Original Article

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Survival of GEJ and gastric adenocarcinoma patients admitted at Imam Khomeini and Aram oncology clinic and treated with preoperative EOX chemotherapy

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ABSTRACT

Objective: We aimed to investigate safety and efficacy of preoperative chemotherapy using EOX regime in patients with locally advanced gastric and GEJ cancer who were admitted at Imam-Khomeini Oncology clinic and Aram clinic.
Method: We performed a mix-cohort study in 51 gastric cancer patients. In the beginning, we performed contrast thorax and abdominal CT scan or ECO cardiograph to determine cancer staging. After that, each patient received 3-weeks EOX regime in 6 cycle. After each three cycles follow-up CT scan was performed to assess any possible progression. Response to the treatment, Overall survival, and Progression-Free Survival were the main outcomes that we evaluated in the current study. We used Kaplan-Meier approach and Cox regression to address survival rate and its prognostic factors.
Results: Overall, 72.5% percent were male and mean age of study participants was 57.6. Complete response rate was observed in 11.1%, while 51.1% showed partial response. Median of overall survival and Progression-Free Survival was estimated 35.0 and 28.0 month, respectively. The 5-year overall survival was 74.2% and for PFS it was estimated at 57.7%.
Conclusion: Preoperative chemotherapy using EOX regime could increase survival rate among patients with gastric and GEJ cancer.

Keywords: Gastric cancer, Progression-Free Survival, Neo-adjuvant chemotherapy, preoperative treatment.

INTRODUCTION:

Gastric cancer is the fifth common cancer and the third leading cause of death due to cancer. According to GLOBOCAN more than 1 billion cases of gastric cancer have been newly diagnosed in 2020 leading to 700,000 global death (1). Incidence of gastric cancer varies geographically and it is estimated that more than 75% of gastric cancer cases are diagnosed in Asia. Iran is located in high risk zone of gastric cancer and it is known as one the leading cancers in Iran particularly in north and northwest (2, 3).

Cardia and non-cardia gastric cancer are the two main topographical categories of gastric cancer. In developed countries like Japan gastric cancer are mostly non-cardia tumors, while in Iran cardia cancer are the most frequent diagnosed topography (3-5). Gastric cancer has poor survival and major part of the diagnosed patients could not experience 5-year survival since diagnosis time. The 5-year survival of gastric cancer patients in US is estimated at 31.0% (5)and in Iran is around 15.0% (6). Several treatment approaches for gastric cancers have been introduced over the last decade leading to sharp increase in survival of patients suffering from gastric cancer. Chemoradiation therapy is on the main part of gastric cancer patient's treatment plan and there are frim evidences indicating that including chemoradiation therapy into treatment plan may lead to better therapeutic outcomes and higher survival rate (7, 8). However, the best chemoradiation regime has been remained as a controversial issue. EOX regime which contains Epirubicin, Oxalipaltin and Capcitabine (Xeloda) has been recently applied for treatment of gastric cancer patients and provided promising results regarding survival of gastric cancer patients (9-11). Chen et al showed that patients who underwent EOX regime has considerably better survival rate compared with standard FOLFOX treatment (12). However, race has been show as on the contribution factor regarding EOX efficacy and it is required to be investigated in different regions and on patients with various races (10). Therefore, we aimed to investigate effect of EOX regime on gastric cancer patients who were referred to Imam Khomeini/ Aram oncology clinics.

Material and methods:

We performed a retrospective cohort study on 51 patients with confirmed diagnosis of GEJ and gastric adenocarcinoma admitted at Imam Khomeini and Aram oncology clinics. All study participants were treated with EOX chemoradiation regime. The treatment included 6 courses and each course has last for three weeks. Inclusion criteria were histologically confirmed gastric or gastroesophageal adenocarcinoma, age>15, ECOG≤2 before second-line EOX, neutrophil <1500, platelet<100,000, normal function of kidney, liver and cardia, no other primary malignancy and no co-existing disorder. The patients received 130 mg/m2 Oxaliplatin and 50 mg/m2 Epirubin on the 1st day of the cycle, then they received 625 mg/m2/day Xeloda infusion for the following 5 days. Treatment cycle repeated every 3 weeks they received the treatment cycle 6 times during their treatment course. We performed Torax and abdominal CT scan with contrast/EUS to determine primary stage. We also performed ecocardigraphy before patients enrollment. After each 3 treatment cycles we performed follow-up CT scan to address whether tumors had progression and in case of progressive tumors we dicided to change chemoradiation regime. Patients who were elgible for neo-adjuvant chemoradition uderwent surgery after their third chemoradtion theraphy course. Overall survival (OS) and Progression-Free Survival (PFS) were the main outcomes of the current study. We also retrived demographic data and data on tumor status from patients medical records. We performed follow-up using patients medical records and the last time they reffered to to clinic.

Statistical analysis:

We reported number and frequency percent as an index for dichtomous variables. We also used Life-table and Kaplan-Meier approches to reporte 5-year Overall and Progression-Free survival over study variables. To determine contributing factors a multiple cox regression model was also applied. We determine the most influet-

ial variable in a simple model and then used the multiple model. All statistical analysis was performed using Stata software ver 14.1.

Results:

Mean (±SD) age of study participants was 57.6 (±13.8) and 72.5% of them were male. Family history of gastric/GEJ adenocarcinoma was 13.7%. In general, 33.3% of the patients were pathologically well-differentiated. Body and antrum were the most frequent tumor sites. T and N stage was also determined for the study participants and T3 (60.5%) and N1 (44.7%) had the highest proportion in this regard. Moreover, we observed metastatic cancer in 45.1% of our study sample. Cancer recurrence was also observed in 16 patients (31.3%) (Table 1).

In table 2 we reported 5-years overall survival and progression-free survival by patients characteristics. Median of survival was 35.0 month and 5-year overall survival was estimated at 74.2%. Metastatic patients were less likely to live more than 5-year and overall 5-year survival was considerably lower among patients who had distant metastasis (HR=15.5, 95% CI= 1.9, 126.3, P-value=0.010). Overall progression-free survival was also estimated 57.5 (95% CI= 40.6, 71.4). Median of PFS was 32.9 month. Metastasis status was the only prognostic factor in 5-year PFS (HR= 39.6, 95% CI= 5.1, 301.9, P-value<0.001) (Table 2).

Table 1. Study participant's characteristics in patients treated with EOX regime at Imam Khomeini and Aram oncology clinics

Variable	Number	Percent
Gender		
Male	37	72.5%
Female	14	27.4%
Age group		
Under 60	29	56.8%
Over 61	22	43.1%
Family history		
No	44	86.2%
Yes	7	13.7%
Pathology		
Well-differentiated	17	33.3%
Poor-differentiated	34	66.6%
Treatment setting		
Adjuvant	6	11.7%
Neo-adjuvant	30	58.8%
Metastatic	15	29.4%
Tumor site		
Cardia	11	21.5%
Fondues and body	20	39.2%
Antrum	19	37.2%

Pillories	1	1.9%
T stage		
T2	10	26.3%
T3	23	60.5%
T4	5	13.1%
N stage		
N0	6	15.7%
N1	17	44.7%
N2	11	28.9%
N3	4	10.5%
Distant Metastasis		
No metastasis	28	54.9%
Bone	1	4.3%
Liver	8	34.7%
Peritoneal	9	39.1%
Lymph node	3	13.0%
Lung	1	4.3%
Multiple metastasis	1	4.3%
Recurrence		
No	35	68.6%
Yes	16	31.3%
Treatment response		
Complete	5	11.1%
Partial	23	51.1%
Stable	16	35.5%
Progressive	1	2.2%
Chemotherapy regime change		
No	42	82.3%
Yes	9	17.6%
Chemotherapy Dose Change		
No	14	27.4%
Yes	37	72.5%
Status		
Alive	39	76.4%
Dead	12	23.5%

Table 2. 5-year overall survival and progression-free survival and 95% CI by study participant's characteristics

Variable	Overall survival		Progression-Free Survival	
	5-year survival	95% CI	5-year survival	95% CI
Gender				
Male	71.0	49.4, 84.6	54.1	33.9, 70.5
Female	83.3	47.6, 95.6	67.4	34.2, 86.5
Age group				
Under 60	80.8	55.8, 92.5	61.3	39.5, 77.2
Over 61	65.9	38.4, 83.3	51.3	23.4, 73.5
Metastasis				
No	96.0	75.2, 99.4	**96.0**	75.2, 99.4
Yes	51.1	26.2, 71.4	17.8	4.8, 37.4
Tumor site				
Cardia	51.4	47.3, 98.5	34.2	8.1, 63.2
Body & fondues	83.3	56.3, 94.3	68.4	42.5, 84.5
Antrum	74.7	38.0, 91.6	55.6	22.2, 79.5
Setting				
Adjuvant	100	-----	100	---
Neo-adjuvant	80.7	55.7, 92.4	65.6	41.8, 81.5
Metastatic	50.6	20.3, 74.8	25.0	5.6, 51.1
Total	74.2	56.6, 85.5	57.7	40.6, 71.4

Discussion:

Survival is referred to number of patients remained alive for a specific given time (13). 5-year survival is totally regarded as an indicator of successful cancer treatment and it implies percent of patients who have been alive for more than 5 years since the diagnosis of cancer (14). In the current study we aimed to investigate survival of gastric and GEJ adenocarcinoma patients who underwent EOX chemotherapy regime in Imam Khomeini and Aram oncology clinics. Median of overall survival and PFS was 38.3 and 32.9 month. 5-year OS and PFS was also estimate 74.2% and 57.5, respectively. The reported values in the current study was pretty higher than previous study. According to one systematic-review overall 5-year survival of gastric cancer in Iran is 15% that is considerably lower than our estimates (6). However, Ostwal et al reported the same results in India. They found that PFS and OS for patients who underwent EOX was 31 and 37 months that is in side of our results (11). We also observed the same findings in the study performed by Mongan et al (15). The same high survival rate was also reported from Japan and South Korea for patients suffering from gastric cancer (13). We also observed that more that 35% of patients in MAGIC trial have experiences 5-year survival that is in side of our findings (16). However, several other researches have reported pretty lower survival for gastric cancer patients treated with EOX preoperative chemotherapy (17-20). As we already mentioned, the efficacy of EOX regime is differ by race and could be considered as a justification for different findings in different studies.

We found that patients with distant metastasis had pret-

ty lower survival rate. Several other previous studies have shown that stage at diagnosis time is one the main prognostic factors in survival of cancer patients. Diagnosis of gastric cancer at more advanced stages is associated with fewer therapeutic options that are considerably less effective. Such findings have been already proven in dozens of researches (11, 21, 22). Mongan et all reported higher survival for less advanced cases of gastric cancer in indicated that EOX regime was more efficient in local advanced cases in comparison to those who had already distant metastasis(15).

The current study is one the least researches that assessed the effect of EOX regime in Iranian patients and our study is unique in this regard. However, our findings must be interpreted in the context of its limitations. We performed a prospective cohort study and our findings might not be generalizable to all groups due to lost to follow-up that is common problem in cohort studies and it is event intense when it is supposed to be performed using medical records in a developing country. We also had sample size limitation and study performed on a quite small sample that also reduces the generalizability of our findings.

We concluded that preoperative chemotherapy using EOX regime in patients with GEJ and gastric adenocarcinoma might be beneficial and prolong their survival for particularly local advanced cases. It is also a practical and feasible treatment without any invasive procedure and therefore it is suggested as an effective treatment in developing countries like Iran.

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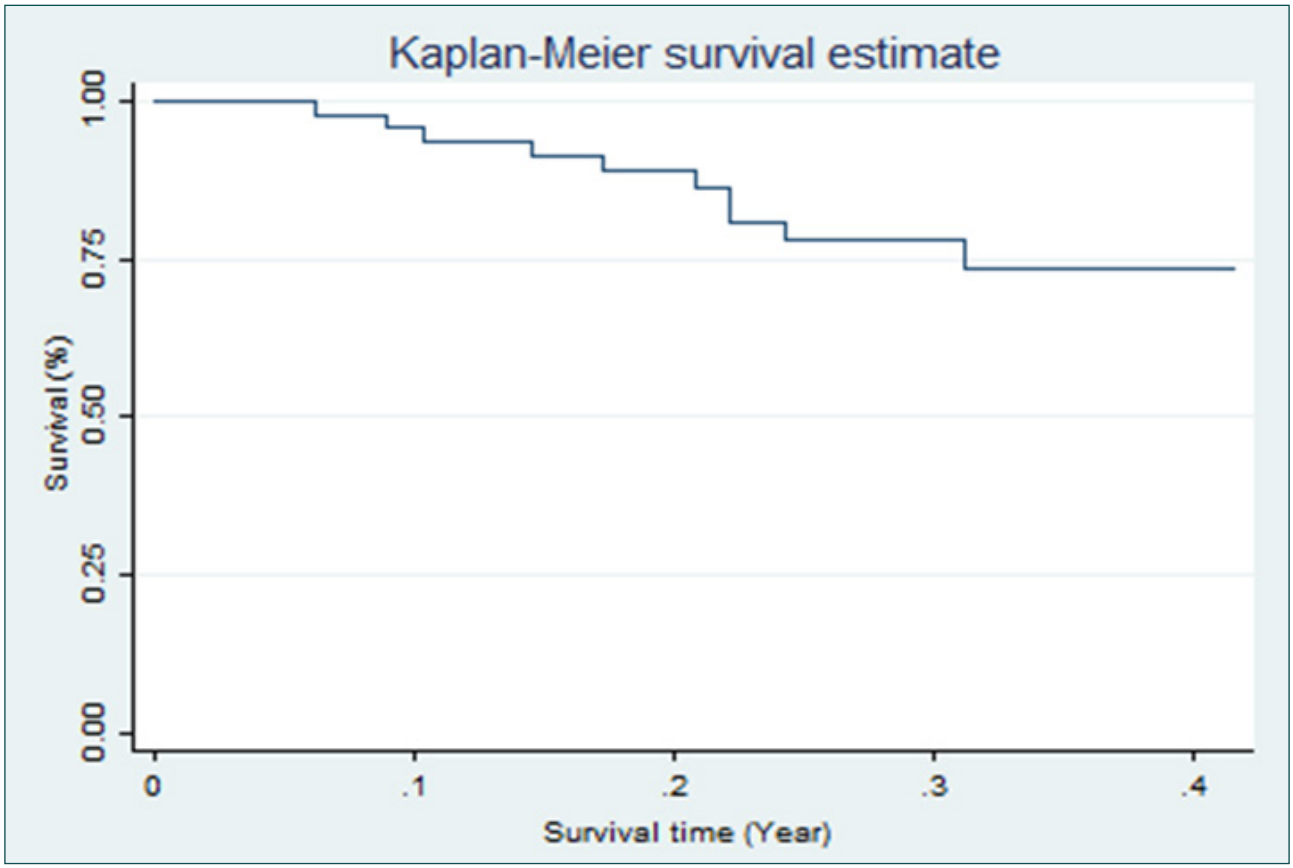
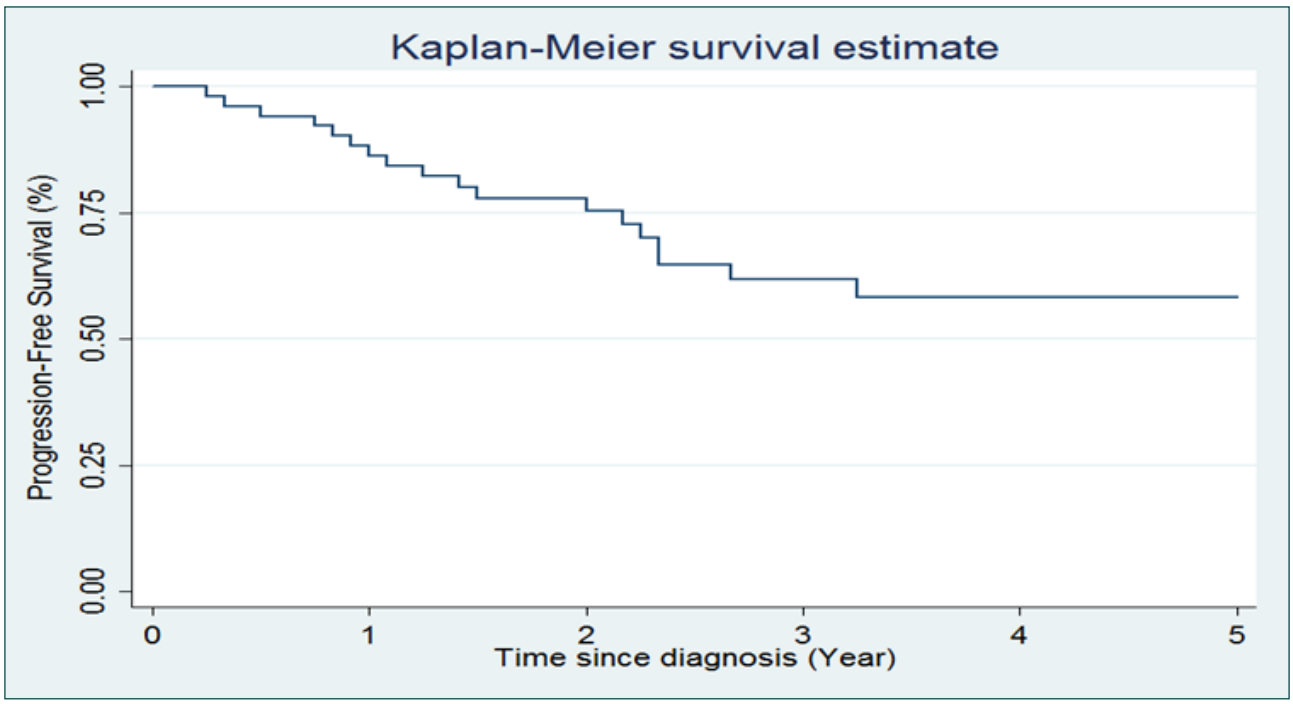
Table 3. Multiple Cox regression to determine to prognostic factor of 5-year OS and PFS in patients treated with EOX regime at Imam Khomeini and Aram oncology clinics

	Overall survival			Progression-Free Survival		
Variable	**Hazard ratio**	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**P-value**
Gender						
Male	**Reference**			**Reference**		
Female	**0.6**	**0.1, 3.0**	**0.577**	**0.6**	**0.2, 2.0**	**0.467**
Age group						
Under 60	**Reference**			**Reference**		
Over 61	**2.1**	**0.5, 7.5**	**0.247**	**0.9**	**0.3, 2.4**	**0.918**
Metastasis						
No	**Reference**			**Reference**		
Yes	**11.9**	**1.5, 94.2**	**0.019**	**32.0**	**4.2, 241.8**	**0.001**
Tumor site						
Cardia	**Reference**			**Reference**		
Body & fondues	**0.3**	**0.07, 1.4**	**0.148**	**0.5**	**0.1, 1.6**	**0.270**
Antrum	**0.4**	**0.08, 1.8**	**0.235**	**0.6**	**0.2, 2.0**	**0.490**



Graph 1: Overall 5-year survival in GEJ and gastric adenocarcinoma patients received EOX preoperative chemotherapy



Graph 2: Progression-Free 5-year survival in GEJ and gastric adenocarcinoma patients received EOX preoperative chemotherapy

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