Does Dose Reduction Compromise Pathological Response in Perioperative Gastric Cancer Chemotherapy? A Real-World Observational Analysis of FLOT and EOX

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Abstract: *Introduction*: Standard of care of locally advanced gastric and Type III GE junction tumors is perioperative chemotherapy followed by radical surgery. There is clear evidence of FLOT outperforming other regimens in current literature. However, there is scarce data on dose modifications of various regimens and its effect on pathological tumor regression grade.

Material and Methods: This is retrospective study from a single institution between 2022 and 2024. Patients diagnosed with locally advanced gastric and Type III GE junction tumors, who underwent perioperative chemotherapy followed by radical surgery were included. Data including histopathological report, tumor regression grade following perioperative chemotherapy, chemotherapy regimen, chemotherapy dose intensity, and completion of chemotherapy, were collected from the medical records.

Results: Forty-one patients diagnosed as locally advanced gastric or GE junction cancers. Twenty patients (61%) received 3 cycles of perioperative EOX and 16 patients (39%) received 4 cycles of FLOT. Pathological complete response was higher in the EOX group than FLOT (75% vs 25%). Among patients receiving <80% of planned chemotherapy dose, none of the FLOT patients achieved TRG 0, whereas 36.4% of EOX patients did. Among patients receiving ≥80% of planned dose, the rate of TRG 0 was similar between regimens: EOX: 35.7%, FLOT: 30%. On logistic regression analysis, dose intensity ≥80% demonstrated higher odds of achieving major tumor regression. Distal tumors and dose intensity >80% increased the odds of improved tumor regression.

Conclusion: EOX regimen numerically showed more pCR rates than FLOT regimen. Dose density of >80% and distal tumors were predictors of better TRG scores.

Keywords: Locally advanced gastric cancer, perioperative chemotherapy, tumor regression grade, FLOT, EOX, dose modification of FLOT, dose modification of EOX, relative dose intensity.

INTRODUCTION

Gastric cancer, a major contributor to global cancer burden, ranks as the fifth most common malignancies. It is also a leading cause of cancer-related mortality in the world. Although incidence rates have declined in several regions, the disease poses significant challenges, particularly in Asia [1]. India is considered a low-incidence country; however, its large population and marked regional heterogeneity contribute to approximately 60,000 new cases annually accounting for ~ 4.5% of all cancers in India [2, 3]. The evolution of gastric cancer management from only radical surgery towards perioperative chemotherapy to improve surgical, pathological and disease outcomes is remarkable. The advent of perioperative chemotherapy, first with ECF and later with FLOT has shown improved overall survival [4-6]. Tumor Regression Grade (TRG) following perioperative chemotherapy acts as a surrogate marker for overall survival [7, 8]. However, its translation to real world scenarios, especially in countries like India and the associated literature is limited. This study aims to find the prognostic and clinicopathological significance of histopathological tumor regression following perioperative chemotherapy in resectable locally advanced gastric and esophagogastric cancers, especially when dose modifications are involved due to patient factors.

MATERIALS AND METHODS

This is a retrospective study carried out in a single institution, Vydehi Cancer Centre, Bangalore, between 2022 and 2024. Patients diagnosed with locally advanced gastric cancers and Type III Gastroesophageal Junction (GEJ), who underwent perioperative chemotherapy followed by Radical surgery with D2 Lymph Node dissection meeting the inclusion criteria were included.

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ISSN: 1927-7210 / E-ISSN: 1927-7229/26

Inclusion Criteria

1. Patients diagnosed as locally advanced gastric and Type III GEJ cancer, requiring perioperative chemotherapy
2. Patient with good performance status - ECOG 1/2
3. Patients with a resectable tumor
4. Patients who started perioperative chemotherapy (3 cycles of EOX pre operatively and 3 cycles postoperatively or 4 cycles of FLOT pre operatively and 4 cycles post operatively)

Exclusion Criteria

1. Upfront surgery in case of bleeding and gastric outlet obstruction
2. Unfit for surgery or chemotherapy due to patient related factors
3. Metastatic disease at presentation
4. Incomplete clinical or histopathological data

Treatment Protocol

Patients diagnosed as a case of locally advanced gastric cancer and Type III GEJ tumors, where subjected to perioperative chemotherapy with either 3 cycles of EOX or 4 cycles of FLOT. The selection of chemotherapy regimen was at the discretion of the Medical Oncologist based on performance status of patients and their financial well being. Following chemotherapy, response to treatment was assessed with CECT Abdomen or PETCT (same imaging used preoperatively) and then proceeded with surgical management. Depending on the location of the tumor, a distal gastrectomy, subtotal gastrectomy, proximal gastrectomy or total gastrectomy. Surgery was performed in open or minimally invasive procedures. All types of gastrectomy were accompanied with a radical D2 lymph node dissection followed by a Roux-en-Y reconstruction. Following surgery, the planned chemotherapy cycles were completed.

Data Collection

The data collected included the baseline characteristics of patients, type of surgery, chemotherapy regimen used, dose modification of chemotherapy, completion of chemotherapy, pre-operative TNM stage of tumor, final histopathology report which also included the histological grade, margin status, number of nodes harvested, number of positive nodes, extranodal extension (ENE), perineural invasion (PNI), lymphovascular invasion (LVSI) and tumor regression grade (TRG) based on CAP protocol. TRG was graded as 0 – no viable cancer cells, 1 – marked response, 2 – minimal Response, 3- poor or no response. Major pathological response included both TRG 0 and TRG 1. Relative dose intensity (RDI) was calculated as the ratio of dose of chemotherapy delivered to standard chemotherapy dose and patients were categorized into <80% and ≥80% of planned dose intensity.

Primary Outcomes

To evaluate the histopathological response to perioperative chemotherapy in patients with resectable locally advanced gastric and esophagogastric junction adenocarcinoma.

Secondary Outcomes

- Association of chemotherapy regimen with pathological response
- Impact of dose intensity (RDI) on tumor regression
- Influence of tumor location (proximal vs distal stomach) on response
- Surgical and histopathological outcomes

Statistical Analysis

All statistical analyses were done using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as mean ± standard deviation and compared using the Student t-test or Wilcoxon rank-sum test. Categorical variables were compared using the χ^2 test or Fisher's exact test. The primary outcome of the study was pathological tumor regression grade (TRG) following perioperative chemotherapy for which binary endpoint of complete pathological response (TRG = 0) versus incomplete response (TRG > 0) was used. Univariable analyses were first performed to evaluate associations between clinicopathological variables and pathological response. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated. To further evaluate predictors of tumor regression, multivariable ordinal logistic regression models were constructed with TRG as an ordered outcome variable. To account for baseline imbalances, a multivariable

model was constructed using variables that were selected a priori based on clinical relevance and observed imbalance between groups, specifically tumor location, dose intensity and type of chemotherapy regimen. The number of covariates was deliberately restricted to minimize overfitting given the limited sample size. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

RESULTS

A total of 41 patients diagnosed as locally advanced gastric or GE junction cancers were included in the study who fulfilled the inclusion criteria. Twenty patients (61%) received 3 cycles of perioperative EOX and 16 patients (39%) received 4 cycles of FLOT. The mean age was 54 ± 17 years in the EOX group and 58 ± 16 years in the FLOT group (p = 0.444). There were no significant differences in baseline clinical stage or toxicity profiles between the two regimens. However, patients receiving the full dose of planned chemotherapy differed significantly (70% of FLOT patients versus 30% in the EOX group) (p = 0.03). The baseline clinical characteristics are enumerated in Table **1**.

Treatment and Surgical Outcomes

Surgical procedures included total gastrectomy, subtotal gastrectomy, proximal gastrectomy and distal gastrectomy. All the surgeries were performed along with a radical D2 lymph nodal dissection. The distribution of surgical procedures did not significantly differ between the chemotherapy groups (p = 0.676). Table **2** shows the distribution of surgeries based on chemotherapy regimen. One case was abandoned due to detection of peritoneal metastasis intraoperatively. The mean lymph node yield was comparable between groups (EOX: 15 ± 10, FLOT: 16 ± 11, p = 0.744).

Histopathological Outcomes

Histopathological examination revealed adenocarcinoma in majority of the patients. Poorly cohesive carcinoma and signet ring cell carcinoma were observed only in the FLOT group. The distribution of pathological stage groups was similar (p = 0.355).

Table 1: Clinical Characteristics of 41 Included Participants, Stratified by Chemotherapy Regimen Received (N = 41)

Variable	EOX group (n = 25)	FLOT group (n = 16)	*p*
Sex, n (%)			0.176
Male	14 (51.9%)	13 (48.1%)	
Female	11 (78.6%)	3 (21.4%)	
Age in years	54 ± 17	58 ± 16	0.444
Preoperative stage			0.432
IIA	4 (44.4%)	5 (55.6%)	
IIB	8 (72.7%)	3 (27.3%)	
III	13 (61.9%)	8 (38.1%)	
Dose reduction			0.753
< 80	11 (64.7%)	6 (35.3%)	
≥ 80	14 (58.3%)	10 (41.7%)	
Completion of chemotherapy			0.051
No	6 (40%)	9 (60%)	
Yes	19 (73.1%)	7 (26.9%)	
Full dose received?			0.03
No	22 (71%)	9 (29%)	
Yes	3 (30%)	7 (70%)	
Response			0.394
Stable	8 (57.1%)	6 (42.9%)	
Partial	17 (65.4%)	9 (34.6%)	
Progressive	0	1 (100%)	

Table 2: Interventions Received

Interventions	EOX group (n = 25)	FLOT group (n = 16)	*p*
Surgery type			0.676
Total gastrectomy	10 (62.5%)	6 (37.5%)	
Subtotal gastrectomy	13 (61.9%)	8 (38.1%)	
Proximal gastrectomy	1 (100%)	0	
Distal gastrectomy	1 (50%)	1 (50%)	
Abandoned*	0	1 (100%)	
Surgery mode			0.031
Open	15 (68.2%)	7 (31.8%)	
Laparoscopy mobilized	10 (66.7%)	5 (33.3%)	
Robotic assisted	0	4 (100%)	

Table 3: Histopathological Outcomes

Outcomes	EOX3 group (n = 25)	FLOT4 group (n = 16)	*p*
Histology			0.08
Adenocarcinoma	25 (65.8%)	13 (34.2%)	
Poorly Cohesive Carcinoma	0	2 (100%)	
Signet Cell	0	1(100%)	
Histological grade*			0.216
0	8 (80%)	2 (20%)	
1	3 (100%)	0	
2	7 (53.8%)	6 (46.2%)	
3	7 (50%)	7 (50%)	
Tumor location			0.332
GEJ-III	6 (85.7%)	1 (14.3%)	
Fundus and/or body	7 (53.8%)	6 (46.2%)	
Pylorus or antrum	12 (57.1%)	9 (42.9%)	
Specimen margins*			0.02
Negative	24 (70.6%)	10 (29.4%)	
Positive	1 (16.7%)	5 (83.3%)	
Lymph nodes*	15 ± 10	16 ± 11	0.744
Positive lymph nodes*	0 ± 3	3 ± 10	0.220
Extra-nodal extension*			0.134
0	24 (64.9%)	13 (35.1%)	
2	1 (100%)	0	
4	0	2 (100%)	
Tumour regression grade*			0.41
0	9 (75%)	3 (25%)	
1	2 (100%)	0	
2	3 (50%)	3 (50%)	
3	11 (55%)	9 (45%)	
Lymphovascular stromal invasion*			0.332
1	18 (66.7%)	9 (33.3%)	
2	7 (53.8%)	6 (46.2%)	
Perineural invasion*			0.178
1	20 (69%)	9 (31%)	
2	5 (45.5%)	6 (54.5%)	

GEJ – Gastro-esophageal junction.
*Missing data of one participant whose surgery was abandoned due to peritoneal metastasis detected intra-operatively.

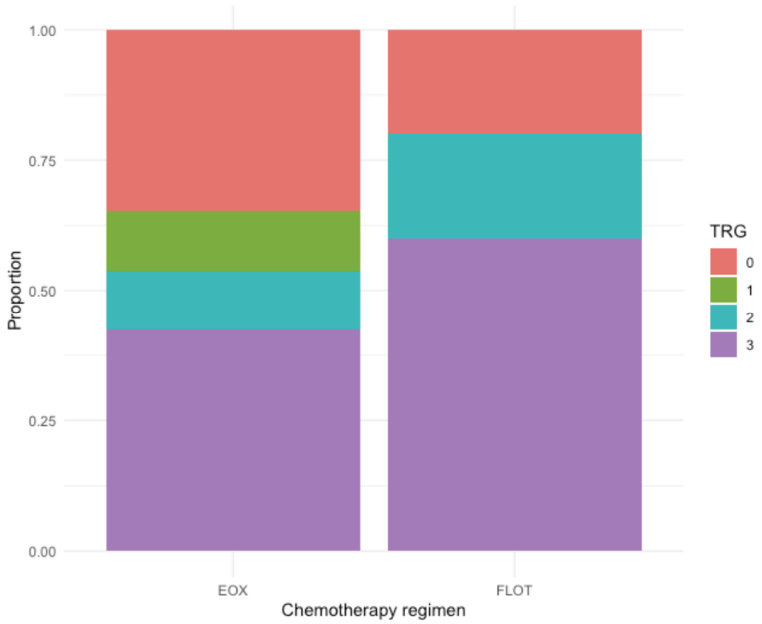

Figure 1: Distribution of TRG following perioperative chemotherapy.

The number of nodes being positive were also similar between the groups (p = 0.220). Positive resection margins were commonly noticed in the FLOT subgroup. Table **3** shows the histopathological outcomes distributed among the two groups.

Tumor Regression Grade

TRG following peri-operative chemotherapy are mentioned in Table **3** and Figure **1**. pCR rates were higher in the EOX group compared to FLOT group, although not significant (75% vs 25%, OR 2.4, 95% CI 0.5–10.9; p = 0.244).

Effect of Chemotherapy Intensity

Dose intensity was calculated as relative dose intensity (RDI), dose given divided by standard dose. Among patients receiving <80% of planned chemotherapy dose, none of the FLOT patients achieved TRG 0, whereas 36.4% of EOX patients did. Among patients receiving ≥80% of planned dose, the rate of TRG 0 was similar between regimens: EOX: 35.7%, FLOT: 30%. This difference was not statistically significant (p = 0.292) (Table **4**, Figure **2b**).

On logistic regression analysis evaluating predictors of major pathological response, maintenance of chemotherapy dose intensity ≥80% demonstrated higher odds of achieving major tumor regression (OR 3.06, 95% CI 0.77-14.35) (Figure **2a**). Although these findings did not reach statistical significance, the direction of effect suggests that higher delivered dose intensity may improve pathological response

Tumor Location and Pathological Response

Tumor location demonstrated a significant association with pathological response. Distal gastric tumors (pylorus/antrum) were more likely to achieve major regression compared with proximal tumors (OR 4.97, 95% CI 1.08-27.99, p = 0.025). This suggests

Table 4: TRG (Primary Outcome) Stratified Treatment Regimens and further Sub-Stratified by Dose-Reduction

Dose	Chemotherapy regimen	TRG = 0	TRG > 0	OR (95% CI)	*p*
Overall	EOX	9 (36%)	16 (64%)	2.4 (0.5 – 10.9)	0.244
	FLOT	3 (18.8%)	13 (81.3%)	(Reference)	
< 80	EOX	4 (36.4%)	7 (63.6%)	7.8 (0.3 – 173.9)	0.195
	FLOT	0	6 (100%)	(Reference)	
≥ 80	EOX	5 (35.7%)	9 (64.3%)	1.3 (0.23 – 7.4)	0.292
	FLOT	3 (30%)	7 (70%)	(Reference)	

OR – Odds ratio.

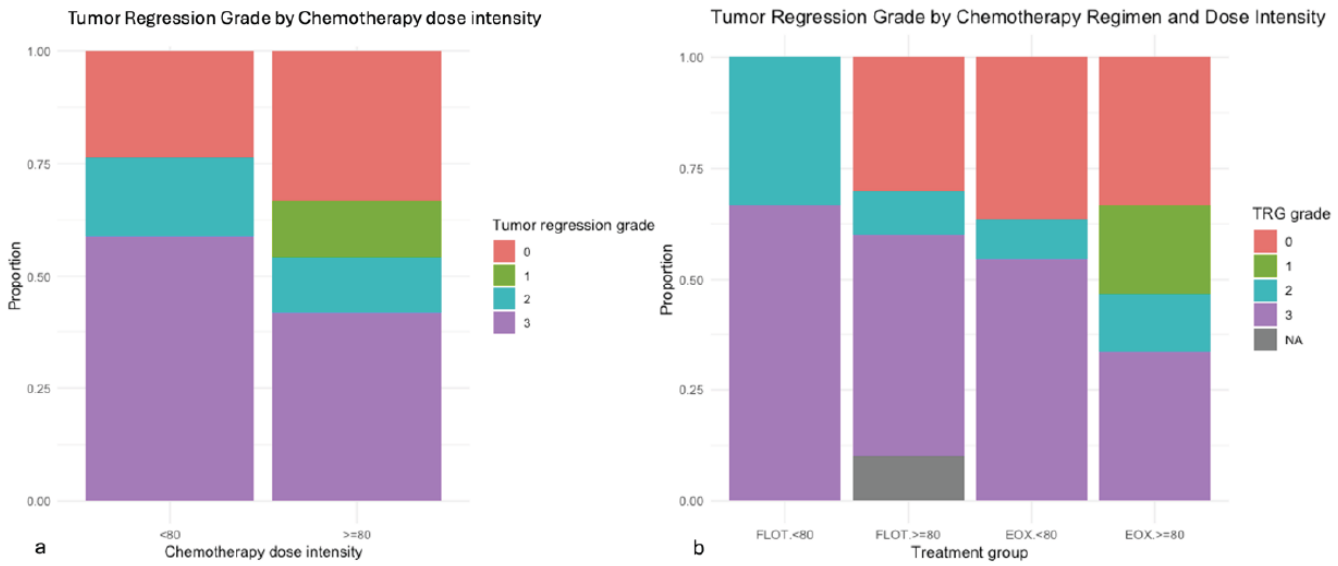

Figure 2: a - Distribution of TRG based on Chemotherapy dose. Patients receiving >80% of the dose showed major pathological response (TRG 0/1). **b** – Distribution of TRG based chemotherapy regimen and dose. Similar TRG 0 rates with >80% dose of either regimen.

that distal gastric tumors may be more responsive to perioperative chemotherapy.

Ordinal Logistic Regression Analysis

To evaluate predictors of overall tumor regression grade, an ordinal logistic regression model was constructed. Maintenance of chemotherapy dose intensity ≥80% increased the odds of improved tumor regression (OR 1.64, 95% CI 0.59-6.70). Distal tumor location was associated with better pathological response (OR 2.69). However, there was no clear advantage of the FLOT regimen over EOX observed (OR 0.42, 95% CI 0.13-1.57). Forest Plot showing the predictors of TRG can be seen in Figure **3**. An interaction model evaluating whether full-dose improved outcomes did not demonstrate a statistically significant interaction suggesting that delivering full-dose chemotherapy did not significantly modify the effect of regimen on pathological response.

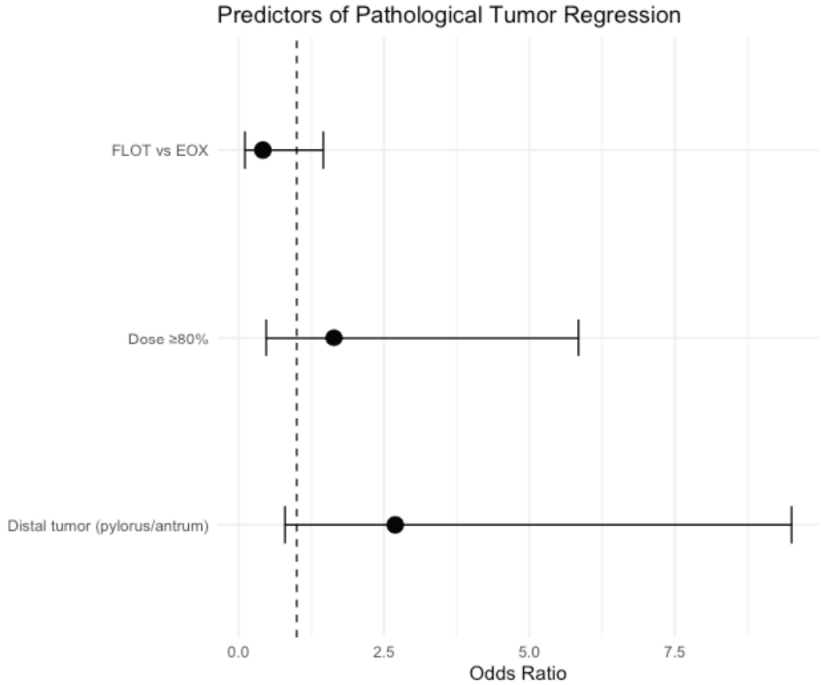

Figure 3: Forest Plot showing the predictors of pathological tumor regression.

DISCUSSION

Perioperative chemotherapy is the standard of care for locally advanced gastric cancer, aiming to reduce tumor size and improve surgical outcomes. Histopathological response, assessed through tumor regression grading (TRG), is a critical factor in evaluating the effectiveness of this treatment. Studies have shown varying degrees of tumor regression and its impact on survival outcomes [9-12]. The prognostic value of histopathological response remains debated, with some studies indicating significant survival benefits while others show limited correlation [13,14]. However, evidence derived from real-world clinical settings remains heterogeneous, with considerable variability in outcomes across studies.

The FLOT regimen has shown superior efficacy in terms of better pathological complete response rates (pCR). Al-Batran *et al.* in the FLOT4-AIO study showed a pCR of 16% whereas the earlier MAGIC trial showed a pCR of around 5%. This also showed an increase in median OS from 36 months to 50 months (~45%) with the FLOT regimen [5,6]. In a study by Bhargava *et al.,* from India, perioperative FLOT showed a complete response in 1% and partial response in 48% patients with 2-year median OS 69.4% [15]. In a later study from the same institute in India, the pCR to perioperative chemotherapy was 9.49%. They along with several other studies commented that pCR and completion of adjuvant chemotherapy had superior OS advantage [7, 16]. MAGIC trial was a landmark trial, creating a turning point in the treatment of locally advanced gastric cancers [5]. Cunningham *et al.,* in their study showed a pCR of <5% and a 13% increase in OS. The difficulties in administering ECF, brought about the REAL-2 trial with the EOX regimen, replacing the infusion of flurouracil to oral capecitabine and cisplatin to oxaliplatin. The REAL-2 trial was proved to be non-inferior to the ECF regimen [17]. pCR rates towards perioperative EOX vary from 6% to 11% [18-20]. The compliance of perioperative EOX in the Indian population is around 64% [18]. In our study, more patients receiving EOX achieved pCR or a major pathological response. Even though the numerical value was higher, it was not statistically significant. A tete-a-tete comparison between FLOT and EOX regimens was conducted at the Tata Memorial Hospital, Mumbai, which showed a modified FLOT regimen outperformed EOX in terms of oncological outcomes. There was however a higher incidence of grade 3 and grade 4 neutropenia and febrile neutropenia with the mFLOT regimen [21].

Data on dose modification of the respective perioperative regimens and its effect on pCR rates are scarce. Massaro *et al.,* in their study of dose modifications of FLOT, showed dose modifications did not show any significant difference in pCR rates or OS [22]. In our study, patients receiving < 80% of the planned FLOT regimen, none of them achieved pCR, whereas those receiving > 80% of the planned dose, 30% achieved pCR. Amongst the EOX, patients receiving > 80% of the planned dose, around 36% achieved pCR, whereas those receiving < 80% dose, 35.7% of them achieved pCR. Even though there was no statistical significance, on regression analysis there was trend towards better pCR rates for those receiving a higher dose density. The number of cycles (> 3), resectability and objective response showed a significant impact on OS and EFS benefits in both regimens. On comparing FLOT versus EOX, dose modification was found to influence survival in EOX group. FLOT regimen showed non-significant favourable survival outcomes compared to EOX, despite dose modification in the locally advanced stage [23]. A meta-analysis showed addition of immunotherapy to chemotherapy provided an increased pathological response compared to chemotherapy alone [24].

There is not much data available in the current literature regarding the correlation of tumor location and pCR rates. Tumor site is a prognostic factor with stomach location being associated with better OS than lower esophagus/GEJ, independent of treatment. However, this reflects biology and resectability more than differential chemo sensitivity [25]. For proximal gastric or GEJ vs distal esophageal adenocarcinoma, site chiefly guides the choice between perioperative chemotherapy and chemoradiotherapy [26, 27].

In a meta-analysis of gastric or GEJ cancers treated with neoadjuvant chemotherapy alone, the average pCR rate was ~6.7% (range 3–15%) [28]. The authors note that pCR rate “is likely to be affected by the location of the tumor, degree of differentiation, Lauren type, and chemotherapy regimens and cycles” but do not provide site-stratified pCR data. For esophageal and GEJ cancer (both histologies), a systematic review found pooled pCR rates after neoadjuvant chemotherapy of 8% overall and 6% for adenocarcinoma, versus 29% overall and 22% for adenocarcinoma with chemoradiation [8]. In our study, distal tumors were more likely to achieve major tumor regression. However, tumor site is not an independent, strong predictor once histology and treatment are accounted for.

Recent randomized trials and meta-analyses consistently report R0 rates of approximately 80–95% with modern perioperative regimens, including combinations such as FLOT, SOX, DOS, and emerging chemoimmunotherapy protocols [4, 6, 29-31]. Determinants of R0 rates include tumor location (distal vs GEJ), histology (signet ring cell), age/comorbidity profile, and surgical expertise can influence both eligibility for surgery post-chemo and ultimate margin status [32, 33]. In our study, R0 rates were 70.6% in the EOX group and 29.4% in the FLOT group. 5 out of the 16 patients in the FLOT group and 1 out of 25 patients in the EOX group had positive margins in the final histopathology report. These patients with R1 margins in the FLOT group has a tumor located in the proximal stomach and the distal esophageal margin was the positive margin. While network meta-analysis confirms superiority over surgery alone for most regimens studied, overall certainty remains moderate due to heterogeneity in study designs and definitions used for “R0” status across trials [34].

In the FLOT4 Trial, median OS was significantly better, while only 37–46% of patients completed all postoperative cycles [6]. Whereas in the MAGIC trial less than half were able to complete the postoperative chemotherapy [5]. In our study, completion rates of the prescribed chemotherapy regimens were 73% in the EOX group and 26.9% in the FLOT group. Across regimens, receiving neoadjuvant (pre-operative) chemotherapy and achieving R0 resection drive most OS benefit; completing every planned postoperative cycle adds but is not essential for survival gains. Patients unable to finish adjuvant therapy should still be considered to have received effective perioperative treatment [5, 6, 25, 31, 35, 36].

STRENGTHS AND LIMITATIONS

This study tackled an unexplored question in real word practice of management of locally advanced gastric cancers. The effect of chemotherapy dose on the histopathological response, in a real-world treatment delivery has not been reported much in literature. In a resource-variable place like India, deviations from protocol-driven therapy are common and may influence outcomes. While landmark trials have established the superiority of specific regimens, few have rigorously examined whether the effectiveness of these regimens is contingent upon maintaining adequate dose delivery. The observed directional association between higher dose intensity and improved tumor regression, although not statistically significant, is biologically plausible and clinically meaningful.

Despite these strengths, several limitations substantially temper the interpretability of the findings. The retrospective, non-randomized design of the study brings selection bias and confounding. The lack of standardization of chemotherapy regimen and treatment allocation to EOX versus FLOT, as well as decisions regarding dose reduction, were influenced by patient fitness, tumor biology, and clinician preference. The limited sample size (n = 41) is a critical constraint and represents the most significant limitation of the study. The resulting lack of statistical power is reflected in the wide confidence intervals. The absence of long-term survival data, including disease-free and overall survival, negates definitive conclusions regarding the clinical impact of the observed associations. Despite adjustment for key clinicopathological variables, residual confounding due to baseline imbalances cannot be excluded, particularly given the limited sample size and restricted multivariable modeling. These findings should be regarded as hypothesis-generating, supporting the concept that maintenance of chemotherapy dose intensity may be as important as regimen selection in optimizing pathological response, and warrant validation in larger, prospective, and ideally multicentric studies.

CONCLUSION

Perioperative chemotherapy and surgery have become the standard of care in locally advanced gastric and Type III GEJ tumors, providing superior oncological benefits in terms of OS and DFS. EOX provided numerically more pCR rates than FLOT. However the trend for better tumor regression although not statistically significant, was favoring FLOT. Chemotherapy dose intensity >80% and distal tumors showed trends towards better tumor regression grades post perioperative chemotherapy. These findings did not reach statistical significance and hence, need to be taken with some caution in clinical use as they are only hypothesis generating.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JTC, AR and CMG. The first draft of the manuscript was written by JTC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY

The data is available from the corresponding author upon request.

FUNDING

The authors have no relevant financial or non-financial interests to disclose.

ETHICS APPROVAL

The Institutional Ethics Committee of Vydehi Institute of Medical Sciences waived off approval in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. The study was conducted in accordance with the Declaration of Helsinki

CONSENT TO PARTICIPATE AND PUBLISH

An informed consent to participate and publish was obtained from all participants.

CLINICAL TRIAL NUMBER

Not applicable.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest and have not received any financial assistance.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Manu Pradeep, for help with the initial statistical work in this study.

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Received on 13-05-2026 Accepted on 22-06-2026 Published on 15-07-2026

https://doi.org/10.30683/1927-7229.2026.15.07