



Efficacy of Neoadjuvant Chemotherapy on Locally Advanced Gastric Adenocarcinoma in Terms of Downstaging and Resectability in a Tertiary Cancer Hospital

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Abstract

Background: Neoadjuvant chemotherapy (NACT) in carcinoma stomach was introduced in an effort to eliminate micro-metastasis and to improve resectability before surgery which improves R0 resection rates. The aim of the current study was to evaluate the effect of neoadjuvant chemotherapy on downstaging and resectability rate in locally advanced gastric cancer.

Material & Methods: This was a single-center quasi-experimental study conducted in the Department of Surgical Oncology in collaboration with the Departments of Medical Oncology, Radiation oncology, and Pathology at the National Institute of Cancer Research and hospital, Dhaka, which is a tertiary care cancer hospital in Bangladesh, between January 2021 and June 2022. Patients with locally advanced adenocarcinoma stomach staged by contrast-enhanced computed tomography (CECT) were randomly included in this study by purposive sampling. Patients in Group I underwent upfront surgery Patients in Group II were started on neoadjuvant chemotherapy, either XELOX or FLOT regimen. Surgery was done following the response assessment CECT. We assessed R0 resection rate, age, sex, comorbidities, tumour size, TNM stage and complications were compared between the two groups. Response to NACT was assessed in Group II. **Results:** The mean age of patients in groups 1 & 2 was 56 ± 11.06 and 55.70 ± 10.46 years of age respectively (p > 0.05). Majority of the respondents (55/74) were male and 19 patients (26%) were female. Male to female ratio was (24/37 & 31/37) in group 1 and (31/37 & 6/37) groups respectively (p > 0.05). Out of 37 patients who received NACT, in 9 patients (24.32%) complete response was noted. Partial response was found in 20 cases (54.05%), p-value (<.0001) while a stable disease was reported in three (8.1%) cases. 5 patients (13.51%) had progressive disease. In the upfront surgery group, R0 resection was feasible in 16 (43.2%) cases, and in the NACT plus surgery group, R0 resection was done in 29 (78.4%) cases. In group 1, R1 resection was done in considerable numbers (19/37) compared to group 2 (5/37), P=0.001. Three patients (8.1%) in group 2 and one (2.7) in group 1 had irresectable lesions. **Conclusion:** In this study it can be concluded that neoadjuvant chemotherapy could downstage tumour and increase tumor resectability rate in patients with locally-advanced gastric adenocarcinoma. However, further studies are necessary to confirm the effect of this modality on patients' overall survival. We await survival analysis to further validate the role of NACT.

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INTRODUCTION

Gastric cancer (GC), in terms of incidence, is the 7th leading cancer in Bangladesh and is a major cause of cancer-related morbidity and mortality worldwide.^[1,2] Recently, it has been observed that the esophago-gastric cancer (EGC) incidence has increased in southeast Asia, and the GC incidence has decreased, but in Bangladesh, about 4792 (5.7%) new cases of stomach cancers were diagnosed in 2018.^[2,3,4] Surgical resection is the only curative treatment for gastric cancer. However, the overall prognosis of gastric adenocarcinoma is poor and advanced disease may even make surgical treatment impossible. It has been theoretically proposed that administration of chemotherapy before surgical resection may down-stage the disease state and facilitate resectability, especially in locally-advanced tumours. Multimodality therapy for gastric cancer, including resection in combination with perioperative chemotherapy or adjuvant chemoradiotherapy, is associated with a survival advantage compared to surgery alone.^[4] Chemotherapy delivery may be more efficient if given prior to the surgical disruption of vasculature, tumour down-staging may substantially facilitate surgical resection,^[5] and preoperative chemotherapy can be used to evaluate tumour chemosensitivity to cytotoxic medications. Furthermore, gastric cancer patients may tolerate preoperative cytotoxic treatment better than postoperative treatment, as performance status is usually negatively

impacted by surgery.^[6] The effect of NAC on gastric cancer has been studied in several prospective trials.^[7,8,9,10] NACT could potentially increase the curative resection rate, improve the tumour downstaging possibilities and reduce the tumour-related symptoms if the chosen drugs have an effect on the specific tumour biology.^[9,10,11,12] However, NACT could potentially increase surgical related complications and as a consequence the perioperative mortality, if it doesn't delay surgical resection.^[13,14,15,16,17,18,19] Neoadjuvant treatment has been the standard approach in advanced GC with the positive results of randomized controlled studies in recent years, but neoadjuvant treatment approach rates are far below the expectations in our country. However, no definite conclusion has been drawn from these trials (Jack et al,^[11] Proserpio et al,^[18] Blank et al,^[15] Oki et al,^[17] Del Rio et al,^[19] Basi et al,^[14] Nagahama et al,^[16] Aoyama et al.^[13] The underlying reasons included insufficient statistical power due to limited sample size, an extended period of time for patient accrual, imbalanced treatment arms, and non-protocol treatment strategy. Therefore, a well-designed randomized clinical trial/quasi-experimental study is needed to define NAC's effect on advanced gastric cancer. This quasi-experimental study was designed to evaluate the role of NAC in the treatment of locally advanced GC and explore the optimal strategy for chemotherapy delivery.

Objectives of the Study

To observe the effect of neoadjuvant chemotherapy on down staging and resectability of locally advanced gastric adenocarcinoma at NICRH.

MATERIAL AND METHODS

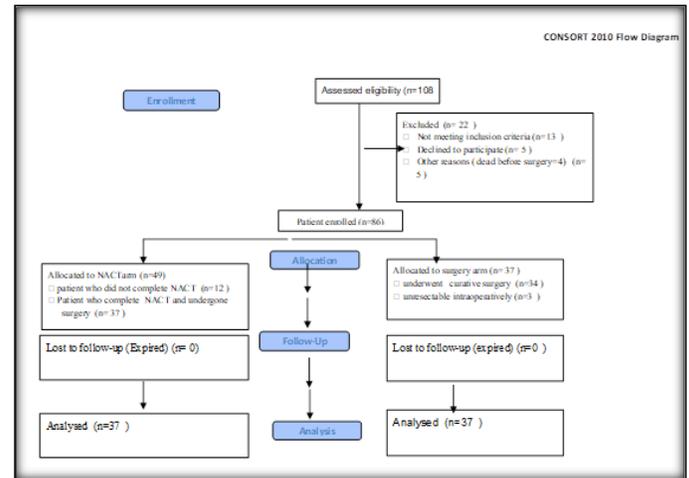
This was a single-center quasi-experimental study conducted in the Department of Surgical Oncology in collaboration with the Departments of Medical Oncology, Radiation oncology, and Pathology at the National Institute of Cancer Research and hospital, Dhaka, which is a tertiary care cancer hospital in Bangladesh, between January 2021 and June 2022. Before initiating the study, approval was obtained from the Institute Ethics Committee (study reference number NICRH/Ethics/2021/82. Written and informed consent was taken from all the participants, and patients were given full freedom to withdraw at any point during the study. Our objectives were to study the down-staging effect of NACT on the Tumor Node Metastasis (TNM) stage and the R0 resection rate with and without NACT. All patients aged 18 years and above with histologically proven adenocarcinoma of the stomach diagnosed by esophagogastroduodenoscopy and biopsy, with stages of T2, T3, T4, any N determined by contrast-enhanced computed tomography (CECT) were assessed for eligibility. The patients excluded were aged more than 80 years and had other coexisting malignancies, distant metastasis, recurrent tumors, and Siewert-Stein Type I, II gastro esophageal junction tumors. The decision on whether the patient received NACT followed by surgery or upfront surgery was decided by a multidisciplinary tumor

board, and they were divided into two groups. Patients in Group II were started on neoadjuvant chemotherapy with XELOX regimen (Injection oxaliplatin 130 mg/m² on day one, oral capecitabine 625 mg/m² on days one to 21) for low or poor ECOG performance status patient patient and FLOT regimen(injection docetaxel 60 mg/m²,oxaliplatin 85mg/m², leucovorin 200mg/m², and 5-flurouracil (2,600 mg/m² as a 24 hr. infusion, all given on day 1 and administered every 2 weeks' thorax, abdomen, and pelvis were done following NACT of three to four cycles to assess response and post-chemotherapy stage of the tumour. Patients underwent distal, subtotal, total gastrectomy, transhiatal oesophago-gastrectomy, D1 plus or D2 lymphadenectomy based on the location of the tumor, and the specimen was sent for histopathological examination. Patients in Group I underwent upfront surgery. Parameters including age, sex, comorbidities, tumor location, tumor size, TNM stage and complications were compared between the two groups. Resection completeness, a number of harvested and positive lymph nodes, and lymph node ratio (LNR) were studied in the histopathological specimen. Pre- and post-NACT stages and response to NACT were assessed using Response Evaluation Criteria in Solid Tumours 1.1 (RECIST) criteria in Group II. The independent variables studied were age, sex, comorbidities, tumor location, Pathological subtype, type of gastrectomy, and extent of lymphadenectomy. The outcome variables studied in Group 1I were pre and post NACT TNM stage and response to NACT by RECIST criteria. Between Group I and II, R0 resection rates, number of lymph nodes dissected and metastatic nodes, lymph node ratio, duration of

surgery, intraoperative blood loss, postoperative complications, and duration of postoperative hospital stay were compared and analyzed. Statistical analysis was done using SPSS 25.0 software version for Windows (IBM Corp., Armonk, NY, USA). The sample size was calculated to be 37 in each Group with an estimated alpha error of 5%, power of 80% and a 12% mean difference in R0 resection rates between the two groups.^[6] Continuous variables were analyzed with the student T-test and Mann Whitney U test as appropriate. Categorical variables were analyzed with the Chi-Square test and Fisher’s exact test as appropriate. Ordinal data such as the TNM stage of the tumor before and after NACT in Group II was compared using the Wilcoxon signed-rank test. P values were derived from 2-sided tests, and a value less than 0.05 was considered statistically significant.

RESULTS

108 patients were assessed for eligibility, between January 2021 to June 2022, out of which 22 patients were excluded from the study.



The remaining 86 patients were distributed into two groups. Group 1, 37 patients underwent surgery alone (surgery arm), and Group 2, 49 patients received neoadjuvant chemotherapy (NACT arm). 37 from the NACT arm were followed up for response assessment CECT. Twenty-nine patients in the NACT arm and 16 patients in the surgery arm underwent curative surgery. Twenty-one patients in the surgery arm and 8 patients in the NACT arm were deemed irresectable intraoperatively and underwent palliative resection.

Table 1: Comparison of patient characteristics between two groups (surgery alone & NACT plus surgery) (N=74).

Parameters	Group 1 (surgery alone n=37)	Group 2 (NACT plus surgery n=37)	Total (N=74)	Pearson Chi-square test (P value)
Sex				
Male	24 (64.86%)	31 (83.78%)	55 (74.32%)	0.062
Female	13 (35.13%)	6 (16.21%)	19 (25.68%)	
Age (Mean±SD)	56±11.06	55.7±10.46		0.382
Personal habit				
Smoking	12 (32.43%)	12 (32.43%)	24 (32.43%)	0.568
Paan, Battle nuts	1 (2.70 %)	3 (8.11%)	4 (5.40%)	
Comorbidities				
DM	7 (18.91%)	3(8.11%)	10(13.51%)	0.519



HTN	2 (5.41%)	2(5.41%)	4(5.41%)	
IHD	2 (5.41%)	1(2.70%)	3(4.05%)	
DM & HTN*	2 (5.41%)	0	2(2.70%)	
DM,HTN& IHD#	0	2(5.41%)	2(2.70%)	
COPD	1(2.70%)	2(5.41%)	3(4.05%)	
Zonal residence				
South coastal zone	12 (32.43%)	14 (37.83%)	26 (35.13%)	
Middle central zone	18 (48.65%)	15 (40.54%)	33 (44.59%)	0.781
North zone	7 (18.92%)	8 (21.62%)	15 (20.27%)	
Economic condition (monthly income in taka)				
>15000<20000	13 (35.13%)	12 (32.43%)	25 (33.78%)	0.300
>20000<30000	17 (45.94%)	11 (29.73%)	28 (37.84%)	
>30000	7 (18.92%)	14 (37.84%)	21 (28.37%)	

DM= diabetes mellitus; HTN= hypertension; IHD= ischemic heart disease; COPD= chronic obstructive pulmonary disease *=DM & HTN,# = DM,HTN& IHD

The mean age of patients in groups 1 & 2 was 56 ± 11.06 and 55.70 ± 10.46 years of age respectively ($p > 0.05$). Majority of the respondents (55/74) were male and 19 patients (26%) were female. Male to female ratio was (24/37 & 31/37) in group 1 and (31/37 & 6/37) groups respectively ($p > 0.05$). More than 24% patients (24/74) were smokers. Four patients (5.4%) were in the habit of paan and betel nut chewing but majority of the patients (45/74) did not have such habits. 24 patients (24/74,32.43%) had diabetes as co-morbidities more in group 2, 10(13.51%). Hypertension was the second leading co-morbidity among them (4/74,5.41%). Three patients (4.05%) did have ischemic heart diseases and three patients (4.05%) reported to have COPD. Four patients (5.4%) have multiple respondents as well. Most of the patients (33/74) were from middle-central part of the country. A considerable number of patients (26/74) were from south coastal zone. Representation from north zone was minimal. Around 38% patients (28/74) had a monthly family income between >15000 to less than 20000 BDT was considered lower socioeconomic group. Twenty-five patients' family income was between <20000 to <300000 BDT lower middle class. Twenty-one patients' monthly family income was over 30000 BDT consider upper middle class.

Table 2: Distribution of the patients by the pathological response after NACT (N=37)

Pathological response	Frequency	percentage	p- value
Complete response	09	24.32	
Partial response	20	54.05	<0 .0001*
Stable disease	03	8.1	
Progressive disease	5	13.51	
Total	37	100.0	

*Non parametric Chi-Square test, p-value

We evaluated response to NACT using standard RECIST 1.1 criteria. The distribution of the patients by the pathological response after NACT followed by surgery is given in the above table. In 9 patients

(24.32%) complete response was noted. Partial response was found in 20 cases (54.05%), p-value (<.0001) while a stable disease was reported in three (8.1%) cases. 5 patients (13.51%) had progressive disease.

Table 3: Comparison of surgical outcome between two groups

Variables	Types	Group		Fisher's Exact test	p-value
		Group 1	Group 2		
Resectability	R0 resection	16 (43.2)	29 (78.4)	13.924	0.001
	R1 resection	19 (51.4)	5 (13.5)		
	R2 resection	1 (2.7)	0 (0.0)		
	Irresectable	1 (2.7)	3 (8.1)		

Group 1= upfront surgery; Group 2=NACT + surgery

In the upfront surgery group, R0 resection was feasible in 16 (43.2%) cases, and in the NACT plus surgery group, R0 resection was done in 29 (78.4%) cases. In group 1, R1 resection was done in considerable numbers (19/37) compared to group 2 (5/37), P=0.001. Three patients (8.1%) in group 2 and one (2.7) in group 1 had irresectable lesions.

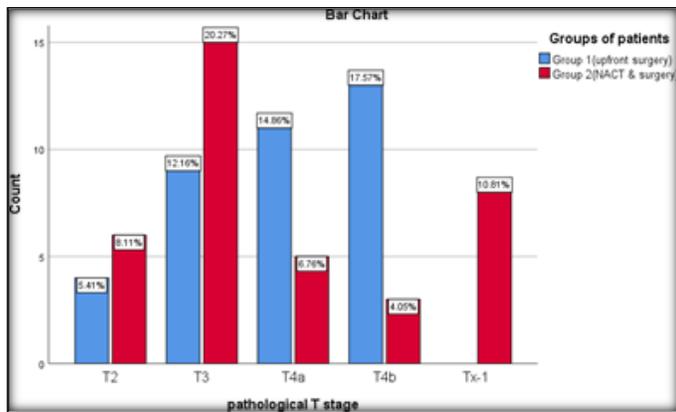


Figure 1: Comparison of pathological T stage between two groups (N=74)

Among T4a and T4b tumors in the NACT arm, 21 patients out of 23 patients (91.30%) downstage to T2 and T3, and 3 patients progressed or stable to T4b making them inoperable. This study found a significant difference in the down-staging effect of NACT on the T stage (p = 0.003). In surgery only arm out of 37 patients, 24 patients (64.86%) are in pathological T4a and T4b stage. (p=0.002)

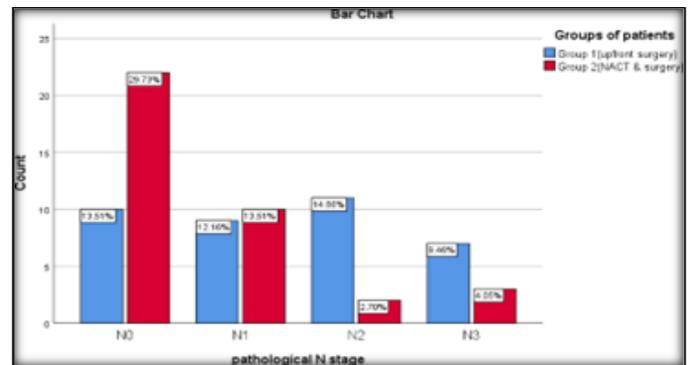


Figure 2: Comparison of pathological N stage between two groups (N=74)

Pathological N stage was comparable between the two groups. In group I, N3 had in 7 patients (9.46%), N2 in 11(29.73%) and 9 patients (24.32%) in N0 in the surgery arm. But in group II, downstaging of N stage seen, N0 in 22 (59.21%) and N1 in 9 (24.32%) respectively with significant p-value =0.001.

DISCUSSION

Neoadjuvant chemotherapy for gastric adenocarcinoma has two different aspects with

respect to the disease state. Administration of chemotherapy regimens before surgery to patients with locally advanced disease may increase the possibility of a curative resection [5,10]. However, in resectable gastric cancers, the administration of neoadjuvant chemotherapy focuses on survival benefits rather than resectability.[5,8] In advanced disease, the effects of preoperative chemotherapy can be followed by computed tomography (CT) to ensure response of primary tumor and perigastric lymph nodes to the administered regimens.[7,8] However, in the cases of resectable gastric cancer, potential concern exists because delaying definite surgical resection may lead to disease progression and unresectability.[5,11,15] In our study, the mean age of patients in group 1 and group II was 56 ± 11.06 and 53.7 ± 10.46 years of age respectively ($p > 0.05$). Male to female ratio was 24/13 and 31/6 in group I and group II respectively ($p > 0.05$). In a similar clinical trial by Hashemzadeh S. et al,[20] showed the mean age of patients in case and control groups was 58.3 ± 9.1 and 59.7 ± 8.7 years of age respectively ($p > 0.05$). Male to female ratio was 15/7 and 41/11 in case and control groups respectively ($p > 0.05$). Out of 37 patients, 9 patients (24.32%) had complete response (CR) was noted, PR was found in 20 cases (54.05%), p-value (< 0.0001) statistically significant while a SD was reported in three (8.1%) cases. Unfortunately, 5 patients (13.51%) had progressive disease (PD). Comparable with Sivacoumarane S. et al,[21] in their study, Out of 47 patients, CR was seen in two patients (4.2%), PR (27.7%), SD (21.3%) and PD (46.8%). There was no significant difference in the down-staging effect of NACT on the T stage ($p = 0.88$). According to Achilli et al,[22] 3% had CR, 34% had PR, 58% had SD and 5% of

patients had PD. The number of PD was more in their study while patients with CR and PR were similar.

Among T4a and T4b tumors in the NACT arm, 29 patients out of 32 patients (93.75%) downstage to T2 and T3, and 3 patients progressed to T4b making them inoperable. This study found a significant difference in the down-staging effect of NACT on the T stage ($p = < 0.03$). Compatible with Sivamourane S. et al,[21] showed a higher proportion of T4a and T4b disease in the NACT group, poor compliance to chemotherapy due to logistic reasons in the patient population may be responsible for disease progression of their cases. The MAGIC trial in the United Kingdom and the trial conducted by the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC) and Fédération Francophone de Cancérologie Digestive (FFCD) in France, have shown better outcomes of NACT with GE junction tumors in concordance with our study. Post NACT, most patients 44 (59.7%) belonged to N1, next N2 17 (18.9%) and 7 (9.5%) down staged to N0 stage, Chi-Square test p value < 0.0001 , significant downstage response. This study had similar outcome with Cunningham D. et al,[23] in their MAGIC trial and FNCLCC and FFCD Multicenter Phase III trial by Ychou M et al,[24] but compatible with Sivamourane S. et al,[21] where N2 included 34 patients (56.7%) in the NACT arm and 21 patients (44.7%) in the surgery arm. N3 included 19 patients (31.7%) in the NACT arm and 21 patients (44.7%) in the surgery arm, reveals no significant downstaging effect.

In this study, the R0 resection rate was higher in the NACT arm compared to the surgery arm (78.42% vs 43.24%) and was statistically

significant ($p=0.001$). Schuhmacher et al. reported a statistically significant R0 resection rate (Z test, $p = 0.036$) of 81.9% in the chemotherapy arm compared to 66.7% in the surgery arm. Cunningham D et al,^[23] in their MAGIC trial reported more R0 resection rate in the perioperative chemotherapy group 79.3% compared to 70.3% in the surgery group. A significant R0 resection rate was also reported in the FNCLCC and FFCD Multicenter Phase III trial by Ychou M et al,^[24] In a meta-analysis by Xu et al,^[25] they reported no significant improvement in the R0 resection rate following NACT (62.86% vs 62.99%, $p = 0.81$). Ramachandra et al. ^[26] reported 87% in the surgery arm and 96% in the chemotherapy arm with no statistical significance ($p = 0.33$). Recently, Sivacoumarane S, et al,^[21] reported, no significant difference in the rate of R0 resection between the two groups (88.2% in NACT group vs 85.1% in surgery group, $P=0.55$). The rate of R0 resection does not significantly improve with neoadjuvant chemotherapy. In view of high progression rates in their study, they suggested that patient selection is required when NACT is planned in carcinoma stomach which are surgically resectable at presentation.

CONCLUSIONS

The present study illustrates that neoadjuvant chemotherapy increases the curability of locally-advanced gastric cancer patients

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because surgical resection is the main curative treatment for gastric cancer. However, it should be addressed that beneficial effects of neoadjuvant chemotherapy in this setting should be confirmed by prospective trials to evaluate disease-free and overall survival rates of patients treated by neoadjuvant chemotherapy and surgery versus surgery alone. The rate of R0 resection significantly improves with NACT. An excellent response to NACT was seen in two third of patients. In view of high progression rates, appropriate selection criteria would be required when NACT is planned for patients with gastric cancer who have a surgically resectable tumour at presentation. We await survival analysis to further validate the role of NACT in patients with locally advanced gastric cancer.

Limitations

Our population subset included most patients from a low socio-economic background who require immense motivation for chemotherapy and subsequent follow-up visits, which may have led to disease progression and treatment defaults. Secondly, this is a quasi-experimental study with a minimum follow-up of 6 months. We are aware that the recurrence would occur in the first 2-5 years. Unfortunately, a large number of patients fail to comply with the follow-up program. Thirdly, it is a single-center study which might be subjected to bias.

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