EARLY VERSUS DELAYED INTERVENTION IN GASTRIC ADENOCARCINOMA - A RETROSPECTIVE STUDY

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Abstract

In the last decade, early intervention of gastric cancer had shown to leave an influence independent of other factors, on overall patient survival and outcome. The aim of our study is to evaluate the surgical outcomes by a comparison of diagnosed gastric cancer patients with an early interventional approach of 48 hours from admission compared with a delayed interventional approach. An eight-year retrospective study comprising of 185 admissions was conducted in patients admitted at the 1st Department of Surgery, Clinical Emergency County Hospital Targu Mures, Romania from 2013 to 2020, that included all patients that were diagnosed and surgically operated for gastric adenocarcinoma, Urgent surgery was defined as definitive surgery within 48 hours of admission. Univariate and multivariate analysis of patient factors, surgical outcomes, and oncologic data was performed. A total of 185 patient data was collected, out of which 107 (57.8%) early interventions and 78 (42.2%) were delayed. With 8 deaths, a total mortality rate of 4.32% was recorded. Postoperative complications were statistically analyzed and no significant correlations were observed in our univariate and multivariate analysis. Moderately positive correlation was observed between total hospital stay and the timeframe between admission and surgery. In comparison with a delayed elective approach, an early interventional approach showed no significant difference in overall patient survival and surgical outcome in all tested modalities including but not limited to the type of intervention, choice of anastomosis, metastasis and chemotherapy. A positive correlation was observed between the admission to intervention timeframe and total hospital stay.

Keywords: emergency, gastric cancer, adenocarcinoma, early versus delayed

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Introduction

Gastric cancer remains to be one of the most significant malignant diseases in the world. The first major statistical analysis of cancer incidence and mortality (using data collected between 1760 to 1839 in Verona, Italy) demonstrated it to be the most common and lethal type of cancer [1]. According to Globocan 2020, Gastric cancer is the 5th most commonly diagnosed cancer and 4th most common cause of cancer death worldwide [2].

Even though there has been a significant but steady decline in the incidence of gastric cancer since the 1980s [3] and 1990s [4], when it used to be the 2nd most commonly diagnosed cancer, due to recognition of smoking and Helicobacter pylori being two of the main risk factors along with significant improvements in storage and preservation of dietary products and changes in daily dietary habits [4][5][6]. Despite this declining trend in incidence, there has been an increase in total number of cases per year, along with a small but significant increase in younger population has been noted, preserving gastric cancer's role as an important cause of cancer-related deaths [2][7][8]. According to an early study from Japan (Tsukuma, 2000), if left untreated 63% of patients diagnosed with early stage gastric cancer progress to advanced stage within 6 to 88 months.

In the last decade, early intervention of gastric cancer had shown to leave an influence independent of other factors, on overall patient survival and outcome. The aim of our study is to evaluate the surgical outcomes by a comparison of diagnosed gastric cancer patients with an early interventional approach (of 48 hours from admission), compared with a delayed interventional approach.

Materials and Methods

An eight-year retrospective study comprising of 185 admissions was conducted in patients admitted at the 1st Department of Surgery, Clinical Emergency County Hospital Targu Mures, Romania from 2013 to 2020, that included all patients that were diagnosed and surgically operated for various stages and types of Gastric Cancer. Gastric cancer staging, including the TNM pathological staging was included and Adenocarcinomas were identified and recorded using the histopathology results.

Other variables from the patient history, including any past history of interventions, comorbidities, admission to intervention timeframe, location of tumor, tumor-related complications, presence of metastasis, involvement of lymph nodes, type of surgical intervention, type of anastomosis, postoperative complication, total hospital stay, deaths and cause of mortality was all included in the study and retrospectively analyzed from patient records and the database.

Patients with incomplete data or with no gastric surgical interventions performed were excluded from the study.

Data was analyzed to investigate the effect of early intervention upon overall patient survival in comparison with delayed intervention.

Patients were divided into two groups, the emergency group consisted of admitted patients with completion of surgical intervention within 48h of admission and diagnosis, while the rest was defined as the elective or delayed group.

Normality of Age at inclusion (years) was assessed with the Shapiro-Wilk test. Alpha risk was set to 5% ($\alpha = 0.05$), the association between Postoperative complications and type of anastomosis along with the total mortality was tested with the Fisher's exact test, the alpha risk was set to 0.05. A multivariate linear regression was performed to assess the relation between Total hospital stay (Days) and the explanatory variables: Gender, Age at Last Consultation, History of Chemotherapy, Timeframe between admission and surgery (days), Metastasis,

Type of Intervention, Mechanical vs Manual Anastomosis and type of anastomosis.

Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. Heteroskedasticity and normality of residuals were assessed respectively by the Breusch-Pagan test and the Shapiro-Wilk test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using EasyMedStats© software.

Results

An overall predominance of male population was observed, with a total of 137 (74.1%) male patients and 48 female patients (25.9%). Out of the total 185 patients, 107 (57.8%) patients were placed in the emergency group, out of which 75 (70.1%) were male patients and 32 (29.9%) were female. Rest of the patients were placed in the elective group

which consisted of 78 (42.2%) patients in total, out of which 62 (79.5%) were male and 16 (20.5%) were female. Out of a total number of 8 deaths, 4 were noted in the emergency group with equal male-female distribution, and 4 deaths were recorded in the elective group, out of which 3 were male deaths and one female (Table 1). Distribution of Age at inclusion (years) seemed issued from a normally distributed population ($p = 0.09450$) with a minimum of 27 years and maximum of 88 years with a mean±SD of 66.1±10.5 and median of 66 years.

Tumor complications at admission were recorded and divided into three subcategories: Stenosis, hemorrhage and perforation or penetration of the tumor into the surrounding tissue. A predominance of hemorrhagic complications was observed followed by perforation/penetration and stenosis (Table 2).

AGE/ SEX	EMERGENCY	DEATHS (%)	ELECTIVE	DEATHS (%)
< 39	1	0 (0,0)	0	0 (0,0)
40 – 49	4	0 (0,0)	3	1 (25)
50 – 59	19	1 (5,0)	16	0 (0,0)
60 – 69	36	2 (5,3)	21	1 (4,5)
70 – 79	36	1 (2,7)	25	0 (0,0)
>80	6	0 (0,0)	7	2 (22.2)
MALE	75	2 (2,66)	62	3 (4,80)
FEMALE	32	2 (6,25)	16	1 (6,25)

Table 1 - Mortality in each age bracket

COMPLICATIONS AT ADMISSION	EMERGENCY	DEATHS (%)	ELECTIVE	DEATHS (%)
STENOSIS	24	1 (4,16)	4	2 (50,00)
HEMORRHAGE	45	3 (6,66)	48	2 (4,16)
PENETRATION/ PERFORATION	34	2 (5,88)	24	0 (0,00)

Table 2 - Complications at admission

In relation to cancer stage, our analysis showed that 62.7% of the total 185 patients included in our data were diagnosed with advanced stage of gastric cancer.

Elective patients presented mostly with advanced stage disease, stages 3 and 4 accounting for 64.1% of the total 78 patients in the group, compared with 61.7% of the total 107 cases in the emergency group ($p < 0.05$) (Table 3).

A similar relationship was seen in patients with early stage (stage I/II) of the disease, accounting for 38.3% of patients in the emergency group and 35.9% of the patients in elective group ($p < 0.05$).

Data for presence of metastasis was collected where metastasis was observed in 50 patients with Liver being the most common site for metastasis (n=17) (Table 4, Figures 1 and 2).

CANCER STAGE	EMERGENCY	DEATHS (%)	ELECTIVE	DEATHS (%)
EARLY **[Stage I/II]**	41 (38.3%)	2 (4.9%)	28 (35.9%)	1 (3.5%)
ADVANCED **[Stage III/IV]**	66 (61.7%)	2 (3%)	50 (64.1%)	3 (6%)

Table 3 – Correlation between cancer stage and mortality

TUMOR LOCALIZATION	EMERGENCY	DEATHS (%)	ELECTIVE	DEATHS (%)
CARDIA - C	17	1 (5,88)	16	2 (12,5)
CORPUS - M	60	1 (1,66)	35	2 (5,71)
ANTRAL - A	44	2 (4,54)	33	0 (0,0)

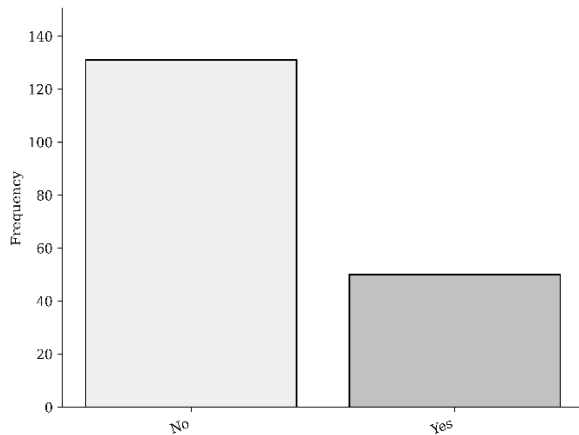**Table 4 – Correlation between tumor localization and mortality**

Figure 1 - Presence of metastasis

Figure 2 - Localization of metastasis

Patients were later subcategorized into two groups; those undergone subtotal gastrectomy (SG) as the main gastric intervention and those with Total gastrectomy (TG) as the main surgical intervention, with mortality observed in each category (Table 5).

INTERVENTION	EMERGENCY	DEATHS (%)	ELECTIVE	DEATHS (%)
SUBTOTAL GaASTRECTOMY	58 (54%) CI: 44,3 – 63,9%	3 (5,2)	47 (61%) CI: 49,2 – 72%	3 (6,4)
TOTAL GASTRECTOMY	49 (45,8%) CI: 36,1-55,7%	1 (2,1)	29 (37%) CI: 26,9 – 49,4%	1 (3,4)

Table 5 – Correlation between type of intervention and mortality

LYMPHADENECTOMY	EMERGENCY	ELECTIVE
D1	14	7
D1+	9	3
D2	9	3
D3	1	1
UNSPECIFIED	74	62

Table 6 – Accuracy of lymphadenectomy in early vs delayed group

TYPE OF ANASTOMOSIS	EMERGENCY	ELECTIVE
Eso-duodenal anastomosis	0	0
Eso-gastric anastomosis	13	12
Gastro-duodenal anastomosis	14	5
Eso-jejunal anastomosis in Ω	25	10
Roux-en-Y Eso-jejunal anastomosis	23	22
Gastro-jejunal anastomosis in Ω	28	27
Roux-en-Y Gastro jejunal anastomosis	5	3

Table 7 – Type of anastomosis in early vs delayed group

Postoperative complications according to the type of anastomosis were statistically analysed and were respectively as such, Cardio-Pulmonary – 37.5% and Fistula of anastomosis – 16.67% in patients with Eso-Gastric anastomosis, Cardio-Pulmonary – 25.0% and Fistula of anastomosis – 16.67% in patients with Eso-Jejunal anastomosis (Omega), Cardio-Pulmonary – 12.5% and Fistula of anastomosis – 16.67% in patients with Gastro-Duodenal anastomosis, Cardio-Pulmonary – 12.5% and Fistula of anastomosis – 16.67% in patients with Gastro-Jejunal anastomosis (Omega), Cardio-Pulmonary – 12.5%, Duodenal Fistula – 100.0% and Fistula of anastomosis – 16.67% in patients with Roux-en-Y Eso-Jejunal anastomosis and Fistula of anastomosis – 16.67% in patients with Roux-en-Y Gastro-Jejunal anastomosis (p=0.942) (Figure 3, Tables 6, 7 and 8).
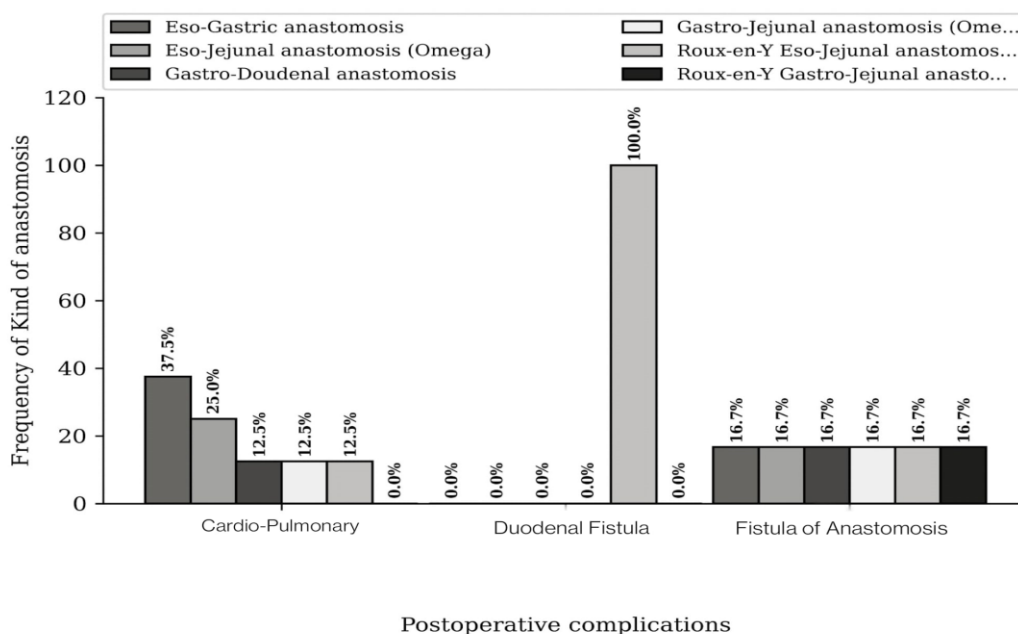
Figure 3 – Correlation between the type of anastomosis and postoperative complications

variable	Cardio-Pulmonary		Duodenal Fistula		Fistula of anastomosis		Total	
Eso-Gastric anastomosis	3 37.5%	75.0% 20.0%	0 0.0%	0.0% 0.0%	1 16.67%	25.0% 6.67%	4	26.67%
Eso-Jejunal anastomosis (Omega)	2 25.0%	66.67% 13.33%	0 0.0%	0.0% 0.0%	1 16.67%	33.33% 6.67%	3	20.0%
Gastro-Doudenal anastomosis	1 12.5%	50.0% 6.67%	0 0.0%	0.0% 0.0%	1 16.67%	50.0% 6.67%	2	13.33%
Gastro-Jejunal anastomosis (Omega)	1 12.5%	50.0% 6.67%	0 0.0%	0.0% 0.0%	1 16.67%	50.0% 6.67%	2	13.33%
Roux-en-Y Eso-Jejunal anastomosis	1 12.5%	33.33% 6.67%	1 100.0%	33.33% 6.67%	1 16.67%	33.33% 6.67%	3	20.0%
Roux-en-Y Gastro-Jejunal anastomosis	0 0.0%	0.0% 0.0%	0 0.0%	0.0% 0.0%	1 16.67%	100.0% 6.67%	1	6.67%
Total	8	53.33%	1	6.67%	6	40.0%	15	100%

Data are displayed as follows: N   Line %

Columns % Total %

Table 8 – Correlation between the type of anastomosis and postoperative complications

With 8 deaths, a total mortality rate of 4.32% was recorded, out of which 3 were observed in the emergency group and 5 were in the elective group, bringing the mortality rate of the groups to 2.8% and 6.4% with CI 1.9-8.4% (p=0.32).

In our multivariate analysis, Timeframe between admission and surgery (days) (β=1.24, [0.62; 1.86], p=0.0001) were associated with higher values of Total hospital stay (days). Metastasis (β=-2.11, [-5.16; 0.93], p=0.1726), Gender=W (β=-0.11, [-3.23; 3.02], p=0.9459), type of anastomosis = Roux-en-Y Eso-Jejunal anastomosis (β=0.22, [-7.24; 7.68], p=0.9534), Mechanical vs Manual Anastomosis = Mechanical (β=0.68, [-2.59; 3.95], p=0.6816), Type of Intervention = Total Gastrectomy (β=0.85, [-6.24; 7.93], p= 0.8133), type of anastomosis = Eso-Gastric anastomosis (β=1.05, [-3.89 ; 6.0], p= 0.6752), type of anastomosis = others (β=1.54, [-2.98; 6.05], p=0.5026), History of Chemotherapy (β=1.64, [-1.26; 4.53], p=0.2661), type of anastomosis = Eso-Jejunal anastomosis (Omega) (β=1.83, [-5.71; 9.36], p=0.6329) were not associated with the value of Total hospital stay (days) (Table 9, Figure 4).

COMPLICATIONS	EMERGENCY	DEATHS (%)	ELECTIVE	DEATHS (%)
Fistula of Anastomosis	3	0 (0,0)	3	1 (25,0)
Duodenal Fistula	1	0 (0,0)	1	1 (100)
Hemorrhage	0	0 (0,0)	0	0 (0,0)
General Complications	4	3 (75,00)	4	3 (100)

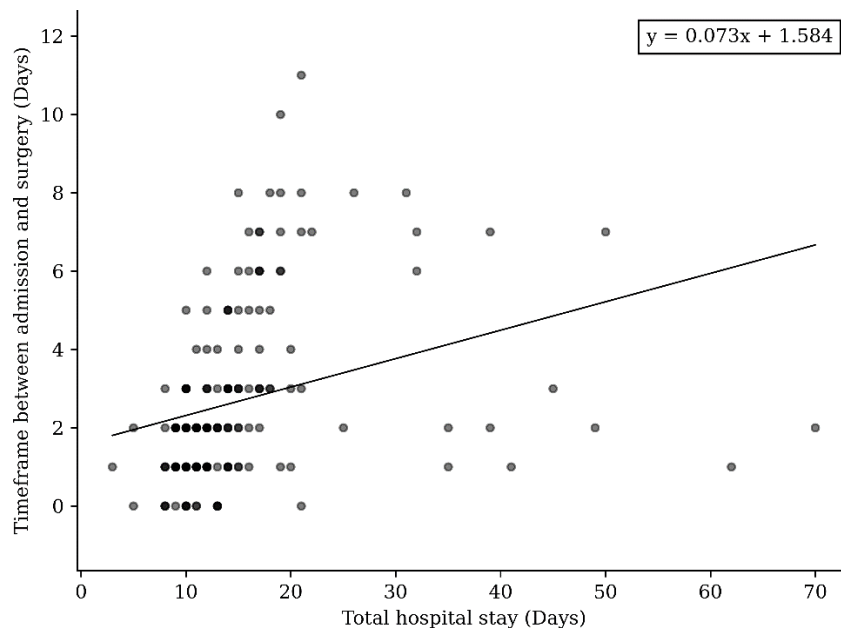**Table 9 – Correlation between postoperative complications and mortality.**

Figure 4 – Bivariate chart: total hospital stay vs timeframe between admission and surgery

Discussions

According to Blackshaw et al. there is a significant association between advanced stage disease and emergency presentation of gastric cancer, it further considers it is an independent marker of poor prognosis [10,11]. In our analysis a similar association is reinforced with 61.6% of emergency interventions being of patients with advanced stage (III/IV) gastric adenocarcinoma.

The poor prognosis in such patients may be due to age, intraoperative tumor-related complications, longer operative time, friability of tissue, blood loss, diminishing physiological reserves and hemodynamic status of the patients at admission [11].

In our study we had an almost equal proportion of patients with early stage and advanced stage disease in each bracket, 64.1% of elective patients and 61.7% of emergency patients presenting with advanced stage disease while 38.3% of emergency patients and 35.9% of elective patients presented with early stage (stage I/II) of the disease, providing us a unique opportunity to better compare and evaluate the analytical data. Opinions regarding emergency resection of gastric cancers are of a mixed nature, Yosuke et al. found that patients that underwent emergency resection of early stage gastric cancers showed a satisfactory long-term survival rate [12]. Similarly, Kasakura et al. showed emergency R0 resections in patients with early stage gastric cancer to have outstanding results [13].

On the other hand, Lehnert et al. advised against a radical early approach [14], Blackshaw et al. also argued that an early emergency approach decreases the patient median survival rate [10].

Even though our analysis has the limitations of being a retrospective unicentric experience, it provides an interesting argument against a fearful approach towards radical gastric interventions, with a total mortality rate of less 5%, no significant difference was observed between an early approach or a delayed interventional approach towards gastric cancers, on the other hand we found a moderately positive correlation between total hospital stay and the timeframe between admission and surgery ($\rho=0.52$; r2=0.089; p <0.001).

Conclusions

In comparison with early versus a delayed interventional approach, our study showed no significant difference in overall patient survival and surgical outcome. A positive correlation was observed between the admission to intervention timeframe and total hospital stay. Timely follow-up of these patients will be able to answer whether and oncological.

Stable patients requiring emergency gastric resections can access the benefits of high-volume centers (in terms of improved resection margins, respectively lymphadenectomy). If this is not possible, consultation with a surgical oncologist may be beneficial for surgeons in low-volume centers – who perform fewer gastric resections.

All patients requiring emergency resections should be referred to surgical oncology/general oncologists to ensure they receive appropriate adjuvant therapy with consequent improvement in survival in gastric adenocarcinoma.

In order to improve the results, it is necessary to establish a national database of gastric cancer (the limitation of the present study – with statistically insignificant results – is determined by the limited group of patients).

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