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Original Article

Peri-Operative FLOT Chemotherapy in Locally-Advanced Gastric and Gastroesophageal Carcinoma: Outcomes in South Asian Population

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ABSTRACT:

Objective: To compare oncological outcomes of perioperative FLOT chemotherapy in terms of tumor response, tumor margin clearance and average positive number of lymph nodes retrieved in surgical resection specimens of locally advanced gastric and gastroesophageal carcinoma.

Materials and Methods: The patients presenting in Department of General Surgery, Shifa International Hospital, Islamabad from July 2020 to March 2023 were included in the study**.** Out of total 108, we included 37 patients who undertook perioperative FLOT chemotherapy in for resectable, locally advanced gastroesophageal cancer. Response to therapy was assessed based on per operative findings, R0 resection and D2 lymphadenectomy and disease regression on histopathology specimens. Patients were also assessed according to post-operative recovery time, mean ICU and hospital stay, as well as post chemo and post-operative complications.

Statistical Analysis: Appropriate statistical analysis was performed using SPSS version 26.

Results: There were a total 37 patients with mean age 57.21 ± 10.04 years. 4(10.8%) had well-differentiated adenocarcinoma, 19(51.4 %) had moderately-differentiated and 14(37.8%) had poorly-differentiated cancer. Perioperative completion rate of 4 cycles of chemotherapy was 100%. 4 patients had dose reduction due to neutropenia. 100% of the patients had R0 resection. Average positive lymph nodes on histopathology were 2.04 ± 3.01 in 13 patients (35.1%). 24 out of 37 patients (64.9%) had no nodal involvement. Histopathology, evaluated for treatment response according to CAP (College of American Pathologists) - TRG criteria, 7 (18.9%) patients out of 37 showed no tumor regression. 22(59.5%) had partial response and 8(21.6%) patients had complete response.

Conclusion: Perioperative FLOT shows highly favourable results in patients with resectable, locally-advanced gastric and gastroesophageal cancer. Considering the burden of this disease in the South Asian population, an optimal therapeutic regime is an absolute requirement. Our initial data in this study provides favourable results to use of perioperative chemotherapy with the FLOT-4 regime in our population.

Keywords: gastroesophageal cancer, neo-adjuvant, locally-advanced, negative margins, chemotherapy

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Introduction:

Gastric and gastroesophageal cancers are commonly occurring malignancies in Asia and the prognosis for advanced disease remains bleak, highlighting the importance of need of more innovative therapeutic approach for management and eradication of gastric and gastroesophageal cancers.[1] Neoadjuvant chemotherapy has been agreed upon as standard of care to achieve curative resections even in advanced gastric and gastroesophageal cancer however differences of practice still occur in regard with type and combinations chemotherapy regimens.[2]

Despite its widespread presence in East, there is an obvious dearth of trial-based data and information originating from these countries. Some data has originated from Japan in the last

few decades but it is lacking in providing applicable information about neo-adjuvant chemotherapy for resectable, locally advanced tumors.[3] German centers have published studies showing FLOT as superior therapy to ECF and ECX therapies.[4] China with an incidence rate of >45% with 50% mortality rate of the total Gastroesophageal cancer cases in the world, has presented results, based on two large scale trials RESONANCE and RESOLVE, pointing at chemo regimens based on a combination of SOX and XELOX.[5,6]

Over the years, advancement in surgical technique has led to considerable improvement in the disease management, but metastasis and recurrence have remained the main causes of morbidity and mortality in gastric and gastroesophageal cancer patients. The need for control of metastasis as well as recurrence, led to the consideration of neoadjuvant therapy, and especially since the MAGIC and FNCLCC/FFCD trials, the purely surgical approach to locally advanced gastric and esophageal cancers has undergone a drastic change. The 2006 MAGIC trial consisted of perioperative intervention with fluorouracil, epirubicin and cisplatin (ECF), and the French FFNCLCC/FFCD trial used a 5- FU and Cisplatin based regimen[7,9]. Both sets of data have revealed a significant role of neoadjuvant chemotherapy in the overall survival rate although debate still exists on the exact combination of the perioperative chemo agents.[10]

The neoadjuvant approach to management of locally advanced gastric and gastroesophageal cancers must include an objective purpose of the chemotherapy as well as the effect it has on the surgical intervention such as gastrectomy or esophagectomy that follows. Overall survival, disease free survival, down-staging of tumor, rate of local recurrence, pathological response, R0 resection and the adverse effects of chemotherapy leading to reduced tolerability and susceptibility, are all important factors to be considered.

Although evidence does exist on the superior benefit of FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel) over neoadjuvant ECF when considering the number of curative surgeries following chemotherapy and survival without disease progression[7], there is still a paucity of evidence on the topic, especially considering the South Asian populations where the incidence rate of gastric and gastroesophageal cancers is high. Countries such as Japan have conducted trials on neoadjuvant chemotherapy, but the regimens were comparatively conservative compared to documented Western chemotherapy regimens.[2]

In our study, the findings of FLOT 4 perioperative chemotherapy in locally advanced gastric and gastroesophageal cancers are discussed. Our study includes 37 cases of locally advanced gastric and gastroesophageal cancers that were managed with FLOT 4 perioperative chemotherapy and subsequently underwent gastrectomy or esophagectomy. The aim of the study was to assess the oncological and pathological efficacy of FLOT 4 as well as the peri-operative morbidity and mortality, lymph node retrieval and to evaluate the feasibility of FLOT regimen in the South Asian population.

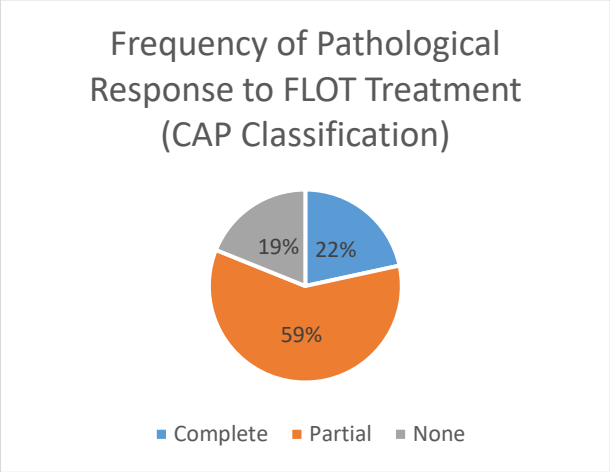
Materials and Methods:

This was a retrospective study and it was carried out at the Department of General Surgery, Shifa International Hospital, Islamabad from July 2020 to March 2023. Approval of IRB was sought before commencing data collection. We reviewed data of 108 patients out of which data of 37 patients with diagnosed, histologically positive, locally advanced (stages cT1b–cT4a; cM0), resectable gastric and esophageal carcinomas who took FLOT-4 regimen as perioperative chemotherapy was analyzed. Staging investigations included CT scans, endoscopic ultrasounds and biopsies for all patients. PET scans, MRI, or bone scans were used if clinically indicated according to the availability. Patients included were those with ages 18 to 80 years with no prior anti-tumor therapies, locally advanced gastric and gastroesophageal cancer (stage cT3 – 4 and N+ M0) according to EUS and CECT. Patients had normal hematopoietic, renal and hepatic function. Excluded patients were those who were clinically unfit for systemic chemotherapy or surgery, had locally advanced inoperable disease or distant metastases, or had undergone prior radiotherapy. FLOT was administered intravenous according to NCCN guidelines recommended dose (4 cycles preoperative and 4 cycles postoperative: Fluorouracil 2600 mg/m^2 IV continuous infusion

over 24 hours, Leucovorin 200 mg/m^2, Oxaliplatin 85 mg/m^2, Docetaxel 50 mg/m^2: repeated every 14 days). Exclusion criteria included patients with gastroesophageal cancer had either undergone upfront surgery, had metastatic disease at the time of surgery or had a different neoadjuvant chemotherapy regimen.
The TNM categories were according to the Union for International Cancer Control tumor-node-mets classification. The clinical efficacy response was evaluated using the response evaluation criteria in solid tumors (RECIST) guidelines. Adverse effects of neoadjuvant chemotherapy were graded (0-IV) according to the Common Terminology Criteria for Adverse Events (CTCAE). The surgical procedure data was extracted from operative notes. The pathological response assessment was scored using the tumor regression grade (TRG) of the Becker criteria. Postoperative complications were defined as any anomaly that occurred within 30 days after surgery stratified using the Clavien-Dindo classification. Descriptive statistics were calculated for patients' characteristics using mean, standard deviation, and percentages using the SPSS 26.0 statistics software. Results is presented in graphs and tables along with inference. The work has been reported in line with the STROCSS criteria.[8]

Results:
Initially, data of 108 patients was analyzed however 37 patients were included in the study according to our inclusion criteria. Out of these 37, 24 (64.9%) were male and 13(35.1%) were female. Mean age was 57.21 ± 10.04 years. All 37 patients completed 04 cycles of perioperative FLOT chemotherapy at an average of 21 days before surgery. 04 patients had dose reduction because of grade 3 neutropenia however all other non-hematological complications were grade 1 or 2 and required supportive therapy only.
21(56.8%) patients underwent total gastrectomy with D2 lymph node dissection and 16(43.2%) underwent esophagectomy for gastroesophageal carcinoma.
All 37 patients had R0 resection. All margins namely circumferential, radial, proximal and distal were tumor free. Average number of lymph nodes retrieved were 22 with a minimum of 12 lymph nodes and a maximum of 37 lymph nodes. Average positive lymph nodes on histopathology were 2.04 ± 3.01 in 13 patients (35.1%). 24 out of 37 patients (64.9%) had no nodal involvement.
Of 37 patients, 4(10.8%) had well-differentiated adenocarcinoma, 19(51.4 %) had moderately-differentiated and 14(37.8%) had poorly-differentiated tumor. (Table 2) Histopathology samples was evaluated for treatment response according to CAP (College of American Pathologists) -TRG criteria.
7 (18.9%) patients out of 37 showed no tumor regression (Minimal/ no tumor killed or extensive residual cancer). 22(59.5%) had partial response (Single cells or small groups of cancer cells) and 8(21.6%) patients had complete response (No viable cancer cells). (Figure 1)

Figure 1: Frequency of Pathological Response to FLOT Treatment (CAP Classification)



Mean post-op stay in hospital was 6 ±1 days. Grade 2 Clavien-Dindo post-op complications were noted in 5 out of 37 patients.
One patient, known case of COPD, developed shortness of breath requiring gradually tapered oxygen therapy. Patient was discharged on day 9. No immediate life-threatening complication or all-cause mortality was noted in 30 day follow up period. These patients are being followed up at year 1, year 3 and year 5 post operatively to see long term outcomes in terms of Overall Survival (OS) and Disease-Free Survival (DFS).

Discussion:
Since the advent of neoadjuvant chemotherapy, the management of gastroesophageal carcinoma has drastically transformed since early 90s.

Several regimens have been studied with regards to their efficacy and safety. The major breakthrough was in 2006 with the MAGIC Trial, a randomized phase III clinical trial from nine centers across UK. This was the largest trial which analyzed the effects of neoadjuvant chemotherapy in gastric and gastroesophageal cancer. Patients were randomly divided in two groups: one underwent surgery alone, the other underwent surgery and perioperative chemotherapy, three cycles in each preoperative and postoperative period. Epirubicin, cisplatin, and fluorouracil (ECF) regimen was used. The results demonstrated significantly better surgical as well as long term outcomes in patients with ECF. Reduction in tumor size and stage lead to more R0 resections and significantly improved progression-free and 5-year overall survival (36% compared to 23% in upfront surgery P = 0.009). [9]

Another significant phase III trial was the 2011 French FFCD9703, with a similar design to the MAGIC trial but used a Cisplatin and 5-Flourouracil based regimen. 224 patients were divided into two groups: a control group which had surgery alone, the other group had 2-3 cycles of FU/Cis regime preoperatively. Again, similar results to MAGIC trial were seen where patients with chemotherapy had better rates of R0 resection (84% vs. 73%, P = 0.04) survival advantage over group who had surgery alone (38% vs. 24%, P = 0.02), and greater disease-free survival for 5 years (34 v. 19%, P = 0.01).[10]

Both these trials cemented the superiority of perioperative chemotherapy regardless of tumor location and were widely adopted throughout the globe.

The role of Docetaxel as combination therapy for gastric carcinoma has been studied in several settings demonstrating improved outcomes in terms of overall survival, response rate, time-to-disease progression. The V-325 study was notable in this series.[11] However, that addition of docetaxel to a frequently used regimen of cisplatin and 5-fluorouracil was associated with severe toxicities and was not tolerated well by the patients.[12] Despite this, several authorities continued to study docetaxel with modified regimens because it appeared to have a significantly higher response rate as compared to the classic duet. However further modification was needed to improve safety and convenience of patients with advanced GE junction and gastric carcinoma so that its usage maybe widely accepted.

In 2008 Al-Batran et al. put forward the docetaxel based FLOT regimen which included, fluorouracil, leucovorin, oxaliplatin and docetaxel.[13] This challenged the earlier ECF regimen and its modified versions as trials validated its efficacy and safety. In 2016 FLOT4 phase II trial was published, demonstrating a significant advantage to patients who received FLOT compared to those who had ECF/ECX in terms of tumor regression (44% vs 27%, P = 0.01) and R0 resections (85% vs 74%, P = 0.02) in 300 patients.[14] However, Phase III showed side effects of both the regimens were same. The median overall survival (50 months compared to 35 months, P = 0.012) and median disease-free survival (30 months compared to 18 months, P = 0.0036) were also significantly longer than those of the ECF/ECX group.[14] This superiority of results led to category 1 recommendation of FLOT as a preferred therapy by NCCN guidelines in 2018. [15]

Several studies have been conducted throughout the world based on these recommendations. However, due to regional differences in practice of number and completion of doses before and after surgery, head-on comparisons of results are lacking.[16] Generally, the fluorouracil-based regimens are widely adapted in Asian regions, while the ECF and FLOT regimen are practiced in European countries.[17]

A Chinese study conducted on 23 patients showed that FLOT is safe and effective in terms of clinical efficacy (69.6%) and R0 resections (91.3%). 13% patients had complete remission. The most common adverse event from chemotherapy was neutropenia (30.4%).[18] However, Favi et al. in Germany observed no significant difference in terms of prognosis and rather better primary tumor response in CROSS-group as compared to FLOT-group: 43% vs 27% in a total of 40 patients.[19]

A Chinese study by Li et.al concluded excellent response and good tolerance in 73 patients who received FLOT with 64% partial response and 6% complete response with 86% R0 resections achieved. Leukopenia was commonest side effect

and grade 3 or 4 side effects or treatment-related deaths were noted.[20]

To our knowledge no such trial has been or is being conducted in Pakistan at the moment to assess the response and tolerability of FLOT regimen in the Pakistani or South Asian population. The delay in the initiation of study and limitation of number of patients recruited in the study is attributed to economic constraints, for example, unavailability of 5-FU pump and patients who could afford a porta-cath insertion. The results of our study show a cumulative frequency of 78.3% in patients who had either complete or partial tumor regression to perioperative FLOT regimen which is comparable to 73.1 % for similar responses in a study conducted in China, which is favorable for achieving a high number of R0 resections.[18] Our study demonstrated a ypN0 of 52.2% which is comparable to 56.3% demonstrated in a Dutch study.[21]

In several small centers across our country, D2 lymphadenectomy is not well-documented and upfront surgery is still being offered to many patients; hence compromising chances of an R0 resection and therefore disease -free as well as overall survival of the patient.These results not only add the knowledge and application in local population but also adds the south Asian pool which has no considerable data on FLOT regimen despite sharing a significant disease burden.

Current clinical trials are being looked up for a consensus on superiority, safety and efficacy of FLOT. The ESOPEC trial is being conducted on 438 patients with locally advanced gastroesophageal adenocarcinoma, comparing two groups, one on CROSS, the other on FLOT, both followed by surgery. The patients will be followed up for 36 months at the minimum also aiming to compare disease-free and progression-free survival in these groups.[22]

Another phase III trial registered in 2020, the RACE trial will compare 340 patients on two limbs: one given FLOT regimen as induction therapy, the other given only FLOT as neoadjuvant therapy. Both groups will undergo surgery followed by adjuvant FLOT. Only patients with locally-advanced disease will be included. The objective of this trial is to demonstrate the superiority of combined treatment with FLOT in terms of progression-free survival.[23]

The limitations of our study included small number of patients who could fit our inclusion criteria, this relatively newer regimen in our part of the world is less opted for due to higher costs and lack of infusion pumps leading to constrained practice by medical oncologists to prescribe FLOT regimen. Several patients present with advanced disease as there are no national screening or disease awareness programs. The initial data shows promising results; therefore, a larger number of patients could be reviewed from multiple centers for validation of our results. Further trials and analyses from our side of the world are needed to further solidify this treatment option and validate its efficacy for overall survival (OS) and disease-free survival (DFS) in such patients.

Conclusion:

Considering the burden of this disease in the South Asian population, an optimal therapeutic regime is an absolute requirement. Our initial data in this study, backed by recommendations and previous literature coming sporadically from around the continent, gives us enough evidence to continue the use of perioperative chemotherapy with the FLOT-4 regime.

Table 1: Total and Positive Numbers of Lymph Nodes Retrieved in D2 Lymphadenectomy

	MINIMUM	MAXIMUM
Total Number of LN retrieved	12	37
Frequency of Positive LN seen on Histopathology	0(64.9%)	9(2.7%)

Table 2: Frequency of Histopathological Grade of Tumor

TUMOR GRADE	FREQUENCY (n=37)	PERCENTAGE %
Well-Differentiated	4	10.8
Moderately Differentiated	19	51.4
Poorly Differentiated	14	37.8
Total	37	100.0

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Author's Contribution:

YM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
RA, MBB, HMK: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.