	Chemoradiotherapy group N=258
Reason for cessation	
Protocol treatment completed	165 (63.9%)
Toxic effects	43 (16.7%)
Patient declined further treatment	22 (8.5%)
Progression of disease	13 (5.1%)
Death	3 (1.2%)
Other	12 (4.6%)

This table shows Reason for cessation, 165 patients 63.9% had Protocol treatment completed, 43 patients 16.7% had Toxic effects, 22 patients 8.5% declined further treatment, 13 patients 5.1% had Progression of disease, 3 patients (1.2%) died and 12 patients 4.6% had other causes.

Table (4): Distribution of major toxic effects of Chemoradiotherapy group

	Chemoradiotherapy group N=258
Type of toxic effect	
Hematologic	139 (53.9%)
Infection	15 (5.8%)
Gastrointestinal	85
Neurologic	10
Cardiovascular	12
Influenza-like	23
Pain	8
Lung-related	3
Hepatic	4
Metabolic	6
Death	2

This table shows toxic effect type, majority of patients 139 (53.9%) had Hematologic toxic effect and only 2 patients died.

Table (5): Overall Survival Among All Eligible Patients, According to Treatment-Group Assignment

	Surgery only group N=247	Chemoradiotherapy group N=258	Test	P value
duration of survival (month)				
Mean± SD	25.5±2.13	34.3±3.5	**t=** 33.8	<0.001
Survival rate				
Live	73 (29.6%)	102 (39.5%)	**X^2=** 5.55	0.02
Dead	174 (70.4%)	156 (60.5%)		

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant, x2: qui square test.

The data shown in this table indicates that statistically significant difference was identified among the groups that were examined with regards to overall survival among all eligible patients with majority of dead rate in surgery only group (70.4%).

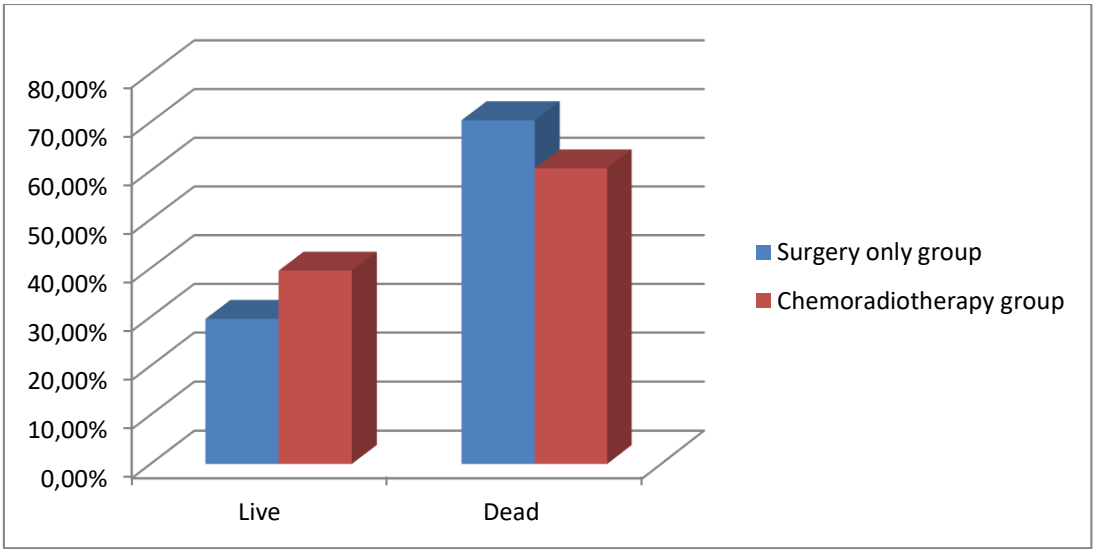

Fig (1): Shows distribution of survival rate between the studied groups

Table (6): Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignment

	Surgery only group N=247	Chemoradiotherapy group N=258	Test	P value
duration of survival (month)				
Mean± SD	21.2±3.1	31.1±4.2	**t=** 33.8	<0.001
Survival rate (without relapse)				
Live	62 (25.1%)	97 (37.6%)	**X^2=** 5.55	0.02
Dead	185 (74.9%)	161 (62.4%)		

P value >0.05: Not significant, P value <0.05 is statistically significant, p<0.001 is highly significant, x2: qui square test.

As shown in this table, an obvious statistically significant difference existed among the groups under investigation with respect to Relapse-free Survival among All Eligible Patients with a majority of dead rate in Surgery only group (74.9%).

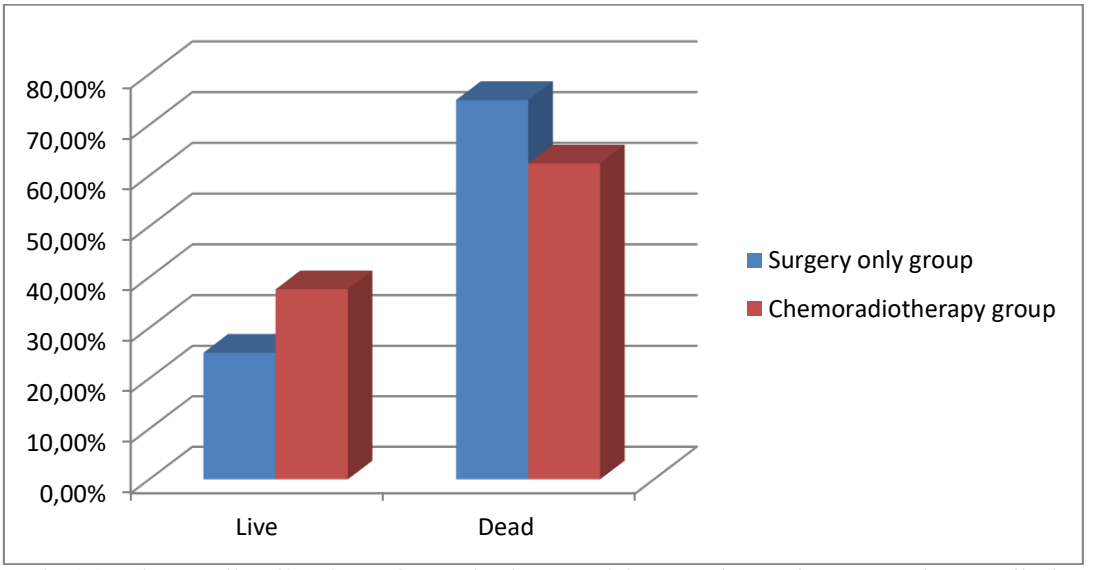

Fig (2): Shows distribution of Survival rate without relapse between the studied groups

Table (7): Distribution of site of relapse between the studied groups

	Surgery only group N=247	Chemoradiotherapy group N=258
	SITES OF RELAPSE	
Local	67 (27.1%)	51 (19.8%)
Regional	178 (72.1%)	165 (63.9%)
Distant	42 (17.01%)	81 (31.4%)

This table shows distribution of site of relapse, with majority of distribution at regional site (72.1%) and (63.9%) in Surgery only group and Chemoradiotherapy group respectively.

Discussion

The present study showed that according to demographic data between studied groups, age and sex did not differ in a statistically significant manner. Our results are consistent with those of Macdonald et al. (8), whose objective was to determine whether patients with resectable adenocarcinomas of the stomach fared better with surgery and postoperative (adjuvant) chemoradiotherapy. A group of 556 individuals who had undergone gastric or GEJ resected adenocarcinoma were assigned at random to receive either surgery alone or surgery in conjunction with postoperative chemoradiotherapy. They found that age and gender did not differ in a statistically significant way.

Ychou et al. (13) conducted a study with the objective of comparing surgical resection in patients with resectable gastroesophageal adenocarcinoma with and without perioperative chemotherapy utilizing fluorouracil and cisplatin. Random assignment was used to allocate 224 patients from 28 centers in France to either the S group (n = 111) or the CS group (n = 113). They found that according to demographic data between studied groups, in regarding age and gender, no statistically significant difference was observed.

Our research findings did not reveal any statistically significant difference among the evaluated groups regarding the T stage, number of positive nodes, or primary tumor location (multicentric, cardia, corpus, antrum).

Similarly, the aim of the study by Kofoed et al. (14) was to compare survival data among GEJ-exclusive patients who received adenocarcinoma curative resection and were assessed as potential candidates for surgical intervention alone or in combination with adjuvant chemoradiotherapy. Their study was conducted on 211 patients. Regarding the number of positive nodes and T stage, no statistically significant difference was observed among the analyzed groups. (P value >0.05)

As well, our results are consistent with Macdonald et al., (8) who revealed that no statistically significant difference was observed among the groups under investigation with respect to positive nodes number, T stage or primary tumor location (antrum, corpus, cardia, or multicentric).

Moreover, Ychou et al. (13) found that there was no statistically significant difference observed in the T stage or the number of positive nodes among the groups under investigation.

In our study we found that according to reason for cessation, 165 patients 63.9% had protocol treatment completed, 43 patients 16.7% had toxic effects, 22 patients 8.5% declined further treatment, 13 patients 5.1% had progression of disease, 3 patients (1.2%) died and 12 patients 4.6% had other causes.

Our findings align with those of Macdonald et al. (8), who documented those 181 patients (64%) kept to the intended course of treatment, while 17 percent stopped treatment due to toxic effects (investigators were not obligated to specify the precise toxic effect that prompted the treatment cessation). An additional 4% of patients ceased treatment for unrelated reasons, whereas 8% declined treatment, 5% experienced disease progression while undergoing treatment, and 1% died during treatment.

Furthermore, our findings align with those of Ychou et al. (13) regarding the factors that led to the withholding of chemotherapy: patient refusal (n = 2), concurrent disease (n = 1), and unknown causes (n = 1). The leading causes of treatment discontinuation among the patients who received the intervention were adverse events (n = 9) and disease progression (n = 3). In our study we found that according to toxic effect type, majority of patients 139 (53.9%) had hematologic toxic effect and only 2 patients died.

As well, our results are consistent with Macdonald et al., (8) who revealed that a total of 273 patients who underwent postoperative chemoradiotherapy experienced toxic effects of grade 3 or higher. The predominant toxic effects were hematologic and gastrointestinal in nature. Leukopenia was the most prevalent hematologic toxic effect. A rare occurrence was severe thrombocytopenia. Among the gastrointestinal effects of the toxin were nausea, vomiting, and diarrhea. In less than 10 percent of the patients, additional forms of toxic effects appeared.

In addition, Ychou et al., (13) who found that forty-one (38%) of the 109 treated patients experienced at least grade 3 to 4 toxicity under preoperative chemotherapy. The most common grade 3 to 4 toxicities were hematologic including neutropenia (20.2%), and thrombocytopenia (5.5%) and nausea/vomiting (9.2%).

Furthermore, Cunningham et al., (7) who found that according to type of toxic effect, majority of patients had hematologic toxic effect. In our study we found that according to overall survival among all eligible patients with majority of dead rate in surgery only group (70.4%), a major statistically significant difference was observed among the groups under investigation with respect to both survival rate and duration.

Our results are consistent with, Ychou et al., (13) who revealed that compared with the surgery group, the chemotherapy group had a significantly higher overall survival (OS) (HR for death, 0.69; 95%CI, 0.50 to 0.95; P=.02). Five-year survival

rates were 38% (95% CI, 29% to 47%) in the CS group compared to 24% (95% CI, 17% to 33%) in the S group.

Similarly, Gaast et al. (15) documented that following a median of 32 months of observation, 70 patients died in the CRT group and 97 patients died in the surgery-only group. In the group of patients treated with CRT, overall survival was significantly higher (p = 0.011) (HR 0.67 [95% CI 0.50-0.92]). In the CRT group, the median survival time was 49 months, compared to 26 months in the surgery-only group.

As well, our results are consistent with Cunningham et al., (7) who found that Chemotherapy significantly increased the likelihood of overall survival in comparison to the surgery group (95 percent confidence interval: 0.60 to 0.93; hazard ratio for death, 0.75; P = 0.009).

Moreover, Ronellenfitsch et al., (16) who found that preoperative chemotherapy was associated with longer overall survival (p < 0.0001). In our study we found that regarding relapse-free survival among all eligible patients with majority of dead rate in surgery only group (74.9%), there was highly statistically significant difference between the studied groups regarding duration of survival and survival rate.

Compared to the chemoradiotherapy group, outcomes of our study are consistent with those reported by Macdonald et al. (8), who identified a hazard ratio of 1.52 (95% confidence interval: 1.23 to 1.86; P< 0.0001) for relapse in the surgery-only group. In the chemoradiotherapy group, the median duration of relapse-free survival was 30 months, whereas in the surgery-only group, it was 19 months.

In addition, Ychou et al., (13) who revealed that regarding relapse-free survival among all eligible patients with majority of dead rate in surgery only group (64%), a statistically significant difference was observed in the relapse-free survival rates among the groups under investigation. On the contrary to our findings, Kofoed et al. (14) discovered that there was no statistically significant difference in relapse-free survival among the groups under investigation. In our study we found that regarding distribution of site of relapse, with majority of distribution at regional site (72.1%) and (63.9%) in surgery only group and chemoradiotherapy group respectively.

Our results are consistent with, Macdonald et al., (8) who revealed that regarding distribution of site of relapse, with majority of distribution at regional site 127 (72%) and 78 (65%) in surgery only group and chemoradiotherapy group respectively. Regional relapse occurs on typical, abdominal carcinomatosis was detected in 72% of patients undergoing surgery-only treatment and 65% of patients undergoing chemoradiotherapy; 18% of patients undergoing surgery-only treatment and 33% of patients undergoing chemoradiotherapy experienced distant relapses. Contrary to our findings, Ychou et al. (13) discovered that in both groups, the majority of patients experienced distant relapse.

Conclusion

We conclude, based on our findings, that postoperative chemoradiotherapy treatment significantly improves overall and relapse-free survival among patients with adenocarcinoma of the lower esophagus, stomach, or GEJ when compared to surgery alone. Patients diagnosed with adenocarcinoma in the aforementioned sites should therefore consider this treatment option.
Further studies are needed with larger scales are needed for conforming our results.

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