Review of the Surgical Outcome of Locally Advanced Esophageal and Gastroesophageal Junction Cancer after Neoadjuvant Therapy Versus Upfront Surgery: NCI Experience

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ABSTRACT

Background: *Surgery represents the cornerstone for the treatment of esophageal cancer which usually presents in advanced stages with very low rate of operability. The preoperative treatment increases the operability and resectability rates in advanced stages.* ***Objective:*** *To review the surgical outcome in terms of morbidities and mortalities, the overall survival and disease free progression for locally advanced (stages 2 and 3) esophageal and gastroesophageal junction cancer(GEJ) whether after upfront surgery or after administration of neoadjuvant therapy.* ***Patients and methods:*** *A retrospective review of the management of patients diagnosed with locally advanced esophageal cancer (LAEC) or gastroesophageal junction (GEJ) cancer (stages 2, 3) presenting to the NCI in Cairo during the period from 2010 to 2015.* ***Results:*** *50 patients met the study criteria, neoadjuvant chemotherapy (NAC) was given to 32% (16 patients) followed by Complete R0 surgical resection in 62.5% while 37.5 %(6 cases) was inoperable. Upfront surgery was done in 68% (34 cases) and all were operable. Overall survival was better after neoadjuvant chemotherapy especially with epirubicin and oxaloplatin, capcitabin (xeloda) (EOX) chemotherapy regimen given for adenocarcinoma pathology subtype followed by surgery with a p value of 0.032. Better disease free survival at 1 and 2 years with a p value of 0.008.ICU admission were shorter after neoadjuvant therapy with a p value of 0.013.No statistical significant difference in morbidity and mortality and the negative resection margins. More radical resections were required in the upfront surgery group.* ***Conclusion:*** *Neoadjuvant therapy should be used as a standard therapy before surgery for all patients presenting with locally advanced esophageal and GEJ cancer due to better overall survival and a disease free survival, shorter ICU admission and less extensive surgery needed.*

Keywords: *Esophageal cancer, overall and disease free survival, extent of surgery, pathological response.*

INTRODUCTION

Esophageal cancer is the eighth most common cancer and sixth most common cause of death from cancer worldwide. Despite improvement in 5 year survival from 4% in the 1970s (1)to 11 % in 2011 (2)the prognosis for esophageal cancer remains poor.

Advanced esophageal cancer (stage IIb (T_{1-2} N_1 M_0) or stage III (T_3 N_1 M_0 or T_4 N_{any} M_0) or IVa (T_{any} N_{any} M1a) and GEJ cancer represents the commonest presentation for esophageal cancer (80%) worldwide. Treatment for locally advanced esophageal cancer has changed worldwide from surgery as a single modality therapy to multimodality treatment due to poor resectability and a high rate of morbidity, mortality and poor local control and survival[(3)].

Complete responders to neoadjuvant treatment showed a survival advantage over partial responders[(4)(5)].

In this retrospective study we reviewed the outcome of the surgical treatment either following neoadjuvant treatment or upfront for the locally advanced esophageal cancer and GEJ cancer in a tertiary cancer care center in Egypt. Upfront surgery is still the main line of treatment adopted if the tumor is deemed radiologically resectable. We aim at auditing the practice in our center in a trial to improve survival and the surgical outcome by adapting the standard protocols used worldwide for these tumors.

PATIENTS AND METHODS

This retrospective study was conducted at the surgical oncology department of the National Cancer Institute, Cairo University during the period from January 2010 till January 2015.The study included patients with LAEC and GEJ treated with surgery either as a single modality or as a part of multimodality therapy. Patients with metastatic disease and early esophageal cancer (stage 1 and CIS) were excluded.Clinicopathologic characteristics of the patients were retrieved from the patients files including: age, family history, history of smoking, clinical presentation, preoperative CT, upper GI endoscopy, type of surgery, pathology data(tumor site, size, histological type, grade, response to chemotherapy), lymph node state, TNM staging, chemotherapy and radiotherapy regimens, timing and site of relapse whether locoregional or distant as well as the condition of the patients in the last visit.

Tumor site was determined by endoscopic examination and radiologic imaging and pathologically confirmed after surgery. Tumor stage was classified according to AJCC TNM staging system[(6)].

For comparison the patients were divided into 2 groups according to the type of treatment they received before surgery: neoadjuvant therapy group (group1) and upfront surgery with or without adjuvant treatment (group 2). Surgical outcome was assessed as regards the postoperative complications, surgery related mortalities, ICU and hospital stay. The secondary outcome was determined by the rate of local recurrence, distant metastases, disease free survival and overall survival. Overall survival was calculated starting from date of first visit to the last date of follow up.DFS was calculated from the date of the treatment either surgery or neoadjuvant to the date of recurrence. The median follow up duration was 2 years.

Statistical methods:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

RESULTS

There were 216 patients diagnosed with esophageal cancer and treated at the NCI during the period from 2010 to 2015. Surgery was the main line of treatment in fifty patients (23%) presenting with locally advanced disease. The neoadjuvant chemotherapy group included 16 patients (32%) while 34(64%) patients underwent upfront surgery with or without adjuvant treatment.

The age of the patients at the date of diagnosis ranged between 30 and 67 years, about 80% of the patients were below 60 years old at the date of diagnosis. Males represented 54% of the patients while females were 46%.

Squamous cell carcinoma represented 58% (29 cases) the most common pathology.Patients presenting as stage IIB were 38%, the next common stage was IIA and IIIA (22% each).Comorbidities were more in the neoadjuvant group. Only few number of patients who underwent upfront surgery had comorbidities mostly diabetes (*11.8*%). The clinical, pathological characteristics for patients in both groups are presented in table (1).

Table (1): Pathological,clinical and radiological characteristics of the patients

Pathological characteristc			Upfront Surgery Count(%)	Surgery after Neoadjuvant chemotherapy Count(%)	P value
Tumor Grade		2	30(88.2%)	8(66.7%)	0.178
		3	4(11.8%)	4(33.4%)	
Tumor Site		GEJ 1	7(20.6%)	4(25.0%)	0.013
		GEJ 2	5(14.7%)	1(6.2%)	
		GEJ 3	2(5.9%	7(43.8%)	
		lower esophagus	8(23.5%)	3(18.8%)	
		mid esophagus	9(26.5%)	0(.0%)	
		upper esophagus	3(8.8%)	1(6.2%)	
Pathological Tumor type		Undifferentiated carcinoma	0(.0%)	1(6.2%)	0.016
		sqamous cell carcinoma	24(70.6%)	5(31.2%)	
		adenocarcinoma	10(29.4%)	10(62.5%)	
T stage		0	0(.0%)	4(25.0%)	< 0.001
		2	13(38.2%)	1(6.2%)	
		3	21(61.8%)	5(31.2%)	
		4	0(.0%)	6(37.5%)	
N stage		0	23(67.6%)	11(68.8%)	0.003
		1	6(17.6%)	3(18.8%)	
		2	5(14.7%)	2(12.5%)	
		3	0(.0%)	0(.0%)	
Stage grouping		2a	8(23.5%)	3(23.1%)	0.003
		2b	18(52.9%)	1(7.7%)	
		3a	4(11.8%)	7(53.8%)	
		3b	4(11.8%)	1(7.7%)	
		3c	0(.0%)	1(7.7%)	
Diabetes	yes		4(11.8%)	3(18.8%)	0.666
	no		30(88.2%)	13(81.2%)	
Hypertension	yes		3(8.8%)	1(6.2%)	1
	no		31(91.2%)	15(93.8%)	
Other comorbidities	yes		1(2.9%)	1(6.2%)	0.542
	no		33(97.1%)	15(93.8%)	
Family History	yes		0(.0%)	0(.0%)	-----
	no		34(100.0%)	16(100.0%)	
Smoking	yes		6(17.6%)	5(31.2%)	0.297
	no		28(82.4%)	11(68.8%)	
presentation	dysphagia		32(94.1%)	15(93.8%)	1
	vomiting		2(5.9%)	1(6.2%)	
CT site	cardia		5(15.6%)	2(13.3%)	0.296
	cervical esophagus		1(3.1%)	0(.0%)	
	GEJ and fundus		2(6.2%)	2(13.3%)	
	lower esophagus		14(43.8%)	10(66.7%)	
	middle esophagus		7(21.9%)	0(.0%)	
	upper esophagus		3(9.4%)	1(6.7%)	
Lymph nodes on CT	yes		8(23.5%)	4(25.0%)	1
	no		26(76.5%)	12(75.0%)	

GEJ:Gastroesophageal junction

The most common Tumor site in the neoadjuvant group is GEJ 3 (Siewert3) (43.8%) while the midesophagus was the most common among the upfront surgery group (26.5%).

Neoadjuvant chemotherapy was received in 75% of cases presenting in stages 3 and 4 with EOX (epirubicin, oxaliplatin, capecitabine (**X**eloda),) chemotherapy protocol was given in (43.8%) of patients while 25% of cases (4 patients out of 16) received cccrth(concomitant chemo radiotherapy in the form of neoadjuvant radiotherapy with gemzar and cispaltin +5 fluorouracil.

Upfront surgery was used for 34 patients who were deemed resectable radiologically presenting at T2 (38.2%) and T3 (61.8%).

All cases in the upfront surgery group were operable and resectable. Ivor Lewis was done in (50%) followed by McKeown (32.4%)

Operable cases accounting for 62.5% after NAT (neoadjuvant therapy) and inoperable cases r (37.5%).Inoperability was due to intraoperative T4b stage. **Treatment modalities** for both groups of patients are shown in table (2).

Table(2):treatment modalities

Preoperative radiotherapy	yes	0(.0%)	4(25.0%)	0.008
	no	34(100.0%)	12(75.0%)	
Neoadjuvant chemotherapy	no	34(100.0%)	0(.0%)	< 0.001
	cisplatin + 5 fu	0(.0%)	2(12.5%)	
	DPF	0(.0%)	1(6.2%)	
	ECF	0(.0%)	2(12.5%)	
	EOX	0(.0%)	7(43.8%)	
	gemzar	0(.0%)	2(12.5%)	
	yes not known	0(.0%)	2(12.5%)	
Number of chemotherapy cycles	2 cycles	0(.0%)	1(6.2%)	----
	3 cycles	0(.0%)	6(37.5%)	
	4 cycles	0(.0%)	2(12.5%)	
	5 cycles	0(.0%)	3(18.8%)	
	6 cycles	0(.0%)	3(18.8%)	
	7 cycles	0(.0%)	1(6.2%)	
Surgery type and extent	abdominal esophagectomy and total gastrectomy	1(2.9%)	3(18.8%)	< 0.001
	inoperable	0(.0%)	6(37.5%)	
	ivor lewis	17(50.0%)	5(31.2%)	
	mckeown	11(32.4%)	1(6.2%)	
	neck dissection	1(2.9%)	0(.0%)	
	total gastrectomy (D2) and roux en y anastomosis	1(2.9%)	0(.0%)	
	total pharyngeo laryngeo esophagectomy	2(5.9%)	0(.0%)	
	transabdominal esophagectomy and partial gastrectomy	1(2.9%)	1(6.2%)	
Adjuvant chemotherapy after surgery	5 fu	1(2.9%)	1(6.2%)	0.008
	5 fu + o	1(2.9%)	1(.0%)	
	CF	3(8.8%)	0(.0%)	
	cisplatin + docetaxel	0(.0%)	1(6.2%)	
	ECF	1(2.9%)	0(.0%)	
	EOX	0(.0%)	5(31.2%)	
	AYO	1(2.9%)	1(.0%)	
	no	23(67.6%)	7(43.8%)	
	xeloda	2(5.9%)	0(.0%)	
Adjuvant radiotherapy after surgery	yes	10(29.4%)	1(6.7%)	0.137
	no	24(70.6%)	14(93.3%)	

EOX: epirubicin, oxaloplatin, xeloda; FU: fluorouracil; AYO: adriamycin, oxaloplatin;
ECF: epirubicin, capcitabin, fluorouracil

Post neoadjuvant treatment TN-stages: is shown in table (1).

43.75% presented at stage IIIA and IIA (18.75%).While 3 patients have complete pathological response stage 0 (18.75%).

Adjuvant EOX chemotherapy protocol was given to 62.5% of patients postoperative.

14 patients received adjuvant treatment in group 1 following upfront surgery in the form of chemotherapy or radiotherapy or

chemoradiotherapy representing (41.17%), the remainder of the patients underwent follow up.

Assessment of response to neoadjuvant therapy was done by CT figure (1).

None of the patients achieved complete radiological response.

Complete Pathological therapy effect (figure2) was achieved in 40% of operable patients without any residual tumor, only one case has positive Lymph node with no residual tumor in the specimen so the number who reached complete pathological response is 30%.

All the tumors with complete therapy effect were males between the ages 51 to 70 years and all the tumors were located at GEJ3 (the gastro-esophageal junction type 3), all the histopathologies were adenocarcinoma and all received EOXchemotherapy protocol.

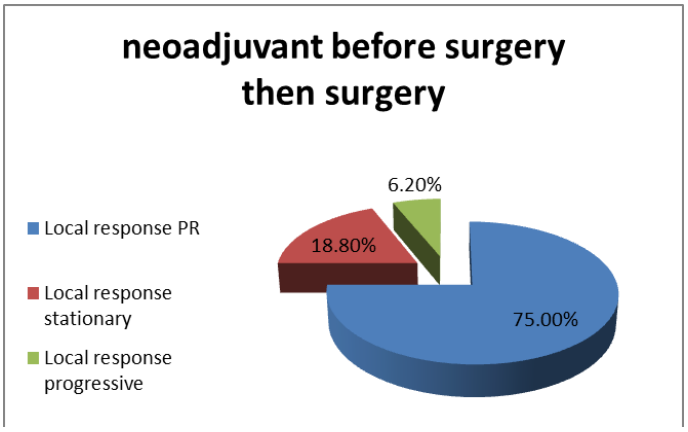

Fig. (1): Representing local response to chemotherapy by CT

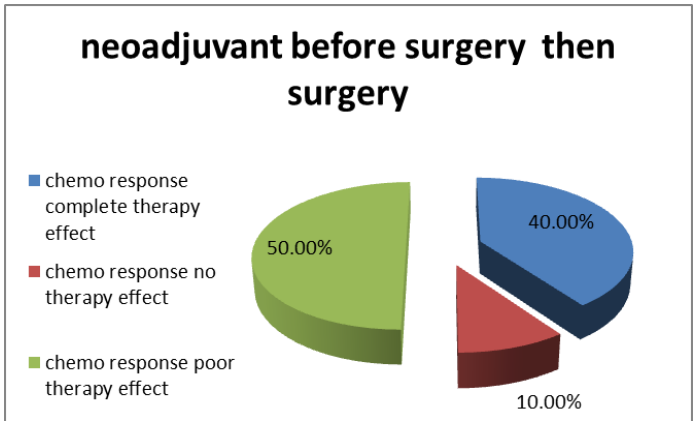

Fig. (2): Chemotherapy effect on tumor pathology

Outcomes after treatment:

No statistical differences in Morbidities, mortalities between the 2 groups (table 5).

Two patients had recurrence after surgical excision and neoadjuvant chemotherapy. One patient had local recurrence at the operative bed diagnosed 22 months after surgery. The other case had distal metastasis to liver and lung 5 months after surgery.

Two patients had recurrence after upfront surgical excision. One patient had local recurrence at the operative bed and diagnosed 51 months after surgery. The other case has distal metastasis to the lung 13 months after surgery.

Overall Survival (OAS) and disease free survival (table3) were better after neoadjuvant therapy compared to upfront surgery p value (0,032) and (0.008) respectively.

Table (3): Outcome of the treatment in both groups

Outcome of the treatment		Upfront surgery	Surgery after neoadjuvant therapy	P value
morbidity	bleeding	1(2.9%)	0(.0%)	0.408
	chest infection	0(.0%)	1(6.2%)	
	fistulae	1(2.9%)	1(.0%)	
	heart attack	0(.0%)	1(6.2%)	
	leakage	4(11.8%)	4(6.2%)	
	no	27(79.4%)	12(75.0%)	
	pleural effusion	0(.0%)	1(6.2%)	
	stenosis at anastomosis	1(2.9%)	0(.0%)	
margin	positive	2(5.9%)	0(.0%)	1
	negative	32(94.1%)	10(100.0%)	
mortality	yes	5(14.7%)	2(12.5%)	1
	no	29(85.3%)	14(87.5%)	
ICU admission days	Mean	5.12	2.56	0.013
	SD	3.36	2.76	
	Median	4.00	2.00	
	Minimum	1.00	.00	
	Maximum	20.00	7.00	
Overall survival	Mean	9.06	12.12	0.032
	SD	12.26	9.52	
	Median	4.00	9.50	
	Minimum	1.00	2.00	
	Maximum	61.00	36.00	
Disease Free Survival	Mean	7.73	12.00	0.008
	SD	11.42	9.54	
	Median	3.00	9.50	
	Minimum	.00	2.00	
	Maximum	52.00	36.00	
recurrence	yes	2(5.9%)	2(12.5%)	0.584
	no	32(94.1%)	14(87.5%)	

DISCUSSION

Our study shows that the use of neoadjuvant therapy mainly chemotherapy followed by surgery for locally advanced esophageal GEJ cancers results in better OAS and DFS. Esophageal cancer patients have an operable localized disease (stages 0, 1 and II) in 20% of cases [(7)] and only the minority of these patients are considered suitable for resection [(8)]. Esophageal cancer is presenting to our institute in advanced stages with only 23% operable cases and squamous cell carcinoma is the predominant pathological subtype.

The management of esophageal cancer relies on surgery however recently the use of multimodality treatment increased the operability rate and the overall survival. Curative treatment options in these patients are challenging as patients have at least involvement of regional lymph nodes (N_1) or loco-regional ingrowth in the surrounding organs (T4).

Despite advances in surgical techniques and aftercare, the mortality rate of surgery remains high. A recent SEERs database reported a mortality rate of 14% for resection in North America and the morbidity of resection remains significant [(9)]. It incurs a considerable impairment of quality of life [(10), (11)].

Operability after neoadjuvant treatment was achieved in 62.5% of our cases of partial responders. The main causes of inoperability were

attachment to vessels and surrounding structures (T4b); also 16.5% were due to undiagnosed metastasis to the peritoneum discovered at the time of surgery.

Previous studies showed that neoadjuvant treatment increased the rate of operability and resectability in locally advanced stage esophageal cancer from 73% in patients undergoing upfront surgery to 84% after neoadjuvant chemo-therapy[(12)].

The main line of neoadjuvant chemotherapy protocol EOX was used in 3 to 6 cycles with complete pathological response in (30%).

Resource limitations in our center prevented assessment of response to chemotherapy by PET CT and computed tomography was the main method used for assessment of the chemotherapy response after neoadjuvant chemotherapy. The CT low sensitivity in contrast to PET was responsible for the inaccurate response assessment in the inoperable cases. The inoperable cases were assessed before surgery by CT showing regressive course in 33.3%, 50% stationary course and 16% progressive. Also CT failed to assess complete response to neoadjuvant therapy which could have changed the treatment of the complete responders.

FDG-PET signals have been used to identify patients who do not respond to neoadjuvant treatment and should be offered alternative treatment options. Higher glucose uptake – as measured by FDG-PET – seems to correlate with a better chance for responding to neoadjuvant therapy [(13)].

The extent of surgery and the surgical approach choices depended mainly on the preoperative location of the tumor, stage, and the patient's risk profile. The surgeon's preferences and experience are important variables in selecting the surgical procedure. The surgeon should be versatile and well versed in the many techniques available in order to adapt to different clinical situations[(14)].

Treatment outcome:

It is to be noted that the upfront surgery group was less advanced than the neoadjuvant group at presentation and this may be the reason of the high rate of operability (100% operable) in this former mentioned group. Despite the relatively earlier stage of the upfront surgery group and the less comorbidities, the morbidities and mortality rates were slightly higher in this group of patients. Surgical access, the extent of resection and lymphadenectomy, the type and the method of preparation of the esophageal substitute, the route of reconstruction, and the technique of esophageal anastomosis are all variables that are interrelated and could affect immediate morbidity and mortality rates, long-term quality of life, and survival.

Patient's age was not associated with a higher risk of complications and it cannot be considered a limiting factor for esophagectomy.

Postoperative complications related to surgery were higher in the upfront surgery group in the form of anastomotic leakage in 4 cases and only in 1 case in the neoadjuvant group.

According to the European Society of Medical Oncology**,** the adoption of neoadjuvant chemoradiotherapy (CRT) or preoperative chemo-therapy (PCT) has led to a 20–35% decreased mortality risk compared with surgery alone for locally advanced esophageal cancers. Similarly, Post-operative mortality in this study is slightly lower in the neoadjuvant group in comparison to the surgery alone group by 2.2%. Furthermore, the results of the study showed that the median time for post-operative ICU admission for group 1 and 2 were 2 and 4 days respectively. This may be explained by the effect of the neoadjuvant treatment in down staging the tumor and decreasing the extent of resection.

In this study, the median overall survival was 9.5 months for the neoadjuvant group while the median OAS for the upfront surgery group was 4 months.

Overall survival at 1 & 2 and >2 years (12.5% & 12.5% respectively) was clearly better when surgery was combined with the neoadjuvant chemo or radiotherapy, patients who were treated by surgery with or without adjuvant treatment had a 1 and 2 years OS of 11.7% and 8.8% respectively. These results are in concordance with published data from other institutions [(7) (15)].

There was also a long-term survival advantage for the PCR group of patients (30%) than for patients with residual tumor. The 1 and 2 years and more than 2 years survival of this study was two times longer for the pcr group than for the partial responders [(16) (17)].

Contrary to the known worse outcome for squamous cell carcinoma of the esophagus(18)the current study showed similar >2 year OAS for both adenocarcinoma 10.5% and 10.3% for SCC.

The prognostic factors affecting OS were age, GEJ tumors, neoadjuvant chemotherapy, and complete pathological response. Predictors of complete response to neoadjuvant chemotherapy in this study were the male sex and the GEJ location of the tumors as well as the adeno-carcinoma pathology.

In the present study, the rate of recurrence was 12.5 % and was comparable to that reported in the current literature (16–39 %).

Concomitant radical chemo radiotherapy for locally advanced tumors is under investigation especially for the subgroup of complete responders. Recently, a large randomized trial showed a significant improvement of overall survival in patients with esophageal adeno-carcinoma and squamous cell carcinoma after neochemoradiotherapy.

The lack of standardized protocols in our center based on stage and multimodal treatment resulted in a small number of patients for each protocol, for example the patients treated with neoadjuvant chemotherapy were almost half the number treated with upfront surgery.

Offering neoadjuvant treatment to all patients with locally advanced disease and borderline resectable tumors can increase the rate of operability and resectability, improve the overall survival and cure rate. Complete response after neoadjuvant chemotherapy was achieved in 30% of patients with a clear survival advantage. The use of PET-CT is recommended for better assessment of the response to neoadjuvant treatment and its operability. Finally, further study on a larger series of patients and introducing new treatment protocols like radical concomitant chemo radiotherapy is necessary for final evaluation.

Abbreviations:
GEJ: gastroesophageal junction cancer
LAEC: locally advanced esophageal cancer
NAC: neoadjuvant chemotherapy
Ccrth: concomoitant chemo radiotherapy
PCT: preoperative chemotherapy
PCR: pathological complete response
EOX: epirubicin, oxaloplatin, capcitabin (xeloda)
OS: overall survival
DFS: disease free survival

Conflict of interests: The authors report no conflict of interest.

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