

# Adjuvant Chemoradiotherapy Vs Neoadjuvant/Perioperative Chemotherapy in Resectable Gastro-esophageal Junction Adenocarcinomas- a Retrospective Analysis

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## Abstract

We aimed to conduct the retrospective analysis of resectable Gastro-esophageal junction adenocarcinomas treated at our facility with either adjuvant chemoradiotherapy (ACT) or neoadjuvant/perioperative chemotherapy (NACT) and investigate their impact on the clinical outcome. A total of 79 patients of Gastro -esophageal junction adenocarcinomas completed treatment with curative intent between January, 2010 and December 2016 and were included in the analysis. 33 patients received adjuvant chemoradiotherapy after curative surgery as per Intergroup 0116 protocol. 46 patients underwent curative surgery after 3 cycles of neoadjuvant /perioperative chemotherapy as per UK MAGIC trial regimen. Statistical analysis was done with SPSS version 16 software. The patients included 68 males and 11 females with age ranging from 22-81 years (median 60 years). The follow up ranged from 6-71 months (median 14 months). The number of lymph nodes removed at surgery was 5-25 (median 12). Only 6 patients were node negative in the whole cohort. The number of positive lymph nodes ranged from 1-9 in rest of the 73 patients. 12.65% (n=10) patients were diagnosed with stage IIB, 44.3% (n=35) patients had stage IIIA, 29.1% (n= 23) patients had stage IIIB and 13.9% (n=11) patients had stage IIIC disease. In the adjuvant chemoradiotherapy group, out of 33 patients, 7 were dead of disease and 12 were alive with disease at last follow up. In the neoadjuvant/perioperative cohort, out of 46 patients, 13 were dead and 16 were alive with disease. Median disease free survival in the adjuvant chemoradiotherapy group was 22 months versus 14 months in the neoadjuvant/perioperative cohort. The difference was significant on Breslow analysis (Generalized Wilcoxon,  $p=0.014$ ) and on Tarone Ware ( $p=0.037$ ) but not on Log rank (Mantel-Cox,  $p=0.190$ ) implying more of the early events in the NACT group. Hazards ratio for ACT vs. NACT was 0.703 (95% CI 0.376-1.317,  $p=0.272$ ). Hazard ratio for positive nodes was 1.125 (95% CI 0.96-1.318,  $p=0.145$ ). Median DFS for the whole group was 18 months (SE 2.912, CI 12.292-23.708) and mean DFS was 23.725 months (SE 2.452, CI 18.919-28.532). Patients receiving adjuvant chemotherapy after surgery had median overall survival of 39 months versus 26 months in the neoadjuvant arm ( $p=0.039$ , Wilcoxon Gehan statistic). In our clinical set-up, adjuvant chemoradiotherapy seems to result in better overall survival and disease free survival in resectable gastro-esophageal junction adenocarcinoma though we should be cautious in interpreting retrospective and non-randomized data.

## Keywords

Gastroesophageal Junction, Adenocarcinoma, Perioperative Chemotherapy, Adjuvant Chemoradiotherapy

## Introduction

GE junction adenocarcinomas (GECs) have become a significant clinical problem because of increasing incidence over the past few decades and are likely to

become a public health problem in near future (1). A major concern regarding GECs is the controversy surrounding optimal management. Traditionally they have

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been treated like either gastric cancers or esophagus cancers though their natural history differs a lot. GECs are associated with chronic gastro-esophageal reflux disease and heart burn, Barrett's esophagus, obesity and hyperacidity. Unlike gastric cancer, GECs are not associated with *H. pylori*. They have worse prognosis with high rates of local and distant failure than gastric cancers (2) .

Curative resection remains the gold standard treatment for GECs in spite of the fact that a successful surgical resection does not always ensure cure (3,4). 30-35% GECs are inoperable upfront and may need down staging with neoadjuvant therapy. Even the resectable tumors have cure rates of 20-25% with surgery alone, for example the recurrence rate in T2N0M0 GEC is 60-70% with surgery alone (5). This bleak scenario compelled researchers to try neoadjuvant or adjuvant chemotherapy and/or radiotherapy in addition to surgery to improve the outcome. So far the adjunctive treatment depends on physician preference or geographic location of the patient. The practice in USA is different from the one that is followed in Europe which in turn differs from that in East Asian countries.

Keeping in mind the controversy surrounding optimal adjunctive treatment, we did a retrospective chart review of patients with the diagnosis of GECs, attending the Department and being treated with either neoadjuvant perioperative chemotherapy approach (MAGIC regimen) (6) or post-operative adjuvant chemotherapy and radiotherapy (INT0116 protocol) (7,8). As of today, both the treatment approaches are extensively and successfully applied in clinical practice in patients with GECs and there is an obvious need to compare the two regimes. The aim of the study was to compare the clinical outcome, efficacy and toxicity of these two treatment approaches.

### Matreial & Methods

This retrospective analysis was conducted on the data from a total of 79 patients of Gastro -esophageal junction adenocarcinomas who completed treatment with curative intent between January, 2010 and December 2016. All patients had histologically proven adenocarcinoma with clinical or pathological stage T3-4, N0-3, M0. The Siewert topographic type I, II and III were included in the database. 33 patients received adjuvant chemoradiotherapy (ACT) after curative surgery as per Intergroup 0116 protocol. Radiochemotherapy included

oral capecitabine or bolus 5-Fluorouracil and leucovorin before, during and after radiotherapy. 46 patients underwent curative surgery after 3 cycles of neoadjuvant /perioperative chemotherapy as per UK MAGIC trial regimen or its modified variant. This regimen comprised of 3 preoperative and 3 postoperative cycles of ECX/ECF or EOF/ ECX. The drugs used were Epirubicin intravenously, Cisplatin or Oxaliplatin intravenously and 5- Fluorouracil intravenously or Capecitabine orally. Statistical analysis was done with SPSS version 16 software. Descriptive statistics calculated included means and standard deviations for continuous data and frequencies and percentages for categorical data. Statistical significance was defined as a p value <0.05 with 95% confidence interval. All eligible patients were included in the Overall survival and Disease free survival analyses.

### Results

A total of 79 patients were evaluable. The patient characteristics are summarized in *Table 1*. There were 68 males and 11 females. The age of patients ranged from 22-81 years (mean age 59.03, SD12.059). The mean follow up was 16.96 months (range 6-71 months). The average number of lymph nodes removed per surgery was 12.75(SD 4.743) (range 5-25). There were only 6 node negative patients in the whole cohort. The number of positive lymph nodes ranged from 1-9 in rest of the 73 patients. The mean number of metastatic lymph nodes was 2.77. The median number of lymph nodes removed in ACT group 13 and positive lymph nodes 3 whereas in the neoadjuvant arm it was 12 and positive lymph nodes 2. 12.65% (n=10) patients were diagnosed with stage IIB, 44.3% (n=35) patients had stage IIIA, 29.1% (n=23) patients had stage IIIB and 13.9% (n=11) patients had stage IIIC disease.

Median DFS for the whole group was 18 months (SE 2.912, 95% CI 12.292-23.708) and mean DFS was 23.725 months (SE 2.452, 95% CI 18.919-28.532). In the adjuvant chemoradiotherapy (ACT) group, out of 33 patients, 7 were dead of disease and 12 were alive with disease at last follow up. In the neoadjuvant/perioperative (NACT) cohort, out of 46 patients, 13 were dead and 16 were alive with disease. Patients receiving adjuvant chemotherapy after surgery had median overall survival of 39 months versus 26 months in the neoadjuvant arm {p=.039, Wilcoxon Gehan statistic}(Fig. 1). Median disease free survival in the adjuvant chemoradiotherapy

group was 22 months (SE1.251, 95% CI 19.548-24.452) versus 14 months (SE 3, 95% CI 8.12-19.88) in the neoadjuvant/perioperative cohort. The difference was significant on Breslow analysis (Generalized Wilcoxon,  $p=0.014$ ) and on Tarone Ware ( $p=0.037$ ) but not on Log rank (Mantel-Cox,  $p=0.190$ ) implying more early events in the NACT group (Fig.2).

Hazards ratio for treatment regime ACT vs. NACT was 0.703(95% CI 0.376-1.317,  $p=0.272$ ). Hazard ratio for positive metastatic nodes was 1.125 (95% CI 0.96-1.318,  $p=0.145$ ). Median DFS for the whole group was 18 months (SE 2.912, 95% CI 12.292-23.708) and mean DFS was 23.725 months (SE 2.452, CI 18.919-28.532). Mean Disease free survival in ACT arm was 24.697 months (SE 2.343, CI 20.105-29.288) versus 23.001 months in NACT (SE 3.786, 95% CI 15.58-30.422). Both the therapies were well tolerated with manageable toxicities. 11 patients in ACT and 18 patients in NACT group had

single or multiple grade III or IV toxicity needing chemotherapy dose reduction (Table 2).

### Discussion

Cancers of GE junction carry poor prognosis and have remained a therapeutic challenge for oncologists despite the improvements in staging, patient selection, surgical techniques and peri-operative management. The 5-year survival rates after surgery alone remain abysmally lower than 30% and median survival <24 months (9). In our series, where more than 90% patients were node -positive and 88% had stage IIIA/IIIB/IIIC, we report a median overall survival of 39 months with adjuvant chemoradiotherapy and 26 months with NACT and median disease free survival of 22 months and 14 months respectively. These survival figures appear comparable with those of historical data from other clinical trials as we discuss in subsequent paragraphs.

More than 70% patients with GECs present with locally advanced or metastatic disease. In the west, 10-15%

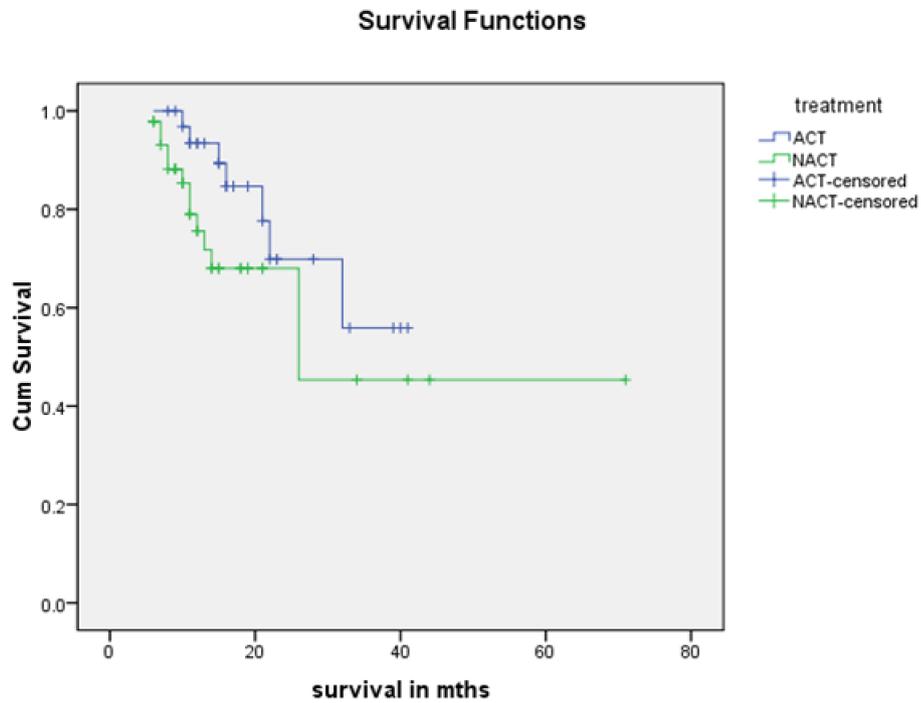
**Table 1. Patients profile**

Variable	ACT (n=33)	NACT (n=46)	Whole Cohort (n=79)
Age	35-81, median 62, mean 60.52	22-80, median 60, mean 57.96	22-81, median 60, mean 59.03
M:F	25:8	43:3	68:11
Positive Lymph nodes	0-7, Mean 2.88	0-9, Mean 2.70	0-9, Mean 2.77
Lymph nodes removed	5-25, median 13, mean 13.73	5-22, median 12, mean 12.04	5-25, median 12, mean 12.75
Follow up (months)	8-41, median 16, mean 19.15	6-71, median 11.50, mean 15.39	6-71, median 14, Mean 16.96
Stage IIB	4	6	10
IIIA	14	21	35
IIIB	8	15	23
IIIC	7	4	11

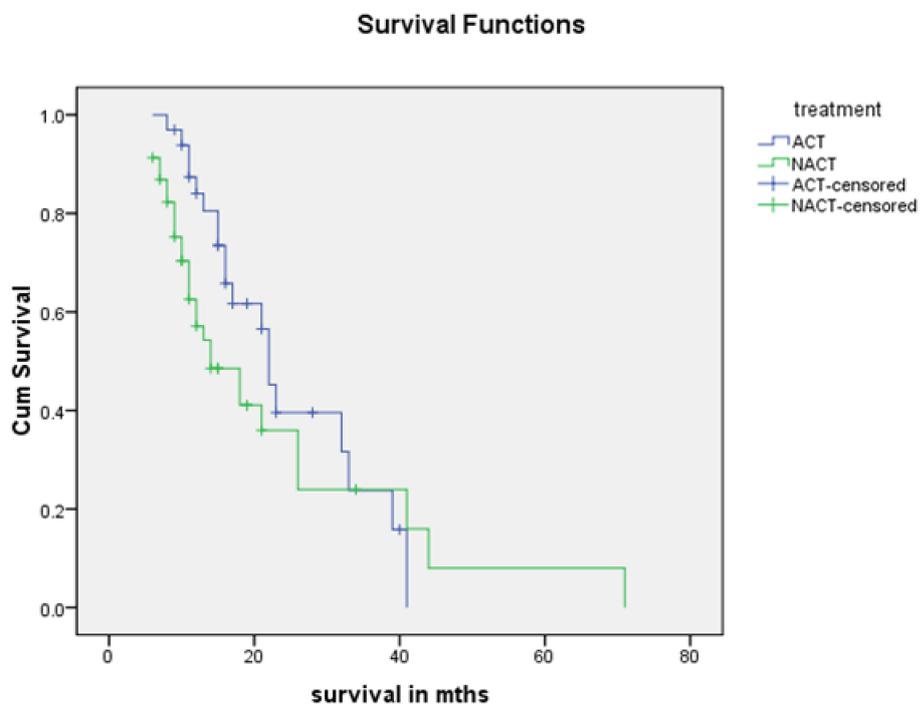
**Table 2: Grade III and IV toxicity experienced**

Toxicity	ACT	NACT	TOTAL
Diarrhea	6	4	10
Vomiting	4	7	11
Neutropenia	8	7	15
Febrile Neutropenia	1	3	4
Thrombocytopenia	2	2	4
Toxic death	0	0	0

*Fig.1. Kaplan-Meier plot of Overall survival by treatment regime*



*Fig.2. Kaplan-Meier plot of Disease free survival by treatment protocol*



patients present in curable early stage disease as compared to 50% such patients in Japan. Our series includes 88% patients in stage III (A/B/C) and represents the typical picture in our region where no screening is done and cancer awareness is low. Patients neglect common symptoms for pretty long time before seeking medical attention.

Optimal surgery is accepted as an integral part of GECs treatment and there is no cure without surgery in GE junction cancers (4). R0 resection and D2 lymph node dissection is associated with longer DFS and lower loco-regional failure. Pre-operative chemotherapy has been shown in randomized controlled trials to improve R0 resection and survival rates by downstaging the tumors. Lymph node positivity is documented in about 70% patients at surgery. So recommendation is to remove at least 15 lymph nodes preferably 20-25 lymph nodes during radical surgery. D1 dissection involves removal of lymph node station 1-6 whereas D2 dissection entails removal of LN station 7-15 in addition. In our series of 79 patients, we report node positivity in 92% cases and the average number of lymph nodes removed per surgery was 12.75(SD 4.743) (range 5-25, median 12). These figures reflect that our patients seek medical care quite late in the natural history of the disease. In spite of the adequate surgery in locally advanced stages, recurrence rate ranges from 40-65%. Locoregional recurrence rate is reduced to 15% with triple modality treatment. In the English medical literature, 5-year survival rate in stage I is 57-71%, in stage II 33-47%, in stage III 9-20% and in stage IV it is dismal 4%.

Perioperative/Neoadjuvant chemotherapy is widely practiced in European countries and is considered the standard of care. This approach to GECs is supported by two phase III trials- ACCORD 07 trial and MAGIC trial. The French FNLCC and FFCD ACCORD 07 trial enrolled 224 resectable patients of adenocarcinoma (64% GEC, 24% gastric and 11% esophageal) (10). The patients were randomized to upfront surgery alone or receive 2 cycles of pre-operative chemotherapy with cisplatin and 5-fluorouracil followed by surgery and 2 more cycles of same chemotherapy in responding patients. The patients receiving preoperative chemotherapy had significant improvement in 5-year overall survival (38% vs. 24%,  $p=.02$ , HR=0.69), disease free survival (34% vs. 19%, HR=0.65,  $p=.003$ ), R0 resection rates (84% vs. 73%,  $p=.04$ ).

The UK MAGIC trial recruited 503 patients of resectable adenocarcinoma (76% gastric, 11% GEC, 14% esophagus). The patients receiving perioperative ECF chemotherapy showed better 5-year overall survival (36% vs. 23%,  $p=.009$ ). Post-operative complication rates were similar in both the arms at 46% vs. 45% and 30-day mortality rates of 5.6% and 5.9% were seen (6).

The third phase III EORTC 40954 could enroll only 144 patients and randomized GECs to 3 cycles of PLF vs. primary surgery. The analysis showed an improvement in R0 resection rate (81.9% vs. 66.7%,  $p=.036$ ), nodal positivity (19.1% vs. 38.6%,  $p=.018$ ), median survival (64.6 vs. 52.5 months,  $p=.466$ ) (11). Two meta-analyses showed 18%-32% reduction in risk of death with neoadjuvant chemotherapy and absolute survival benefit of 7% at 2 years with preoperative chemotherapy in resectable esophageal cancers including GECs. The improved survival was significant in adenocarcinoma (HR0.78, 95%CI 0.64-0.95,  $p=.014$ ) (12,13,14).

In USA, adjuvant chemotherapy and radiation therapy in high risk gastric cancers and GECs is a valid option based on the results of the clinical trial INT0116 (7,8). The INT0116 trial randomized 511 patients of resectable gastric cancers and GECs to surgery alone versus surgery followed by adjuvant chemoradiotherapy. 3 year OS (50% vs. 41%,  $p=.005$ ) and RFS (48% vs. 31%,  $p=.001$ ) was significantly better with adjuvant chemoradiotherapy. Ten years follow-up has reconfirmed the benefit.

Our study has shown improvement in overall survival and disease free survival in the adjuvant chemoradiotherapy arm compared with neoadjuvant perioperative chemotherapy though it needs to be interpreted with caution as the data is non-randomized and retrospective in nature. In our series, where more than 90% patients were node -positive and had IIIA/IIIb/IIIC stage we report median overall survival of 39 months with adjuvant chemoradiotherapy and 26 months with NACT and median disease free survival of 22 months and 14 months respectively. The evidence for a definite survival advantage for GECs is hard to find as completed randomized controlled trials comparing adjuvant chemoradiation with neoadjuvant/perioperative chemotherapy have not been published in full text so far. Ours is an indirect comparison based on pooled and heterogeneous patient cohorts.

Preoperative chemotherapy definitely improves R0 resection rates in borderline resectable cases and improves survival in such cases but it has not shown unequivocal improvement in cases where R0 resection can be achieved in upfront primary surgery. Such cases achieving R0 resection in primary surgery but having high risk features on postoperative histopathology are likely to benefit from adjuvant chemoradiotherapy. A recent analysis of 3656 patients of gastric cancer in National Cancer Data Base (2004-2012) divided into two groups -perioperative chemotherapy without RT and adjuvant chemoradiotherapy showed a significant overall survival advantage with adjuvant chemoradiotherapy (median OS 51 months versus 42 months,  $p=0.013$ ) (15). The hazards ratio with RT in margin positive cases: 0.650 vs. 0.952,  $p$  for interaction  $< .001$ . This indicates that adjuvant RT might compensate for somewhat sub-optimal surgery.

In USA, the focus is now shifting to preoperative chemoradiation especially after the publication of CROSS trial (Chemoradiotherapy for Esophageal Cancer followed by Surgery Study) which was awarded as the top-10 medicine progress in 2012. The CROSS trial randomized 366 patients to receive pre-operative concurrent chemoradiotherapy with weekly paclitaxel and carboplatin or surgery alone. The preoperative chemoradiation improved R0 resection rate (92% vs.69%), median survival (49 months vs. 24 months), and 5-year overall survival (47% versus 34%).The hazards ratio for adenocarcinoma was 0.73(0.55-0.98;  $p=0.038$ ) indicating significant margin of survival benefit (16). The CROSS protocol is being tested extensively in several ongoing trials which will help establish the optimal standard of care in adenocarcinoma of gastroesophageal junction. The Neo-AEGIS trial is a phase III randomized controlled trial presently going on and comparing the MAGIC regimen with the CROSS protocol in adenocarcinoma of the esophagus and junction (17).The interim analysis of first 120 patients in TOPGEAR(Trial Of Preoperative therapy for Gastric and Esophagogastric junction Adenocarcinoma) trial have shown that preoperative chemoradiation can be safely added to perioperative chemotherapy(18). The impact of this approach on survival outcome is awaited. The ESOPEC trial will randomize 438 patients of adenocarcinoma of esophagus to either the FLOT regimen followed by surgery or the CROSS protocol (19).

One big disadvantage mentioned with adjuvant chemoradiation is the high rate of treatment drop out and therefore in daily clinical practice is preferred only in selected up-front operable patients who do not receive neoadjuvant treatment and are found to have occult nodal disease at the time of surgery. We could not find a phase III trial comparing perioperative chemotherapy with adjuvant chemoradiotherapy except for the CRITICS study abstract. This is a large phase III trial presented at the ASCO 2017 annual meeting. 17% patients had GE junction adenocarcinomas (20). Patients with Ib-IVa resectable gastric cancers and GECs were randomized to either preoperative chemotherapy followed by surgery or adjuvant chemotherapy versus preoperative chemotherapy followed by surgery and chemoradiotherapy. Neo adjuvant chemotherapy in both arms consisted of 3 cycles of ECX/EOX. Surgery was total or partial gastrectomy with en bloc lymphadenectomy and a minimum of 15 lymph nodes removed. Adjuvant chemotherapy consisted of an additional 3 courses of ECX/EOX and adjuvant chemoradiotherapy consisted of 45Gy with concurrent weekly cisplatin and capecitabine. Five year survival was 41.3% versus 40.9%. The results suggest that performing an adequate node dissection might eliminate the need for radiation. At our institute we assess each GEC patient for operability upfront and if he/she is found operable, primary surgery is done and adjuvant chemoradiotherapy is given depending on risk factors in postoperative histopathology. Patients found inoperable or borderline operable are treated with neoadjuvant/perioperative chemotherapy. Very selected patients with good performance status are being offered the choice of preoperative neoadjuvant chemoradiotherapy.

### Conclusion

The optimal management of resectable Gastro-esophageal junction adenocarcinomas remains a clinical dilemma and both the options of upfront surgery followed by adjuvant chemoradiotherapy and neoadjuvant / perioperative chemotherapy appear to be equivalent in terms of clinical outcome and survival in the long run. In our clinical set-up, adjuvant chemoradiotherapy seems to result in better overall survival and disease free survival in resectable gastro-esophageal junction adenocarcinoma though we should be cautious in interpreting retrospective and non-randomized data.

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