

Original Article

Clinico-pathological features and the role of CD4/CD8 lymphocyte ratio in predicting response to neoadjuvant FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) chemotherapy in locally advanced gastric cancer

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ABSTRACT

Objectives: Neoadjuvant chemotherapy (NACT) is recommended in resectable, locally advanced gastric cancer (GC) patients, but only about 40% have a pathological response. There is a delay in definitive management for those who don't respond. Predictive biomarkers will show which group of patients benefits from NACT. The aim was to study clinic-pathological features and CD4/CD8 ratio as a predictive marker for response to NACT in GC patients.

Material and Methods: A prospective study of GC patients was conducted at our institute from January 2023 to December 2024. Patients >18y, PS 0/1, gastric or gastroesophageal junction (GEJ) adenocarcinoma, stage \geq T2 and/or Node positive, non-metastatic patients who underwent curative surgery after NACT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) chemotherapy were included. CD4 and CD8 cells were calculated by immunohistochemistry (IHC) on the pre-chemotherapy biopsy. Tumor regression grade (TRG) assessments were done by the modified Ryan criteria. Clinicopathological factors, including the CD4/CD8 ratio, were correlated with TRG.

Results: 90 patients were studied. 83% (N=75) of the patients underwent definitive surgery and were included for analysis. Median age was 55 years (35-70). Males were 71%. The most common symptom was abdominal pain (55%). 39% were smokers. The most common site was GEJ (40%). 9% had signet-ring histology. 27% had grade 3/4 neutropenia. All had R0 resection. 8% achieved pathological CR. 60% received adjuvant chemotherapy (21% FOLFOX or 5FU/LCV, 39% FLOT). There was a statistically significant correlation between TRG and smoking history (p value 0.02); site of tumor (Proximal versus distal) (p value 0.03); and CD4/CD8 ratio (p value <0.001).

Conclusion: Patients who were nonsmokers, those with proximal GCs, and those with a higher CD4/CD8 ratio showed better response to FLOT NACT. CD4/CD8 ratio can be used as a biomarker that predicts response to FLOT NACT in operable gastric cancer patients.

Keywords: FLOT, Gastric cancer, Neo-adjuvant chemotherapy, Pathological response CD4/CD8.

INTRODUCTION

Gastric cancer ranks 5th according to incidence in the world and ranks 5th as a cause of death worldwide. In India, it ranks

7th according to incidence and ranks 6th as a cause of death.

^[1] The largest incidence of stomach cancer is seen in Asia

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(mainly Japan and China). In India, the incidence is 3.5 per 1 lakh population as of 2022.^[1,2] Gastric cancer has a 5-year survival rate of about 20% (all stages included). More than 50% of the cases present with metastatic disease, and these patients have dismal outcomes.^[3]

In patients who present with locally advanced gastric cancer ($\geq T2$ and/or N+), perioperative chemotherapy with FLOT – fluorouracil, leucovorin, oxaliplatin, and docetaxel is the standard treatment as per the FLOT4 – AIO trial.^[4] This has been shown to improve c, improve the rates of pathological complete response (PCR), and improve overall survival (OS). The recently published MATTERHORN trial has shown improved PCR and improved 2-year event-free survival (EFS) with the addition of perioperative Durvalumab along with FLOT chemotherapy.^[5] However, PCR is seen only in 15-20% of patients treated with perioperative therapy, and partial or complete response is seen in 35-40% of patients.^[6] There is a delay in definitive surgery for the patients whose tumors don't respond to neoadjuvant chemotherapy, with no added benefit over adjuvant chemotherapy. There are also the increased toxicities (Neutropenia, infection, peripheral neuropathy, mucositis) with chemotherapy.^[7]

Immunohistochemistry (IHC) is a pathological tool that provides prognostic biomarkers and treatable targets in oncology. In gastric cancer, biomarkers detected on IHC are prognostic and/or therapeutic, like E-cadherin and human epidermal growth factor receptor 2 (HER2-neu).^[8] Tumors with a low level of tumor-infiltrating lymphocytes (TILs) are considered immunologically “cold,” and those with high levels of TILs are immunologically “hot.” Higher TILs are associated with better response to systemic therapy.^[9,10] However, there are no biomarkers to predict response to NACT. The CD4 (Cluster of Differentiation 4)/CD8 ratio is a surrogate marker of active immune function. A lower CD4/CD8 ratio is related to worse outcomes in Human Immunodeficiency Viruses (HIV) related diseases, cardiovascular diseases, and malignant conditions.^[11] Both CD4 and CD8 T cells are important parts of the tumor milieu, and their interaction with other immune cells, such as Natural killer T cells (NK-T), tissue macrophages, and antigen-presenting cells (APC), influences the efficacy of the host immune response to the tumor.^[12] In a study done by Skubleny *et al*, they demonstrated that a higher CD4+/CD8+ ratio, detected via IHC, is a useful biomarker that predicts a favorable pathological response to neoadjuvant chemotherapy with FLOT in locally advanced gastric cancer.^[13]

There is a paucity of data on Indian patients treated with this perioperative regimen, considering that Indian patients present with more advanced disease and are also poorly nourished, which may alter the responses to NACT. Hence, we performed a prospective study to evaluate various clinic-

pathological factors associated with a favorable response to NACT in locally advanced Gastric cancer.

MATERIAL AND METHODS

We conducted a prospective observational study at our institute from January 2023 to December 2024 to evaluate the clinic-pathological factors associated with a favorable response to NACT in locally advanced Gastric cancer. After obtaining approval from the institutional scientific review board and institutional ethical committee, (Number: KMIO/MEC/2023/04/PG/MO/20) we included patients aged more than 18 years, who had Eastern Cooperative Oncology Group - Performance Status (ECOG PS) 0-1 with treatment naïve, locally advanced Gastric adenocarcinoma ($\geq T2$ and/or N+), with adequate cardiac, renal and hepatic functions and those who underwent definitive surgery after neoadjuvant chemotherapy. Patients with HIV, and patients with distant metastasis upfront or those who developed metastasis during or after completion of planned NACT were excluded from the study. Informed consent was taken from all patients. Diagnostic laparoscopy before initiation of chemotherapy was preferred; however, it was not mandated. After obtaining informed consent, epidemiological data, presenting complaints, co-morbidities, risk factor history, tumor characteristics, including location of the tumor, histology, grade of the tumor, and HER2 statuses of the tumor were obtained and recorded. Diagnosis was established by a biopsy taken during the endoscopy.

CD4/CD8 ratio in the pre-chemotherapy endoscopic biopsy specimen was done by IHC. Paraffin blocks of biopsy-diagnosed adenocarcinoma cases were retrieved. 4 m tissue sections taken, deparaffinized, and rehydrated. Endogenous peroxidase was quenched using hydrogen peroxide. Antigen retrieval by Microwave heat-induced was done with the help of ethylenediaminetetra acetic acid (EDTA). Tissue sections were stained using primary antibodies Anti-CD4 (mouse monoclonal antibody, 4B12 clone, Biogenex) and Anti-CD8 (rabbit monoclonal antibody, SP16 clone, Biogenex). Antibody detection was done using avidin-biotin complex/horseradish-peroxidase and 3,3-diaminobenzidine tetrahydrochloride (DAB). These tissue sections, which were stained for CD4 and CD8, were then counterstained with harris hematoxylin. Manual counting of CD4 and CD8 cells, which showed positivity, was done under high-power magnification (10x eyepiece, 40x objective). CD4 and CD8 positive cells in the tumor stroma are counted. A minimum of 5 high-power fields were observed, and the average D4:CD8 ratio was calculated.

Patients were given neoadjuvant chemotherapy - FLOT as per institutional protocol. After appropriate premedication, Docetaxel at the dose of 50 mg/m² IV infusion over 1 hour,

Oxaliplatin at the dose of 85 mg/m² IV infusion over 2 hours concurrently in a separate IV bag via Y connector with Calcium Leucovorin at 200mg/m² followed by 24 hours continuous IV infusion of 5-fluorouracil at 2600mg/m². Dose adjustment was done as per the physician's discretion. Adverse events were graded as per CTCAE v5. After completion of planned cycles of NACT, patients underwent definitive surgical resection. Pathological treatment response was assessed on the postoperative specimen. The Tumor Regression Score grading was done according to the College of American Pathologists protocol by Modified Ryan classification on a 4-point scale (0: Complete response, 1: near complete response, 2: partial response, 3: poor or no response).^[14] Adjuvant chemotherapy was then given as per the treating physician's discretion.

Statistical analysis

Sample size calculated by the Wilcoxon Mann-Whitney U test with a 2-sided alpha of 0.05, a power of 0.8, and a dropout rate of 0.2. Data was entered into a Microsoft Excel sheet, and SPSS 22 version software was used for analysis. Frequencies and proportions were used to represent categorical data. Chi-square test or Fisher's exact test (for 2x2 tables only) was used as a test of significance for qualitative data. Continuous data was represented as mean and standard deviation. ANOVA (One-way analysis of variance) was used as a test of the significance of more than two quantitative variables. Statistical significance was considered with a p-value (Probability that the result is true) of <0.05.

RESULTS

Ninety patients were included in the study. Ten patients had metastatic disease or were inoperable post-NACT and were excluded from the study. Four patients were lost to follow-up. One patient died due to non-neutropenic sepsis after the 3rd course of NACT. Seventy-five patients completed the planned number of NACT cycles and were included for analysis.

Baseline characteristics

Median age of the study population was 55 years (Range: 35 – 70 years). 71% of the patients were males. Abdominal pain was the most common presenting symptom, seen in 55% of patients, followed by Dysphagia in 24% of the patients. Median duration of symptoms was 2 months (Range: 0.5 to 5 months). 12% of the patients had Diabetes Mellitus, 13% had hypertension. 40% were either current or former smokers. 27% and 23% had a history of alcohol and tobacco consumption, respectively. Based on the site of disease in the endoscopy, growth in the Gastroesophageal junction (GEJ) was the most common site, accounting for 40%. It was followed by growth in the Antropyloric region (31%), body

of the stomach (24%), and fundus of the stomach (5%). 59% had grade 2 tumors and 41% had grade 3 tumors. HER2 Neu was positive in 2.6% of patients [Table 1]. Mean CD4 value in the pre-chemotherapy biopsy specimen was 2.2 (Standard Deviation {SD}: ±1.4). Mean CD8 ratio was 20.8 (SD: ±11.4).

Table 1: Baseline characteristics.

Characteristic	Patient distribution: Number (%)
Age in years (Median)	55 (Range: 35 – 70 years)
Male	53 (71%)
Presenting Complaint:	
1. Pain abdomen	41 (55%)
2. Vomiting	18 (24%)
3. Dysphagia	16 (21%)
Comorbidities:	
1. DM	9 (12%)
2. Hypertension	10 (13%)
Addictive habits:	
1. Smoking	30 (40%)
2. Alcohol Consumption	20 (27%)
3. Tobacco Consumption	17 (23%)
Tumor location:	
1. Proximal Stomach and GEJ	34 (45%)
2. Body of Stomach	18 (24%)
3. Distal stomach	23 (31%)
Signet ring histology	7 (9%)
Grade:	
1. 1	0
2. 2	44 (59%)
3. 3	28 (41%)
Her 2 Neu Positive	2 (2.6%)
ECOG PS:	
0	25 (33.3%)
1	50 (66.6%)

GEJ: Gastroesophageal junction, ECOG PS: Eastern cooperative oncology group - Performance status, DM: Diabetes mellitus

Table 2: Adverse events.

Adverse event	All grades	Grade 3/4
Neutropenia	41 (55%)	20 (27%)
Febrile Neutropenia	-	6 (8%)
Diarrhoea	30 (40%)	19 (25%)
Mucositis	20 (26%)	12 (16%)

Adverse events

Hematologic Toxicity: Grade 3/4 neutropenia occurred in

27% (n=20) of patients. Febrile neutropenia was documented in 8% (n=6) of patients and was managed with inpatient hospitalization and broad-spectrum antimicrobial therapy according to institutional protocols. Non-hematologic Toxicity: Gastrointestinal toxicities were the predominant non-hematologic adverse events observed. Grade 3/4 diarrhea developed in 25% (n=19) of patients, whilst grade 3/4 mucositis occurred in 16% (n=12) of patients [Table 2]. These toxicities were generally manageable with supportive care and did not necessitate permanent treatment discontinuation in the majority of cases.

Dose modifications

Dose reductions were implemented in the first cycle as per the treating physician's discretion, depending on the patients' ECOG Performance Status and comorbidity profile. Dose reductions of 5-fluorouracil to 80% of the planned dose were done in 20% (n=15) of patients, and docetaxel dose reduction to 80% of the planned dose was performed in 7% (n=5). Subsequent cycles required dose modifications in 28% (n=21) of patients in response to treatment-related toxicities (Reductions were made in cases of Adverse events \geq CTCAE grade 3). Despite these modifications, the majority of patients completed the planned neoadjuvant chemotherapy course.

Pathological response

We found 8% of the patients had a pathological complete response (Tumor Regression Grade [TRG] – 0). 10.6% had a TRG of 1, 38.6% of them had a TRG of 2, and the remaining 42.6% had a TRG of 3 [Table 3, Figure 1]. On analyzing the correlation between various clinic-pathological factors and TRG, we found that there was no statistically significant correlation between age, sex, history of alcohol or tobacco consumption, number of NACT cycles, HER2 expression, or grade of the tumor with TRG score [Table 4]. However, there was a statistically significant correlation between history of smoking (p value – 0.02), CD4/CD8 Ratio (p value – <0.001), and the location of the tumor (p value – 0.03) with the TRG score.

Patients who were non-smokers had a higher CD4/CD8 ratio in the pre-chemotherapy biopsy, and patients with GEJ tumors had a better response to NACT.

Table 3: Pathological response to NACT.

Pathological response (TRG)	Number (%) (N=75)
Complete / Partial Pathological response (TRG - 0,1,2)	43 (57%)
No Pathological response (TRG – 3)	32 (43%)

NACT: Neoadjuvant chemotherapy, TRG: Tumor regression grade

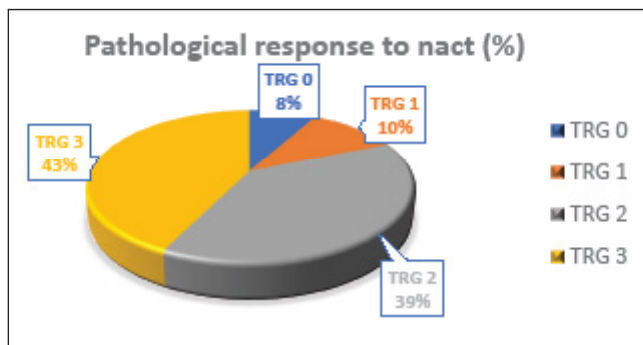


Figure 1: Pathological response to NACT (FLOT) in locally advanced gastric cancer. NACT (FLOT): Neoadjuvant chemotherapy (Fluorouracil, leucovorin, oxaliplatin, docetaxel), TRG: Tumor regression grade

Table 4: Correlation of clinicopathological factors with response to NACT.

Clinicopathological factors	Complete / Partial response (TRG 0,1,2)	Poor/ No response (TRG 3)	P value
Age in years (Mean \pm SD)	56.8 \pm 9.020	53.6 \pm 10.021	0.664
Male (%)	57%	43%	-
Risk factors:			
Smoking			
Yes	16%	24%	0.02
No	41%	19%	
Alcohol consumption			0.171
Yes	12%	16%	
No	40%	32%	
Tobacco consumption			0.527
Yes	9%	7%	
No	47%	37%	
Grade of tumor:			0.087
2	40%	20%	
3	17%	23%	
Number of NACT cycles:			0.998
3	4%	4%	
4	45%	32%	
6	8%	7%	
Site of tumor:			0.03
Gastroesophageal junction	18 (24%)	12 (16%)	
Body/ Distal stomach	25 (33%)	20 (27%)	
CD4/CD8 Ratio	0.2646 (\pm 0.087)	0.1074 (\pm 0.084)	<0.001

NACT: Neoadjuvant chemotherapy, SD: Standard deviation, TRG: Tumor regression grade, Significant if p value <0.05

DISCUSSION

Currently, Perioperative systemic therapy is the standard of care management for locally advanced gastric cancer.^[15] The benefits of NACT are downstaging of the tumor and improving resectability, treating micro-metastasis, and it also helps provide symptomatic relief to patients, such as relieving dysphagia and abdominal pain. However, less than half of the patients have a response to NACT in gastric cancers. We evaluated the clinic-pathological features that are associated with a favorable response to NACT with special reference to the CD4/CD8 ratio in the pre-chemotherapy biopsy specimen.

In our study 83% of the patients completed the planned number of NACT cycles and underwent definitive surgery, which is similar to the Indian data by Bhargav *et al.*^[16] Grade 3 or 4 adverse events were seen in 36% of patients. R0 resection was done in 100% of the patients. 60% of the patients received adjuvant chemotherapy. In them 39% (N=29) were able to complete adjuvant FLOT chemotherapy, and 21% (N=16) received either FOLFOX or 5FU-Leucovorin in the adjuvant setting.

In our study 57% had a TRG of 0, 1, or 2 (Complete or partial pathological response) with a pathological CR (TRG 0) in 8%. In the study by Lin Jiyang *et al.*, where S1 + oxaliplatin was used as NACT, they found a TRG of 0,1 or 2 in 60% of the patients, with a TRG of 0 in 13%.^[17] In the pilot study by Skubleny D *et al.*, they found partial response in 50%, complete response in 5%, near Complete in 17% and poor or no response in 27% of the patients.^[13] Complete/partial response rates in our study were similar to those of others from Asia.

Age did not correlate with response to NACT in our study, similar to the study by Liang *et al.*^[18]; however, Lin Jiyang *et al.*^[17] showed that age < 60 years had a statistically significant correlation with age. The number of patients above 60 years included in our study was less 26%, which might have skewed the observation. There was no significant difference in pathological response with respect to sex, alcohol, or tobacco consumption. Patients with a history of smoking had a poor response to NACT, similar to the observation by Lin Jiyang *et al.*^[17] Smokers have an impaired immune response mechanism by attenuating the reactive oxygen species-generating capacity of neutrophils and monocytes, which may be the reason for poor pathological response in them. Our study showed that GEJ tumors have a better response to NACT as compared to distal gastric tumors, which is in concordance with other Asian studies, such as the study by Liang *et al.*^[18]

There is evidence that the CD4 and CD8 T-cells are involved

in tumor surveillance by the immune system, response to systemic chemotherapy, and survival. Effective immune response against the tumor needs CD4 T cells, which improve the effector CD8 T cell response. CD4 cells also have a role in direct anti-tumor activity via Interferon-gamma and other cytokines.^[19] We found that the CD4/CD8 ratio showed a statistically significant correlation to response to NACT, with higher values showing better response to NACT. Our study is the first one to show that this marker predicts response to NACT in the Indian scenario.

Limitations of our study were the sample size, which was limited, and that it was a single-institution study, which reduces the generalization of the study results. Also, dMMR / MSI-H, which has been shown to have a poor response to NACT in a few studies^[4], could not be tested in our patients due to logistical issues. However, ours is one of the first studies from India to look at clinicopathological predictors of response to NACT in gastric and GEJ tumors. Further studies are essential to affirm the findings in our study. Management plan of upfront surgery followed by adjuvant chemotherapy may be a plausible one in cases of distal gastric cancers and ones with low CD4/CD8 ratios.

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CONCLUSION

We found that in locally advanced Gastric cancer patients, non-smokers and patients with GEJ tumors had better response to NACT.

CD4/CD8 ratio in the pre-chemotherapy biopsy specimen can be a biomarker for predicting response to NACT in locally advanced gastric cancers. Further studies to validate this may help in choosing patients for perioperative systemic therapy or upfront resection followed by adjuvant chemotherapy.

Author contributions: RAH and PD: Provided overall guidance for the study, supervised the research process, and contributed to the conceptualization, methodology, and critical revision of the

manuscript; SMC, LKN, LKR, SCS, and GGV: Contributed to academic inputs, expert discussions, and critical review of the study at various stages; KGA and YP: Contributed through constructive feedback, collaborative discussions, and support in refining the research content; VBM and RAH: Responsible for conducting the research, data acquisition, analysis, interpretation, and drafting of the manuscript. All authors reviewed and approved the final manuscript.

Ethical approval: The research/study was approved by the Institutional Review Board at Kidwai Memorial Institute of Oncology, number KMIO/MEC/2023/04/PG/MO/20, dated 27/01/2023.

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