Original Research Article

Evaluation of role of preoperative chemotherapy for carcinoma of the gastro-esophageal junction

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ABSTRACT

Background: Preoperative chemotherapy has become an established management of locally advanced carcinoma of gastro-esophageal junction. Determining the down staging effect and predicting the pathological response to preoperative chemotherapy are mandatory.

Methods: This is a prospective study which started by 40 patients presenting with gastro-esophageal junction (GEJ) tumor to the General surgery and Oncology outpatient clinics of the Menoufia University Hospitals during the period from July 2017 to July 2020. Pretreatment staging and multidisciplinary group discussion were done for all patients. Inclusion criteria were patients with locally advanced GEJ carcinoma, performance status≤2 and no previous history of chemo or radiotherapies. We excluded patients with distant metastasis, performance state>2 and previous chemo or radiotherapies. Preoperative chemotherapy ECX regimen (epirubicin, cisplatin, capecitabine) was planned. Only 20 patients completed chemotherapeutic regimen for 3 to 4 cycles followed by a radical surgery. All patients were allocated a clinical stage before and after preoperative chemotherapy and were compared to post-operative pathological stage. Postoperative complications were recorded. Follow up of patients was done for 2 years.

Results: Among total number of 40 patients, only 20 patients completed our study by preoperative ECX chemotherapy followed by radical surgery. The median overall survival was 30 months and the 2-year disease free survival ranged from 24-40 months with median time of 25.5 months. Complete pathological response was found in 6 patients (30%).

Conclusions: Pre-operative chemotherapy using ECX regimen followed by surgery could be used for treatment of locally advanced GEJ carcinoma and has showed a favourable survival.

Keywords: Preoperative chemotherapy, Neoadjuvant, ECX, Gastro-esophageal junction carcinoma

INTRODUCTION

Esophageal and gastro-esophageal junction (GEJ) malignancies are aggressive fast growing cancers worldwide.[1]

In the past, GEJ cancers have been considered either an esophageal or a gastric cancer. These controversies and disagreement about the exact definition of GEJ cancers have led to discrepancies in literature regarding the classification, pathophysiology, surgical approaches and prognosis. Siewert et al have proposed the widely accepted definition of GEJ cancer. This led to the tumors being classified as a distinct entity from esophageal and gastric cancers. He proposed that GEJ tumors are those having epicenter of the cancer within 5 cm proximal or distal to the Z-line.[2]

American joint committee on cancer (AJCC) suggests that cancers involving the GEJ that have epicenter within

proximal 2 cm of the cardia (Siewert type I / II) are to be staged as esophageal tumors while those that are more than 2 cm distal to the cardia should be staged as gastric cancer.[3,12]

Several studies have proposed neoadjuvant chemotherapy as a promising approach to increase overall and disease free survival for patients with carcinoma of GEJ. Different neoadjuvant chemotherapy regimens have been used; CF regimen (cisplatin and 5-flurouracil), ECF (epirubicin, cisplatin and 5-flurouracil), ECX (epirubicin, cisplatin and capecitabine) and TPF (docetaxel, cisplatin and 5-flurouracil).[4]

Preoperative chemotherapy might improve outcomes by down-staging of tumor leading to higher rates of tumor free resection margins, elimination of micrometastases, rapid preoperative improvement of tumor related symptoms which lead to better tolerability of the upcoming large surgical intervention. All contribute to higher overall and disease free survival.

The one concern about administering preoperative chemotherapy is the potentially higher level of treatment related morbidity and mortality due to cytotoxic effects which might be particularly hazardous during and directly after surgical procedures.[5]

The aim of this work was to study the outcome of preoperative chemotherapy in patients with locally advanced gastro-esophageal cancer and its' impact on median overall survival and disease free survival for 2 years.

METHODS

This study was prospectively conducted during the period from July 2017 to July 2020; on 40 patients presenting with gastro-esophageal junction tumor to the General surgery and Oncology outpatient clinics of the Menoufia University Hospitals.

Each patient underwent demographic data, history and clinical examination including performance status and body mass index (BMI), Laboratory tests: CBC, PT, serum albumin, serum electrolytes, liver and kidney function tests, tumor markers, Esophago-gastro-dudenoscopy and biopsy and CT chest, abdomen and pelvis.

After diagnosis of gastro-esophageal cancer was made, accurate staging according to 8th edition of AJCC staging manuals was done. All patients were discussed in multidisciplinary tumor board for appropriate treatment plan.[6]

Inclusion criteria were patients with locally advanced GEJ carcinoma (T3-4a N0, T1-4a N positive M0), performance status 0-2 and no previous history of chemo or radiotherapies.

Patient with distant metastases (T4b, M1), performance state>2 and previous chemo or radiotherapies were excluded.

Preoperative chemotherapy ECX regimen (epirubicin, cisplatin, capecitabine) was planned. Calculation of dose according to body surface area was done.

Four patients refused neoadjuvant treatment.

The other 36 patients started the neoadjuvant regimen as one cycle every 3 weeks.

Epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 were given intravenously on day 1. Capecitabine 1250 mg/m^2 daily was given orally continuously over the whole cycles.

Labarotory tests (CBC, serum electrolytes, tumor markers, hepatic and renal function tests) and complete clinical evaluation were done before receiving each cycle to detect chemotherapy toxicities. Modification of doses in the form of reduction of dose and cycle postponement were provided in toxicities.

Esophageal stent was done for 5 patients developing severe dysphagia and tumor overgrowth. Mortality was in 2 patients due to chemotherapeutic toxicity. There was lost follow up of 3 patients. Three patients were excluded as they developed distant metastases to liver and they were shifted to palliative therapy.
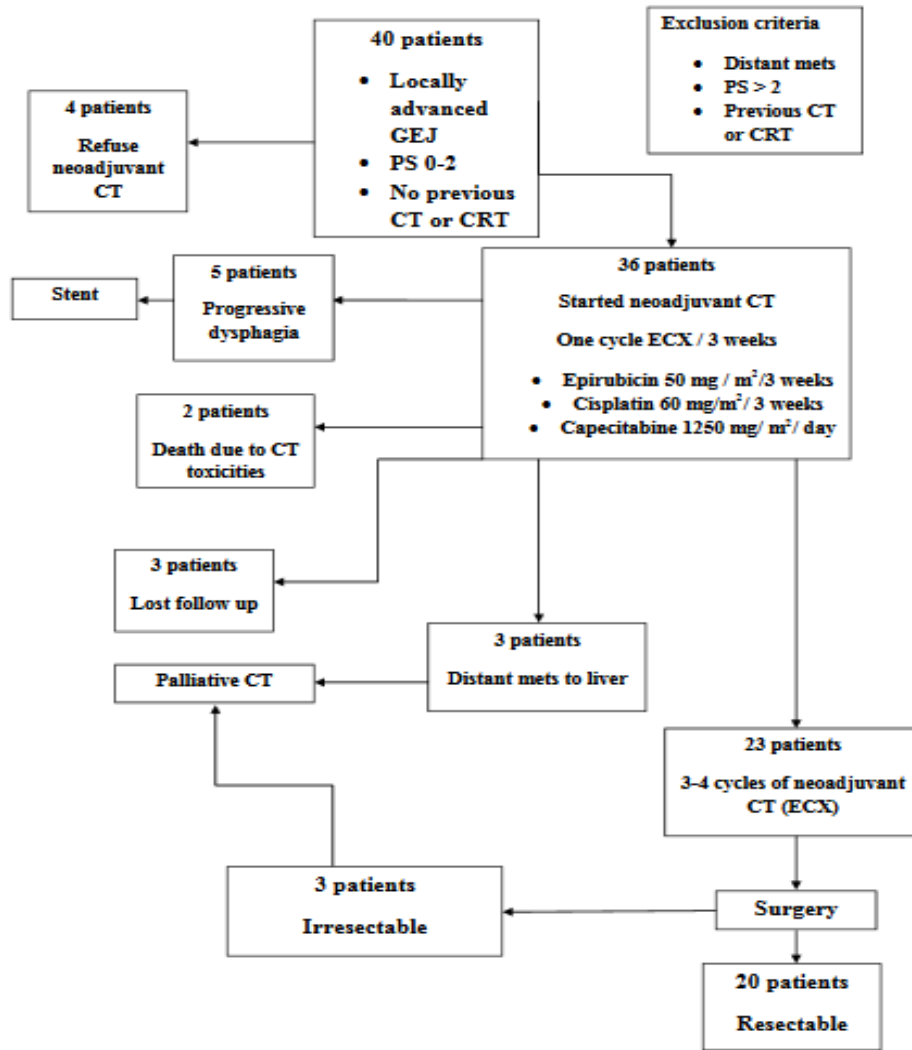
After 3-4 cycles of ECX regimen, patients were re-evaluated by PET-CT and prepared for surgery. Three patients were found irresectable and were shifted to palliative chemotherapy. These patients were excluded from the study. The other 20 patients were included in our study (Figure 1).

Preoperative preparation

Good nutritional support was provided for all patients. Control of blood pressure for hypertensive patients and control of diabetes were done. Smokers were asked to stop smoking. Chest physiotherapy and spirometry were used for all patients.

Routine preoperative laboratory investigations in the form of complete blood count, prothrombin time and INR, liver and renal functions tests and serum electrolytes were done. Blood grouping and cross matching with preparation of PRBC's and plasma were done. Preoperative chest x-ray, pulmonary function tests and Echocardiography were done.

Informed consent was taken. Preparation and shaving of skin were done. Clear fluids in the day before surgery were only allowed and patients are asked to fast for 6-8 hours preoperatively.

40 patients
- **Locally advanced GEJ**
- **PS 0-2**
- **No previous CT or CRT**

Exclusion criteria
- **Distant mets**
- **PS > 2**
- **Previous CT or CRT**

4 patients

Refuse neoadjuvant CT

5 patients

Progressive dysphagia

Stent

36 patients

Started neoadjuvant CT

One cycle ECX / 3 weeks

- Epirubicin 50 mg / m^2/3 weeks
- Cisplatin 60 mg/m^2/ 3 weeks
- Capecitabine 1250 mg/ m^2/ day

2 patients

Death due to CT toxicities

3 patients

Lost follow up

Palliative CT

3 patients

Distant mets to liver

23 patients

3-4 cycles of neoadjuvant CT (ECX)

3 patients

Irresectable

Surgery

20 patients

Resectable

Figure 1: Diagram of the study.

After marking the site of incision, general anaesthesia using double lumen endotracheal tube with isolation of right lung was inducted. Elastic stockings and urinary catheterization are done. Nasogastric tube is inserted. Prophylactic antibiotics were given to all patients.

Sterilization of skin from neck to mid-thigh and toweling were done.

Operative procedures

The surgery was started by upper midline laparotomy in all patients for exploration and determination of respectability. Ivor-Lewis esophagectomy and stomach pull up were done in 6 patients, while the other 14 patients underwent transhiatal extended gastrectomy and D2 lymphadenectomy. Operative time was recorded.

Post-operative management

Follow up of patients during hospital admission for recording surgical and non-surgical complications.

Processing of the surgical resection specimens and histopathological assessment were done to identify histopathological type, tumor grade, post neoadjuvant staging, number of LN yield, resection margin tumor necrosis index and pathological response.

All patients started adjuvant chemotherapy and follow up for 2 years was done to calculate disease free survival and overall survival.

RESULTS

This study included 20 patients of locally advanced GEJ carcinoma who completed 3-4 cycles of preoperative ECX regimen and underwent radical surgery.

Results were statistically analyzed by SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Two types of statistics were done.

Descriptive

e.g. percentage (%), mean and standard deviation SD

Analytical

1) Mann-Whitney test: it is a nonparametric test of Student's t-test. It is used to collectively indicate the presence of any significant difference between two groups for a not normally distributed quantitative variable 2) Chi-Squared (χ2): It is used to compare between two groups or more regarding one qualitative variable in 2×2 contingency table or r c complex table 3) Fisher's exact test: It is used to compare between two groups regarding one qualitative variable in a 2×2 contingency table when the expected count of any of the cells less than 5 4) Monte carlo test is used in a table when the expected count of any of the cells less than 5 5) Mc Nemar test: is used for pre–post qualitative data 6) P value<0.05 is considered significant.

Baseline characteristics of the studied patients (n=20)

Age varied from 40-70 years with mean 57.5±10.12. Male represented the majority of our included patients (60%). As obesity is considered a main risk factor for carcinoma of GEJ, increased BMI for the patients was expected. The main presentation of our patients was dysphagia with body loss and the mean BMI was 25.69±3.59 ranging between 20-33.20. Nonsmoker patients were 50%. Twenty percent were smokers and 30% were ex-smokers. Half of patients had no co-morbidities. Ten percent of patients were diabetic and 20% were hypertensive. The other 20% were both diabetic and hypertensive (Table 1).

Table 1: Baseline characteristics of the studied patients (n=20).

Variables	N	%
Age		
Mean±SD	57.50 ±10.12	
Range (in years)	40-70	
BMI		
Mean±SD	25.69 ±3.59	
Range	20-33.20	
Surface area		
Mean±SD	1.55 ±0.13	
Range	1.40-1.80	
Sex		
Male	12	60.0
Female	8	40.0
Co-morbidity		
Diabetes mellitus	2	10.0
Hypertension	4	20.0
Both	4	20.0
Free	10	50.0
Smoking		
Smoker	4	20.0
Ex-smoker	6	30.0
Non smoker	10	50.0

Pretreatment and neoadjuvant characteristics of the studied patients (n=20):

Before starting neoadjuvant chemotherapy, all patients were evaluated for determining the performance status. Calculation of the surface was done to determine the dose of chemotherapeutic agent. The performance status was 0 in 40%, 1 in 50% of patients 2 in 10%. The mean surface area was 1.55±0.13

Adenocarcinoma was the common histopathology. Only 20 % was signet ring carcinoma. Ten patients had three cycles and the other ten had 4 cycles. The mean duration of neoadjuvant chemotherapy was 83.65 ±15.97 days.

This delay was correlated to patient's regularity on the chemotherapeutic cycles.

Seven patients (35%) were regular on the preoperative chemotherapeutic cycles taking one cycle every 3 weeks. The other 13 patients (65%) had irregular cycles. This irregularity was due to drug toxicities in 92.3% of these patients and non- compliance or patient ignorance in 7.7%.

Drug toxicities lead to delaying the next cycle. Mean time of delay was 15.07±5.60 days. Cycles was postponed in 13 patients. Three patients were postponed once and five patients twice. Cycles were postponed thrice in 5 patients.

Also dose reduction was done to overcome drug toxicities in 14 patients (70%). Drug toxicities were in the form of diarrhea in 20% of patients and vomiting in 20%.

Table 2: Pretreatment and neo-adjuvant characteristics of the studied patients (n=20).

Variables	N	%
Performance state		
0	8	40.0
1	10	50.0
2	2	10.0
Histology		
Adenocarcinoma	16	80.0
Signet ring carcinoma	4	20.0
Cycles		
Three	10	50.0
Four	10	50.0
Regularity of cycles		
Yes	7	35
No	13	65
Cause of irregularity (n=13)		
Drug toxicity	12	92.3
Non-compliance	1	7.7
Postponed cycles		
No	7	35
One	3	15
Two	5	25.0
Three	5	25.0
Neo-adjuvant delay time in days (n=13)		
Mean±SD	15.07±5.60	
Range	7-21	
Dose reduction		
No	6	30.0
One	6	30.0
Two	8	40.0
Neo-adjuvant-surgery interval		
Mean ±SD	39.80±13.52	
Range	21-60	
Duration of neo-adjuvant		
Mean±SD	83.65±15.97	
Range	63-105	
Side effects		
Diarrhea	4	20.0
Nephropathy	2	10.0
Thrombocytopenia	4	20.0
Neutropenia	1	5.0
Vomiting	4	20.0
No	5	25.0

Two patients suffered from nephropathy (10%). Thrombocytopenia was in 20% of patients and 5% patients had neutropenia. Quarter of the patients had completed their cycles without side effects.

We advised patients to perform surgery 3 weeks after the last chemotherapeutic cycle. The interval time ranged from 21 days to 60 days. Mean time was 39.80 ±13.52. This lag is due to patient's delay in performing preoperative investigations due to ignorance or financial problems (Table 2).

Surgery characteristics of the studied patients (n=20)

The surgery was started by upper midline laparotomy in all patients for exploration and determination of respectability. The Ivor-Lewis operation was performed on 30% of patients and the other 70% of patients had abdominal transhiatal extended gastrectomy. The choice of approach has depended on the ability to achieve negative proximal margin transhiatally. Operative time ranged from 120 minutes to 420 minutes. The mean operative time was 301±86.86 minutes.

Ivor-Lewis operation with 2 field surgery took more operative time. Performing intra-operative upper GI endoscopy in 2 patients also increased the operative time.

Post-operative events

Twelve of our patients were admitted to ICU (60%). ICU admission was for 24-72 hours. Non-surgical complication, in the form of DVT, was only in 2 patients (10%). Surgical complication as Anastomotic leak was in 6 patients (30%) which was minimal and managed conservatively by nothing per oral, nasogastric tube, IV fluids and antibiotics.

Table 3: Surgery characteristics of the studied patients (n=20).

Variables	N	%
Type of surgery		
Ivor Lewis	6	30.0
Abdominal transhiatal extended gastrectomy	14	70.0
Complications		
Chylothorax	2	10.0
Leak	6	30.0
No	12	60.0
DVT		
Yes	2	10.0
No	18	90.0
Operative time		
Mean±SD	301±86.86	
Range	120-420	
ICU admission		
Yes	12	60.0
No	8	40.0

Leak stopped after 7-14 days. Chylothorax in 2 patients (10%) was managed by intercostal tube insertion,

antibiotics and low fat diet. There was no need for re-exploration (Table 3).

TNM staging of the studied patients (n=20)

Table 4 shows the clinical TNM staging of our study sample before and after neoadjuvant chemotherapy. There was significance improvement in the T and N stage after neoadjuvant chemotherapy. All patients were M0 with no distant metastases. T stage was T1-T2 in 6 patients (30%) while after the preoperative chemotherapy 12 patients were T1-T2. Also down staging of N stage was found. N2-N3 stage was in 16 patients before starting chemotherapy, but only 8 patients were N2-N3 after chemotherapy.

Table 4: Pre and post preoperative chemotherapy TNM staging (n=20).

Variables	Pre-treatment		Post treatment		Test of sig	P value
	N	%	N	%		
T staging						
T1	2	10.0	2	10.0	x^2=43.20	<0.001*
T2	4	20.0	10	50.0		
T3	10	50.0	4	20.0		
T4	4	20.0	4	20.0		
N staging						
N0	2	10.0	2	10.0	x^2=41.33	<0.001*
N1	2	10.0	10	50.0		
N2	12	60.0	4	20.0		
N3	4	20.0	4	20.0		
Adenocarcinoma						
Yes	16	80.0	14	70.0	McNemar	0.754
No	4	20.0	6	30.0		

*significant

Table 5: Post-surgery pathology results of the studied patients (n=20)

Variables	N	%
Histology results		
Adenocarcinoma	14	70.0
No viable malignant cells	6	30.0
Grade		
No viable malignant cells	6	30.0
I	2	10.0
II	8	40.0
III	4	20.0
Pathology results		
T0	6	30.0
T1	3	15.0
T2	5	25.0
T3	2	10.0
T4	4	20.0
N0	10	50.0
N1	2	10.0
N2	4	20.0
N3	4	20.0
LN number		
Mean±SD	14.40±3.61	
Range	10-21	

Table 6: Disease free and overall survival of the studied patients (n=20).

Variables	No
2 Year disease free survival	
Mean±SD	28.30 ±5.17
Median	25.5
Range	24-40
Overall survival	
Mean±SD	33.50 ±5.13
Median	30.0
Range	27-42

The post-operative pathological TNM staging (ypTNM) is showed in (Table 5. There was complete pathological response with no viable tumor cells in 6 patients (30%). The total number of retrieved lymph nodes ranged from 10-21 LN with median number of 14.4±3.61. Lymphadenectomy was mainly for abdominal LN in transhiatal extended gastrectomy, and it also involved the mediastinal LN in the Ivor-Lewis operation. R0 resection margin was reached in all patients.

Survival

According to national cancer institute (NCI) dictionary of cancer, the disease free survival is defined as the length of time after primary treatment of a cancer ends that the

patient survives without any signs or symptoms of that cancer. The 2- year disease free survival of our studied group was between 24 to 40 months. Median time was 25.5 months and the mean was 28.30±5.17. The overall survival is the length of time from either the date of diagnosis or the start of treatment for a cancer that the patients diagnosed are still alive. Median overall survival was 30 months and the mean was 33.50±5.13 (Table 6).

Response to neo-adjuvant chemotherapy

To evaluate the response to the neoadjuvant chemotherapy we divided the studied patients to: 1) Responders which were 10 patients (50%): complete responders were 6 patients and partial responders were 4 patients 2) non-responders: with no pathological response and were 10 patients (50%)

Baseline characteristics according to response to neoadjuvant chemotherapy

No significance was found between the 2 groups as regard age, sex or associated co-morbidities (Table 7).

Survival and response to neoadjuvant chemotherapy

There was no significance found between the 2 groups in 2-year disease free and overall survival.

Table 7: Distribution of the baseline characteristics according to response to the applied neo-adjuvant.

Variables	Yes (n=10)		No (n=10)			
	N	%	N	%		
Age (mean ±SD)	58.0±8.99		57.0±11.62			
Median	62		55		Mann-Whitney =0.45	0.649
IQR	48.50-65.50		49.0-68.50			
Sex						
Male	8	80.0	4	40.0	2x=3.33	0.170FE
Female	2	20.0	6	60.0		
Co-morbidity						
Diabetes Mellitus	2	20.0	0	0.0		
Hypertension	2	20.0	2	20.0	2x=2.40	0.0596MC
Both	2	20.0	2	20.0		
Free	4	40.0	6	60.0		

MC: Monte Carlo, FE: Fisher's exact test *: significant

Table 8: Distribution of the survival (disease free and overall survival), tumor necrosis index, drug side effects and ICU admission according to response to the applied neo-adjuvant.

	Yes (n=10)		No (n=10)			
	Mean±SD		Mean±SD			
Disease free survival	28.0±6.35		28.60±3.97		0.15	0.877
Median	25		31			
IQR	24.75-29.50		24-32			
Overall survival	32.0±5.69		35.0±4.26		1.37	0.169
Median	30		37			
IQR	27.75-35.25		31.75-38.25			
Tumor necrosis index	59.50±10.65		4.0±5.16		3.86	<0.001*
Median	90		0			
IQR	80-100		0-10			
	N	%	N	%	2x	
Drug side effects						
Diarrhea	4	40.0	0	0.0		
Nephropathy	0	0.0	2	20.0	12.20	0.015*MC
Neutropenia	0	0.0	1	10.0		
Themocytopenia	0	0.0	4	40.0		
Vomiting	3	30.0	1	10.0		
Free	3	30.0	2	20.0		
ICU admission						0.001*FE
Yes	2	20.0	10	100.0	13.33	
No	8	80.0	0	0.0		

MC: Monte Carlo, FE: Fisher's exact test *: significant

Table 9: Distribution of the baseline characteristics according to cycle regularity of the applied neo adjuvant.

Variables	Yes (n=7)		No (n=13)			
	N	%	N	%		
Age (mean ±SD)	59.28±7.63		56.53±11.42			
Median	62		55		Mann-Whitney =0.08	0.938
IQR	51-67		45-68			
Sex						
Male	4	57.1	8	61.5	2x=0.03	1.0FE
Female	3	42.9	5	38.5		
Co-morbidity						
Diabetes Mellitus	1	14.3	1	7.7		
Hypertension	1	14.3	3	23.1	2x=0.87	.0911MC
Both	2	28.6	2	15.4		
Free	3	42.9	7	53.8		

MC: Monte Carlo, FE: Fisher's exact test *: significant

Table 10: Distribution of the survival (disease free and overall survival), tumor necrosis index, drug side effects and ICU admission according to cycle regularity of the applied neo-adjuvant.

Variables	Regularity of cycles				Mann-Whitney	P value
	Yes (n=7)		No (n=13)			
	Mean ±SD		Mean ±SD			
Disease free survival	30.0±7.21		27.38±.370			
Median	25		26		0.64	0.536
IQR	25-40		24-32			
Overall survival	33.42±6.72		33.53±4.37			
Median	30		33		0.24	0.817
IQR	28-42		29-38			
Tumor necrosis index	81.42±32.36		28.07±39.34			
Median	90		10		2.75	0.006*
IQR	80-100		0-75			
	N	%	N	%	2x	
Drug side effects						
Diarrhea	3	42.9	1	7.7		0.014*MC
Nephropathy	0	0.0	2	15.4		
Neutropenia	0	0.0	1	7.7	13.18	
Themocytopenia	0	0.0	4	30.8		
Vomiting	0	0.0	4	30.8		
Free	4	57.1	1	7.7		
ICU admission						0.004*FE
Yes	1	14.3	11	74.6	9.37	
No	6	85.7	2	15.4		

MC: Monte Carlo, FE: Fisher's exact test *: significant

Tumor necrosis index (TNI)

There was significance for the responders over the non-responders group.

Drug toxicities

Only seven patients of the responder group showed drug toxicities in the form of vomiting and diarrhea. There were 8 non-responder patients with nephrotoxicity, neutropenia, thrombocytopenia and vomiting.

ICU admission

All non-responders were admitted to ICU due to poor general condition, while only 2 responder patients were admitted to ICU and this showed significance between the 2 groups. Increase response to neoadjuvant chemotherapy was strongly correlated to lower drug toxicity which also leads to decrease ICU admission in the responder group (Table 8).

Regularity of neoadjuvant chemotherapeutic cycles

Baseline characteristics of group

No significance between the 2 groups as regard age, sex and associated co-morbidities (Table 9).

Survival and cycle regularity

Patients who were regular on neoadjuvant cycles did not show significance in the 2-year disease free survival and overall survival over the non-cycle regular group.

Tumor necrosis index

Patients who were regular on cycles showed significance over the non-regular patients.

Drug toxicities

Only 3 patients of the cycle-regular group showed drug toxicities in the form of diarrhea. There were 12 cycle non regular patients with nephrotoxicity, neutropenia, thrombocytopenia, vomiting and diarrhea.

ICU admission

One patient of the cycle regular group was admitted in the ICU while 11 patients of the cycle non-regular group were admitted in the ICU.

Drug toxicities were strong cause for neoadjuvant cycle irregularity leading to decrease tumor necrosis index and response to neoadjuvant chemotherapy in this group. It also leads to more frequent ICU admissions (Table 10).

DISCUSSION

Esophageal and GEJ carcinoma are aggressive disease and may present in advanced stage. Now, preoperative chemotherapy followed by surgical resection is the treatment of choice in locally advanced cancers. Preoperative chemotherapy prevents the delay in administration of systemic treatment. Also it provides a tool for selecting patients likely to benefit from surgery according to their response to treatment and other factors.

In the current study, mean age of patients was 57.5 years with predominant male gender (60%). Smoking is a major risk factor for carcinoma of esophagus and GEJ. Smokers were 20% and ex-smokers were 30%. This was also found in Ahmed et al study with age of patients above 50 and male commonly affected (61.1%).[7]

Adenocarcinoma was the common histopathology of our studied group (80%). This finding was found in previous studies demonstrating that adenocarcinoma occurs in the distal esophagus in approximately 75% of cases.[8] It was frequently linked to gastroesophageal reflux disease.[9]

Several chemotherapeutic regimens were used in a study by Reim et al. These regimens included; PLF (cisplatin, 5 flurouracil, leucovorin), OLF (oxaliplatin, 5 flurouracil, leucovorin), Xelox (oxaliplatin, capecitabine), EAP (etoposide, adriamycin, cisplatin), ECF (epirubicin, cisplatin, 5 flurouracil) or EOX (epirubicin, oxaliplatin, capecitabine).[10]

In our study the ECX neoadjuvant chemotherapy was used. Three cycles were given to 50% of the patients and the other half had one more cycle. In other study by Alderson et al, 3cycles of ECX was given in 8% of patients and 4 cycles for 81%.[11]

Most of our patients (75%) have experienced drug toxicities in the form of diarrhea in 20%, vomiting in 20%, nephropathy in 10%, thrombocytopenia on 20% and neutropenia in 5%. This has led to irregular chemotherapeutic cycles in about 65% of patients. Dose reduction in 70% and cycle postponement in 13 patients (65%) were done to overcome the toxicities. The mean time of delay in the next cycle was 15 days. Alderson et al compared between the CF and the ECX regimens. Drug toxicities in the ECX arm were neutropenia in 50% of patients, vomiting in 46%, diarrhea in 38% thrombocytopenia in 7% and nephropathy in 8%. Delay in cycles was in 33% of patients and reduction in doses was in 42%.[11]

Surgery was done 21-60 days after completion of the preoperative chemotherapy. The mean interval time was 39.8. The median delay time in surgery was 57 days in a previous study by Alderson et al.[11]

All surgeries had started by abdominal exploration to assess the resectability and the ability to achieve proximal negative margin without need to proceed to thoracotomy. Right thoracotomy with 2 fields Ivor-Lewis operation was performed only on 30% of our patients. Only 60% of patients were admitted to ICU.

Postoperative non-surgical complications were found in 2 patients (10%) in the form of DVT. These patients were managed by limiting the mobilization and shifting to therapeutic dose of anticoagulants.

Surgical complications like anastomotic leak occurred in 30% and chylothorax in 10%. The leak was minimal and there was no need for re-exploration. These patients were managed conservatively by NPO, IV fluids, antibiotics and intercostal tube insertion for chylothorax.

In a study done at the national cancer institute in Egypt, the abdominal approach was preferred in 50% of GEJ carcinoma patients. Ivor-Lewis was done only for 35.7% of patients. All the patients were admitted to ICU. Postoperative complications were leak in 14.3%, intraoperative blood loss in 7%, tracheopleural fistula in 4.8% and pneumonia in 29.8%. Only one case developed chylous fistula.[7]

Median overall survival for our patients was 30 months compared to 26.1 months in Alderson et al and 17 months in Ahmed et al.[7,11]

There was complete pathological response in 6 of our patients (30%) with R0 in all patients. Other study by Alderson et al showed complete regression in 11% of their patients and R0 resection in 66%.[11]

Comparing the post neoadjuvant pathological T stage, ypT0 was in 30%, ypT1 was in 15%, ypT2 in 25%, ypT3 in 10% and ypT4 in 20% of our patients. In other study by Alderson et al it was (5%, 14%, 16%, 62%, and 3% respectively). The ypN stage of our study was 50% for ypN0, 10% for ypN1, 20% for ypN2 and 20% for ypN3 compared to (39%, 53%, 5% and 2% respectively) in Alderson et al.[11]

CONCLUSION

Pre-operative chemotherapy using ECX regimen followed by surgery could be used for treatment of locally advanced GEJ carcinoma and has showed a favorable survival.

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