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Establishing a Suitable Time for Chemotherapy in Gastric Cancer: Before or After Surgery

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Introduction:

Gastric cancer (GC) is the fourth most common cancer and stands in second place regarding the rate of cancer-related death (Saedi *et al.*, 2014; Sitarz *et al.*, 2018). This is an aggressive and invasive disease (Smalley *et al.*, 2012). Each year, worldwide approximately one million new cases are detected (Sitarz *et al.*, 2018). Asia, Eastern Europe, and South America are endemic regions for GC (Zندهdel, 2019). In Iran, GC is the most common cancer in males & 6th common cancer in females (Zندهdel, 2019). The overall survival (OS) for the resectable type of GC is about 20-30%, worldwide (Ozden *et al.*, 2015). Various studies compared adjuvant chemotherapy (AC) with surgery alone, but there is still no certain evidence about the efficacy of neoadjuvant chemotherapy (NAC) on OS (Ozden *et al.*, 2015; Smalley *et al.*, 2012). A Cochrane review showed that chemotherapy, even in advanced stages of the disease, increases life expectancy (Wagner *et al.*, 2017). Gastrectomy with lymphadenectomy is the only curative therapy that can improve patients' condition and OS but metastasis and

Abstract

The effect of Chemotherapy as a neoadjuvant or adjuvant treatment on patients' survival & complications has been investigated by a retrospective cohort on Patients with GC that got chemotherapy before or after surgery. Cox's regression hazards models were applied to obtain hazard ratios with 95% confidence intervals to assess the association between gastric cancer survival and potential risk factors. In addition, logistic regression model to assess the association between complications, hospital mortality, length of stay in ICU and potential risk factors among patients. Among the two hundred patients enrolled in the study, 55 (27.5%) were females and 145 (72.5%) males. A total of 82 (41%) patients received NAC and 118 (59%) received adjuvant chemotherapy (AC). There were no significant differences between the AC and NAC groups in overall survival. Also, post-operation complications and hospital mortality didn't differentiate between both groups. But the duration of staying in ICU is significantly higher in the NAC group versus the AC group. Finally, it seems that both neoadjuvant and adjuvant chemotherapies were suitable treatments for gastric cancer regarding the patients' conditions. Although our study did not find an obvious advantage or any main difference in side effects for any of these methods

repeated relapses result in unsatisfactory prognosis (Wagner *et al.*, 2017; Saedi *et al.*, 2014; Ozden *et al.*, 2015). Nowadays NAC and AC are added to treatment with the goal of increasing prognosis (Saedi *et al.*, 2014). The aim of AC is to increase rates and years of survival but didn't succeed (Ajani *et al.*, 2016; Devita, 2016; Wilke *et al.*, 2013). In recent years some believe that there were significant changes in the five-year survival of patients undergoing neoadjuvant therapy plus surgery (Devita, 2016; Wilke *et al.*, 2013; Cunningham *et al.*, 2006; Wang *et al.*, 2013; Sun *et al.*, 2015; Jin *et al.*, 2009; Bartlett *et al.*, 2014). However, the aim of NAC is to increase the likelihood of R0 resection i.e., the access to negative margin and treat the primary micro-metastasis of the disease during treatment (Sun *et al.*, 2015).

Chemotherapy regimens have different side effects, considering the complications and their impacts on the patients, quality of life are important (Wagner *et al.*, 2017). Some surgeons and specialists have doubts about the use of NAC prior to surgery rather than surgery alone. They believe that the use of NAC can increase the risk of mortality or

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complications during or after the surgery and still have uncertainty about the effective role of NAC in increasing OS of patients compared to surgery alone. Despite the numerous reports about the role of neoadjuvant therapy in the treatment of GC, its comprehensive implementation is still controversial (Devita, 2016; Cunningham *et al.*, 2006; Macdonald *et al.*, 2001). There has never been a study to compare different therapy methods in our country. Our cancer institute is a referral center in Iran and we have patients from all over the country and therefore we have a suitable sample. We designed our study in order to determine the complication and effectiveness of NAC in comparison to AC in operable GC.

Materials and methods:

In this retrospective cohort hospital-based study, all gastric cancer patients referred to the Cancer Institute of Iran, between the years 2011-2014, met the inclusion criteria, were identified retrospectively through archived medical records. Patients with gastric cancer that got chemotherapy before or after surgery were included in our study & who got radiotherapy, had distant metastasis & lost to follow up were excluded. We included 82 patients who had received NAC and 118 patient that received AC (totally 200 patient). Demographic characteristics, clinical and pathological data were obtained from medical records. These data included age, sex, tumor subtypes such as Signet Ring cell or other, type of surgery (total gastrectomy, distal gastrectomy), surgical complication (pneumonia, deep vein thrombosis, arrhythmia, anastomosis leak) and hospital mortality. Data on death and survival of patients were obtained via telephonic communications. The duration of the overall survival was estimated from the time of diagnosis to death or the final follow up. In addition, because the type of surgery must be identical, so we put the laparotomy surgery for gastrectomy and D1 plus lymphadenectomy as a base and excluded other treatment methods and techniques, including thoracotomy. Consents from the patients were taken by telephone.

Statistical analysis was performed using STATA version 11 (State Corp., College Station, TX) and all considered p-values were two-sided. In order to signify the data distribution, Shapiro-Wilk test and considered normal distribution were conducted based on p-value = 0.05. Cox's regression hazards models were applied to obtain hazard ratios with 95% confidence intervals to assess the association between gastric cancer survival and potential risk factors. In addition, the logistic regression model was applied to assess the association between complications, hospital mortality, stay in ICU and potential risk factors among patient who underwent NAC versus those who had undergone AC. We reported the un-adjusted OR, HR and 95% CI for each variable and then by considering other covariates, overall survival (OS) curves were created using the Kaplan-Meier method.

Results:

Two hundred patients enrolled in the study. They included 55 (27.5%) females and 145 (72.5%) males. 82 (41%) patients received NAC and 118 (59%) received AC. Their mean age was 61(±12.24) years and 104 (52%) patients were aged over 61.5 years old. The median follow-up of this study is 23.26 months. The diagnosed pathology of the tumor in all patients was adenocarcinoma and 35 patients (17.5%) had a signet ring type. Generally, 133 patients (66.5%) underwent total gastrectomy and 67 patients (33.50%) underwent distal gastrectomy (Table-1).

Table-1: Demographic patient's characteristics Number (%)

Variable		Neo-adjuvant	Adjuvant	Pvalue
Sex	Female	20 (24)	35 (30)	>0.4
	Male	62 (76)	83 (70)	
Age	<61.5	43 (52)	53 (45)	>0.3
	>61.5	39 (48)	65 (55)	
Subtype	Not Signet ring	68 (83)	97 (82)	>0.8
	Signet ring	14 (17)	21 (18)	
Surgery Method	Total Gastrectomy	60 (73)	73 (62)	>0.09
	Distal Gastrectomy	22 (27)	45 (38)	

Patients' survival rate was measured after six months, 1 year, 2 years, 3 years and 5 years. (Table-2). There were no significant differences between the AC and NAC groups in OS (Fig.-1). The hazard ratio for survival in patients who received neoadjuvant vs adjuvant therapy was 0.86 (CI: 0.6-1.2), which was insignificant ($p>0.3$).

Figure-1: Kaplan-Meier curves estimating the overall survival for each group

There was no significant relationship between the occurrence of complications and patients' gender, adjuvant and neoadjuvant treatment, surgery method (total or distal gastrectomy), and cancer histology (signet ring or not signet ring). However, our results proved that the complications are significantly more recurrent in patients whose age is 61.5 years or more ($p<0.02$). Hospital mortality was not significantly relevant to patients' age, gender, method of chemotherapy, method of surgery and cancer subtype. Length of stay in ICU was significantly longer in older patients (61.5 or more years old) ($p<0.003$). Also, patients who received neoadjuvant therapy had a significantly longer stay in ICU ($p<0.002$). It seems that receiving neoadjuvant therapy has caused patients to stay in

Table-3: Univariate & multivariate analysis of factors associate with complications (*stay longer than 48 hr in ICU considered yes)

Variable	Complication			Hospital Mortality			stay in ICU*		
	Yes/ No	Crude OR*	Adjusted OR	Yes/ No	Crude OR*	Adjusted OR	Yes/ No	Crude OR*	Adjusted OR
Age									
<61.5	6/90	Ref.	Ref.	6/90	Ref.	Ref.	49/ 47	Ref.	Ref.
>= 61.5	19/85	3.4 (1.3, 8.8)	3.3 (1.2, 9.2)	8/96	1.3 (0.4, 3.7)	1.2 (0.4, 4.7)	33/ 71	2.24 (1.3, 4.0)	2.5 (1.4, 4.6)
P-Value		0.01	0.02		0.4	0.5		0.006	0.003
Sex									
Female	10/45	Ref.	Ref.	2/53	Ref.	Ref.	24/ 31	Ref.	Ref.
Male	15/130	0.5 (0.2, 1.2)	0.5 (0.2, 1.2)	12/133	2.4 (0.5, 11.0)	2.0 (0.4, 9.3)	58/ 87	1.2 (0.6, 2.2)	1.1 (0.5, 2.1)
P-Value		0.1	0.1		0.2	0.4		0.6	0.8
Type of treatment									
adjuvant	16/102	Ref.	Ref.	8/110	Ref.	Ref.		Ref.	Ref.
Neo-adjuvant	9/73	0.8 (0.3, 1.9)	0.8 (0.3, 1.9)	6/76	1.1 (0.4, 3.2)	1.1 (0.4, 3.5)	58/ 60	2.3 (1.3, 4.2)	2.6 (1.4, 4.9)
P-Value		0.6	0.6		0.7	0.8	24/ 58	0.005	0.002
Surgery method (Gastrostomy)									
Total	21/112	Ref.	Ref.	8/125	Ref.	Ref.	54/ 79	Ref.	Ref.
Distal	4/63	0.3 (0.1, 1.0)	0.3 (0.1, 1.0)	6/61	1.5 (0.5, 4.6)	1.5 (0.5, 4.5)	28/ 39	0.9 (0.5, 1.7)	1.1 (0.6, 2.1)
P-Value		0.06	0.6		0.4	0.5		0.8	0.7
Sub Type									
Not signet ring	20/145	Ref.	Ref.	14/151	Ref.	Ref.	66/ 99	Ref.	Ref.
Signet ring	5/30	1.2 (0.4, 3.5)	1.1 (0.4, 3.6)	0/35	NA	NA	16/ 19	0.8 (0.4, 1.6)	0.9 (0.4, 2.1)
P-Value		0.7	0.8		NA	NA		0.5	0.9

ICU for a longer period. (Table 3).

Table-2: Overall survival between patients who treated neo-adjuvant chemotherapy and adjuvant chemotherapy

	6 mon	1yr	2yr	3yr	5yr.	Pvalue
NAC (%)	83	65	45	38	27	>0.3
AC (%)	94	73	54	45	30	

Discussion:

In this study, we tried to answer a challenging question, which treatment combination is the safest and most beneficial for patients with gastric cancer? A lot of studies have taken place to investigate different treatment options. Although it is clear that surgery is the only cure for this disease, there is not a certain consensus on the auxiliary treatment (Coccolini *et al.*, 2016). The selected auxiliary treatment varies based on specialist' opinion, patients' condition and even the region (Yang *et al.*, 2015).

Each of adjuvant and neo-adjuvant therapies has its own advantages. Using AC can help to prevent tumor relapses due to micro- metastases, it is believed that NAC can decrease micro-metastases as well. However, It is also able to facilitate the surgical resection by decreasing the tumor's size and stage and also reduces lymph node metastasis (Liao *et al.*, 2013). It is better tolerated by the patients and can point at the tumor's sensitivity to chemotherapy medications which could be as guidance for adjuvant therapy (Fujitani, 2013). Patients with a localized disease tend to benefit from surgery alone with low relapse rates having better overall survival. However, only less than 25% of patients of the early stages are referred to specialists (Edge *et al.*, 2010; Foo & Leong, 2014). Most patients are diagnosed and refer to surgery when the tumor has a loco-

regional invasion. Therefore, it was concluded that auxiliary treatment is necessary for most patients in order to increase the overall survival and reduce the relapse rate. The accepted auxiliary treatment and surgical techniques are different in the western and eastern parts of the world. In western countries, neoadjuvant chemotherapy and adjuvant chemo-radiation are both considered standard methods; whereas in eastern countries adjuvant chemotherapy is more frequently used (Smyth *et al.*, 2016; Foo & Leong, 2014). The logic of the western method is NAC increases overall survival without an increase in surgical complications.

Liao *et al.* (2013) did a meta-analysis on 781 gastric patients from 6 RCTs. Patients divided into 2 groups based on the treatment protocol, NAC + surgery versus surgery alone. This meta-analysis showed no significant difference OS in both groups. Among 6 studies, 2 studies compared post-operation complications in both groups where no significant difference was observed. This result supports NAC as a safe treatment for gastric cancer but the efficacy of NAC is not clear (Liao *et al.*, 2013). Another meta-analysis on perioperative chemotherapy included both preoperative & postoperative chemotherapy where 557 patients received PC & 683 patients received AC. Patients who had received PC had a better prognosis than patients treated with AC, significantly. But there is no significant difference in post-operation complication rate in both groups. Similar complication rate and reducing mortality rate confirmed the PC more useful than AC (Zhao *et al.*, 2016).

Yang *et al.* (2015) believed that NAC alone or AC alone isn't enough to improve the survival of GC patients. Their study showed that in patients treated with surgery & AC if

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add NAC to their treatment protocol death hazard decreases more than half. But in patients that didn't give AC, add NAC to their treatment plan can't change in their survival. Finally, Yang et al suggest that NAC + surgery +AC is the best treatment combination for GC patients. However, as per a recent review, there is not enough evidence about the survival benefit of neoadjuvant therapy in comparison to surgery alone (Reddavid *et al.*, 2018).

A few studies have discussed the approved auxiliary therapies in the Middle East. Ozden *et al.* (2015) conducted a retrospective study in a hospital in Turkey in order to determine the post-operative treatment effect on patients' survival. All patients went through surgery. It was concluded that adjuvant chemo-radiotherapy (CRT) likely has survival benefits but did not have survival differences between AC & adjuvant CRT. A clinical trial on 25 patients compared to neoadjuvant CRT with adjuvant CRT in Iran revealed no significant difference between the two groups in 3-year survival. Yet, the present data on the preferred auxiliary treatment in the Middle East seem to be inadequate and the mentioned studies recommended further studies with larger sample sizes to reach a better agreement on the subject.

We compared the overall survival and aftereffects of surgery of GC patients who received NAC with those who received AC. As indicated by our study the contrast between these two strategies did not significantly affect patients generally 5-year survival or occurrence of complications and hospital mortality. However, our study showed that patients who received NAC spent significantly more days in ICU. Also, we concluded that the type of treatment that we examined in our study cannot affect hospital mortality. One of the concerns in neo-adjuvant therapy was complicated. Our results indicated that there was no significant difference in complications between the two groups. These results are in line with a meta-analysis conducted by Zhao *et al.* (2016), Yang *et al.* (2015). As mentioned earlier, the present studies in Iran on this matter did not provide sufficient information. Therefore, there was no certainty about the superiority of adjuvant or neoadjuvant therapies over one another while knowing that different races and ethnic groups show different responses to each treatment method (Foo & Leong, 2014). Considering the fact that different subsidiary treatment approaches are implemented in different geographic regions, it sounds vital to collect as much information as possible in different regions about different treatment methods. Also, our cancer institute is a referral center in the capital of Iran and patients are referred to our treatment center from different parts of the country. This created a sample with an acceptable ethnic diversity for us which makes it easier to generalize our results to a national level. Yet, the authors are well aware that several more studies are required in order to reach more accurate results on this topic at the national level. Unfortunately, some of our patients have been lost in

follow-up. If we would have gained more reliable results had a larger sample size we recommend more studies with larger sample sizes on this matter.

In conclusion, it seems that both neoadjuvant and adjuvant chemotherapies are suitable treatments for gastric cancer regarding the patients' conditions. Although our study did not find an obvious advantage or any main difference in side effect for any of these methods, further studies are required to reach a clearer understanding.

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