Article published online: 2021-05-14

Original Article

Does Neoadjuvant Chemotherapy Increase the Survival in Patients with Locally Advanced Gastric Cancer Patients? – A Real-World Evidence

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Abstract

Background: In locally advanced gastric cancer (LAGC), perioperative chemotherapy has shown to improve the survival to a larger extent compared to surgery alone. In India, the treatment followed for gastric carcinoma widely varies based on the type of health-care provider and treatment access. There is a paucity of data on the role of neoadjuvant chemotherapy on survival among LAGC patients in the Indian context. **Aim:** The aim of this study was to compare the disease-free survival (DFS) and overall survival (OS) between neoadjuvant and adjuvant chemotherapies among LAGC patients. **Subjects and Methods:** This was a retrospective cohort study involving clinical record review of LAGC patients enrolled between 2015 and 2017 from four tertiary cancer centers in South India. The date for the following events, namely diagnosis, recurrence, death, and last day of visit, was extracted in a mobile-based open-access tool. The median duration of OS and DFS between the neoadjuvant and adjuvant groups was compared using Kaplan–Meier survival curves. **Results:** Of the 137 patients, 70 (51%) had received neoadjuvant chemotherapy followed by surgery and 67 (49%) had adjuvant chemotherapy following the surgery. The mean (standard deviation) age of participants was 55.4 (11.4) years. Seventy-eight percent of the patients were diagnosed at Stage 3 or 4. Regional lymph nodes were involved in 83.9%. The median duration of follow-up was 15 months. The OS in the neoadjuvant and adjuvant groups was 18.6 months and 8.3 months, respectively. Nonregional lymph node involvement and adjacent organ involvement had independently increased the risk of death. **Conclusion:** Among LAGC patients, the neoadjuvant chemotherapy indicated a better median and DFS compared to the adjuvant group. However, these findings were statistically not significant. The current study has contributed an important finding to the existing evidences of clinical practice in an Indian setting. Further large-scale studies are required to validate the promising trend of using neoadjuvant chemotherapy in LAGC.

Keywords: *Collaborative Medical Oncology Group, D2 lymphadenectomy, gastric carcinoma, stomach neoplasm, Structured Operational Research and Training Initiative*

Introduction

Globally, gastric cancer ranks the fourth most common cancer and second most common cause of cancer-related mortality. Among all cancer-related deaths, 8.2% of deaths occurred due to gastric cancer.[1] Despite the annual 1.45% decrease in the incidence of gastric cancers, every year, an estimated one million gastric carcinomas are diagnosed worldwide[2] and are accountable for 783,000 deaths. More than 50% of the new cases of gastric carcinoma occur in developing countries.[3] The recent Indian Council of Medical Research (ICMR) report based on Indian cancer registry has estimated the incidence of gastric cancer to be approximately 34,000 which is predicted to become 50,000 by 2020.[2] Approximately seven out of ten cases are diagnosed at an advanced stage.[1] The standard treatment for gastric cancer is complete curative resection of the tumor with a standardized D2 lymphadenectomy.[3] Despite curative resection, nearly 50% of the patients recur with a median survival of 12 months.[4,5]

Chemotherapy given during the perioperative period (neoadjuvant and adjuvant chemotherapies) was found to influence the recurrence pattern and survival in locally advanced gastric cancer (LAGC) patients.[6,7] Neoadjuvant chemotherapy may potentially downstage the tumor, treat the micrometastasis, and prevent the new onset of metastatic lesions.[8] Evidence shows that both peri- and postoperative chemotherapies may increase the disease-free survival (DFS) and overall survival (OS) in

How to cite this article: Janarthinakani M, Kalaiselvi S, Priyadarshini R, Arun S, Shashidhar K, Krishnakumar R, *et al*. Does neoadjuvant chemotherapy increase the survival in patients with locally advanced gastric cancer patients? – A real-world evidence. Indian J Med Paediatr Oncol 2020;41:832-40.

Submitted: 24-Apr-2020
Revised: 06-Jul-2020
Accepted: 23-Oct-2020
Published: 31-Dec-2020

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_188_20

Quick Response Code:

LAGC patients.[9,10] Evidence by Cunningham *et al*. based on perioperative chemotherapy trial had shown the 5-year survival rate of 36% for perioperative chemotherapy arm compared to 23% survival among patients who underwent surgery alone.[11]

Depending on the extent of the disease and the patient tolerance level, perioperative chemotherapy is given alone or in combinations with radiotherapy.[12] However, there is a regional difference in the preferred chemotherapy regimen in India due to various factors such as poor access to regional cancer centers (catering to large population), physician preference, affordability issues, and different clinical circumstances. There are several approaches being followed by health-care providers. There is a paucity of evidence in the Indian context, whether these varying treatment approaches with or without neoadjuvant chemotherapy will make a difference in disease progression and survival.[13] The recent ICMR guidelines emphasized the lack of quality evidence on neoadjuvant regimens to guide the standard of care.[14]

Hence, the present study was conducted to compare the effectiveness of neoadjuvant chemotherapy to adjuvant chemotherapy among patients with locally advanced stomach cancer in terms of DFS and OS in selected tertiary care cancer centers in South India.

Subjects and Methods

Study design

This was a retrospective multicentric cohort study involving the review of patients' clinical records.

Study setting

This study was conducted across four centers in South India. These study sites are functioning as corporate hospitals, and the treatment-related expenditures are paid by the patient. As a part of the hospital information system, these centers maintain the patient demographic and clinical characteristics in an electronic as well as paper-based format. The patient management group involves a team of multiple specialists including a medical oncologist, radiation oncologist, surgical oncologist, and surgical gastroenterologist.

The National Comprehensive Cancer Network guidelines are widely followed with the discretion of treating physicians. The process involved in patient care management for locally advanced gastric carcinoma is depicted in Figure 1. The figure explains the chemotherapy types, adjuvant and neoadjuvant chemotherapies, and the duration. The various regimens used in the study are epirubicin + oxaliplatin + capecitabine (EOX), capecitabine + oxaliplatin, 5-fluorouracil (5-FU) + leucovorin calcium, epirubicin + Adriamycin + cisplatin + 5-FU, cisplatin + 5-FU, and 5-FU + leucovorin + oxaliplatin + docetaxel. All the node-positive patients had received radiotherapy with the discretion of a multidisciplinary tumor board.

Study population

The study population included all locally advanced gastric carcinomas (Stage 2 or more) registered for treatment from January 2015 to December 2017 and attended a minimum one follow-up visit after 3 months of treatment in the abovementioned study sites. All eligible patients were followed till February 28, 2019. Patients with metastatic stomach cancer and those who did not undergo gastrectomy or with a previous history of chemoradiotherapy were excluded from the analysis.

Data collection

From each study site, investigators extracted the data in a structured data extraction pro forma. The pro forma included patient characteristics such as age, gender, stage of disease-based computed tomography abdomen and

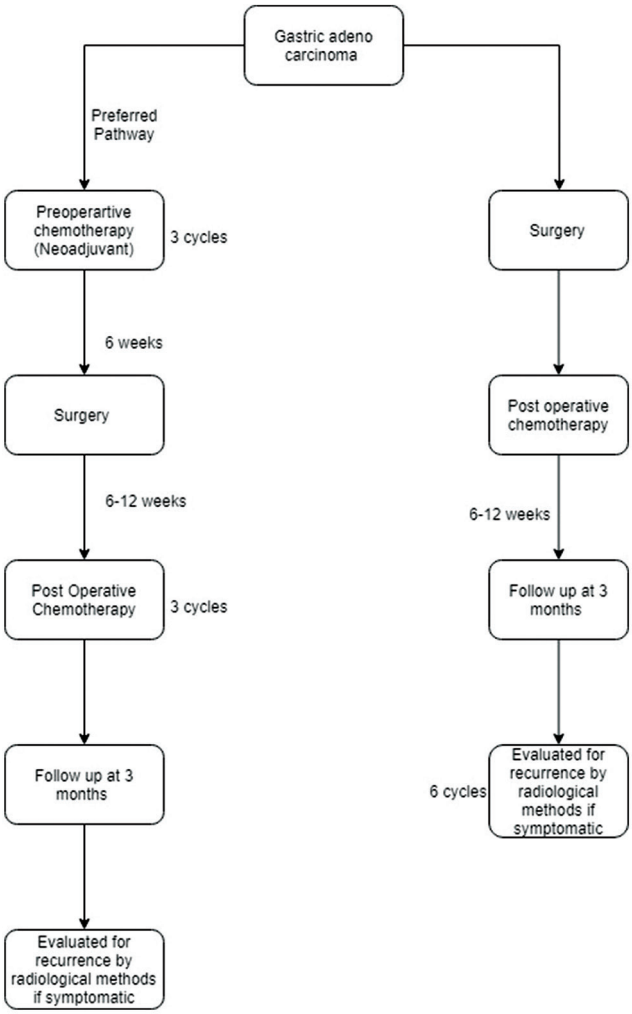

Figure 1: Process involved in patient care management for the locally advanced gastric cancer patients who underwent neoadjuvant and adjuvant chemotherapies during 2015–2017

pelvis, and histopathological examinations. The study also included type of surgery, chemotherapy regimen used, timing of chemotherapy in relation to surgery (neoadjuvant or adjuvant) and number of cycles given, adverse events, date of each visit, and date of recurrence. The definition of the terms used in the present study such as lost to follow-up, radiological response, DFS, and OS is given in Box 1.

Data analysis

Data captured in data extraction pro forma were entered in EpiCollect5 (Imperial College, London). Data were analyzed using Stata (version 14, University of Texas, StataCorp). Continuous variables such as age and tumor size are summarized as mean (standard deviation [SD]). Clinical staging, comorbidities, grade of tumor, and chemoresponses are summarized in terms of frequencies and percentages. Outcomes considered in this study are DFS after surgery and OS after the diagnosis. The database was frozen on February 28, 2019. The duration of survival and DFS is summarized as a median. The difference in duration of DFS was initially analyzed through Kaplan–Meier survival analysis using log-rank test. The hazard ratio (HR) adjusted for background characteristics such as age group, staging, grade of tumor, and mode of treatment was estimated using the Cox proportional hazard model. Factors associated with overall and DFS are presented as adjusted HR (aHR) with a 95% confidence interval (CI).

Ethics approval

Administrative approval was obtained from all the participating institutes for accessing data. Ethics approval was obtained from the Institutional Ethics Committee (IEC) of the GVN Cancer Institute (dated July 30, 2018), Trichy, and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France (EAG number 30/18). As the study involves a review of patient records (secondary data), a waiver for informed consent was sought, and the same was approved by the IEC.

Results

Patient characteristics

A total of 137 patients with LAGC were enrolled in the study. Of the 137 patients, 94 (69.3%) were men. The mean (SD) age was 55.4 (11.4) years, and one-third (35%) were above 60 years. The body of the stomach was the most common site of cancer (23.6%), followed by antrum and pylorus (~17%). About 20% had a tumor at the esophagogastric junction or cardia. Seventy-eight percent were diagnosed at late stage (third or fourth). Regional lymph nodes were involved in 83.9% of the patients. Except for the site of tumor and number of nodal sites involved, other patient demographic and clinical characteristics were found to be similar [Table 1]. Tumor at upper one-third of the stomach (cardia, gastroesophageal junction, and fundus) was more frequently observed in the neoadjuvant group compared to the adjuvant group (64.9% vs. 17.9%, $P < 0.0001$).

Treatment

Of the 137 patients, 51% had received chemotherapy followed by surgery (neoadjuvant) and the remaining had undergone surgery directly. The common chemotherapy regimens given during the neoadjuvant phase were EOX (n = 36; 51.4%) and epirubicin + Adriamycin + cisplatin + 5-FU (n = 30; 42.9%). After surgery, 80% received chemotherapy (adjuvant), of which 25% had received oxaliplatin with capecitabine-based regimen. About 68 patients (49.6%) had undergone partial gastrectomy, and it was more in the adjuvant group (70%) compared to the neoadjuvant group (30%). Overall, 89% had D2 node dissection during surgery. The mean (SD) number of chemotherapy cycles received in the neoadjuvant group was more compared to the adjuvant

Box 1: Operational definition

Locally advanced gastric carcinoma: Stage II-III as per AJCC staging manual 2017

Loss to follow-up: The time point after receiving either of the modalities is 6 months. When the study participant does not turn up for 6 months, it will be considered as loss to follow up

Radiological response

- Complete response: Disappearance of all target lesions
- Partial response: >30% decrease in the sum of the longest diameters of target lesions compared with baseline
- Stable disease: Neither partial response nor progressive disease
- Progressive disease: >20% increase in the sum of the longest diameter of target lesions compared with the smallest sum longest diameter recorded or appearance of one or more new lesions

Regional lymph nodes: Perigastric, paracardial, suprapyloric, infrapyloric, left gastric, celiac, common hepatic, hepatoduodenal, splenic hilar lymph nodes

Disease-free survival: Duration between the date of surgery and onset of new symptoms, clinical manifestations, radiological diagnosis, or cancer-related death

Overall survival: Duration between the date of diagnosis and day of death or last day of follow up whichever is later

AJCC – American Joint Committee on Cancer

Table 1: Comparison of demographic and clinical characteristics between the locally advanced gastric cancer patients who underwent neoadjuvant and adjuvant chemotherapies during 2015–2017

Characteristics	Neoadjuvant therapy group, *n* (%)	Adjuvant therapy group, *n* (%)	*P*
Total	70 (100)	67 (100)	
Gender			
Male	53 (75.7)	42 (62.7)	0.098
Female	17 (24.3)	25 (37.3)	
Comorbidities			
Diabetes	13 (18.6)	11 (16.4)	0.740
Hypertension	13 (18.6)	11 (16.4)	0.740
Coronary artery disease	2 (2.9)	5 (7.5)	0.268
Others	0	3 (4.5)	0.114
Stage			
Second stage	13 (18.5)	17 (25.4)	0.520
Third stage	51 (72.9)	45 (67.2)	
Fourth stage	6 (8.6)	5 (7.5)	
Tumor site			
Cardia	23 (32.9)	4 (6.0)	0.001*
Fundus	16 (22.9)	5 (7.5)	0.012
Body	25 (35.7)	25 (37.3)	0.846
Antrum	20 (28.6)	18 (26.9)	0.824
Pylorus	13 (18.6)	22 (32.8)	0.055*
Lesser curvature	14 (20.0)	4 (6.0)	0.021*
Greater curvature	6 (8.6)	2 (3.0)	0.275
Gastroesophageal junction	11 (15.7)	3 (4.5)	0.046*
Number of tumor sites			
One	35 (50.0)	53 (79.1)	0.001*
Two	17 (24.3)	13 (19.4)	
Three	14 (20.0)	0	
More than three	4 (5.7)	1 (1.5)	
Tumor size mean (standard deviation)	4.88 (2.17)	5.89 (3.62)	0.070
Lymph node involvement			
Nil	5 (7.2)	8 (12.5)	0.494
Regional nodes	62 (89.9)	53 (82.8)	
Nonregional lymph nodes	2 (2.9)	3 (4.7)	
Preoperative imaging			
Yes	64 (97.0)	52 (96.3)	1.000
No	2 (3.0)	2 (3.7)	

group (5.6 [1.2] vs. 4.3 [2.4]; $P < 0.001$). Patients who completed all six cycles of chemotherapy were more in the neoadjuvant group (80.3%) compared to the adjuvant group (50.3). The rate of complete surgical resection (R0 resection: 97% and 91.7%) was similar in both the neoadjuvant and adjuvant groups. Forty percent received radiotherapy after surgery, and it was comparable in both the groups (37% vs. 41%). Patients with pN0 were significantly more in the neoadjuvant group (29% vs. 9%, $P = 0.02$) [Table 2].

Outcome

The median duration of follow-up was 15.5 months, with an interquartile range of 6.6–26.6 months. The recurrence rate was comparable in both the groups (neoadjuvant: 25.6/1000 person-years and adjuvant: 19.2/1000 person-years, $P > 0.05$). The median duration of DFS was 13.3 months in the neoadjuvant group and 10.3 months in the adjuvant group, both of which were not statistically significant [Table 3]. Similarly, the median duration of survival was more in the neoadjuvant group (18.6 months) compared to the adjuvant group (8.3 months) but without statistical significance [Figure 2]. When the DFS was compared across several characteristics, surgical staging, grade of tumor (Grade 3 [aHR: 2] and Grade 4 [aHR: 8.6]), and nonregional lymph node involvement (aHR: 26.6) were found to independently increase the risk of recurrence [Table 4]. Similarly, nonregional lymph node involvement and adjacent organ involvement had independently increased the risk of death. Patients who received at least four cycles of chemotherapy had aHR of 0.28 (95% CI: 0.11, 0.70; $P = 0.006$), and in those who received more than 6 cycles, it was 0.19 (95% CI: 0.08–0.46; $P = 0.001$) [Table 5].

Table 2: Comparison of postoperative treatment outcome between the locally advanced gastric cancer patients who underwent neoadjuvant and adjuvant chemotherapies during 2015-2017

Effect of treatment	Adjuvant therapy group, *n* (%)	Neoadjuvant therapy group, *n* (%)	*P*
Total	67 (100)	70 (100)	
Radiological response			
Complete response	3 (5.8)	12 (18.8)	0.0001
Partial response	19 (36.5)	49 (76.6)	
Stable disease	3 (5.8)	2 (3.1)	
Progressive disease	27 (51.9)	1 (1.6)	
Missing*	15	6	
Type of gastrectomy			
Partial gastrectomy	47 (70.15)	21 (30)	0.0001
Total gastrectomy	14 (20.90)	37 (52.86)	
Sleeve resection	1 (1.49)	0	
Esophagogastrectomy	3 (4.48)	5 (7.14)	
Others	2 (2.99)	7 (10.00)	
Number of chemotherapy cycles			
<6	28 (46.67)	13 (19.70)	0.001
>6	32 (53.33)	53 (80.30)	
<4	20 (33.33)	8 (12.12)	0.004
>4	40 (66.67)	58 (87.88)	
Surgical stage			
pT1	0	2 (2.86)	0.551
pT2	14 (20.90)	16 (22.86)	
pT3	39 (58.21)	39 (55.71)	
pT4	14 (20.90)	13 (18.57)	
Pathological node stage			
pN0	6 (8.96)	20 (28.57)	0.027
pN1	24 (35.82)	18 (25.71)	
pN2	20 (29.85)	20 (28.57)	
pN3	17 (25.37)	12 (17.14)	
Surgical response			
R0	55 (91.67)	64 (96.97)	0.131
R1	5 (8.33)	1 (1.52)	
R2	0	1 (1.52)	
Postoperative chemotherapy			
Yes	55 (82.1)	55 (78.6)	0.731
No	5 (7.5)	8 (11.4)	

pT1 – Tumor invades the lamina propria, muscularis mucosae, or submucosa; pT2 – Tumor invades the muscularis propria; pT3 – Tumor invades adventitia; pT4 – Tumor invades adjacent structures; pN0 – No regional lymph node metastasis; pN2 – Metastases in one or two lymph nodes; pN2 – Metastases in three to six lymph nodes; pN3 – Metastases in seven or more regional lymph nodes; R0 – No residual disease postsurgery; R1 – Microscopic residual disease postsurgery; R2 – Macroscopic residual disease postsurgery

Discussion

The present study is one of the very few studies to congregate evidence and to compare the treatment outcomes of neoadjuvant and adjuvant therapies in locally advanced gastric carcinoma among the Indian population. The present study shows better OS rates and DFS rates in the neoadjuvant group as compared to the adjuvant group. The high pathological staging, tumor grade, and nonregional lymph nodal involvement had independently increased the risk of recurrence and death.

In terms of absolute number of recurrences, the neoadjuvant group had more recurrences. Though it seems to be contradictory to the expected low recurrence in the neoadjuvant group, it is possible due to the following reasons: (1) outcome in cancer survival studies includes the number of events and also the time taken to develop that event. (2) As the survival is more in the neoadjuvant group, the recurrences also logically will be more in the neoadjuvant group.

The study conducted by Cunningham *et al*. (MAGIC trial)[11] has been the pioneering trial that paved the way for administering chemotherapy along with surgery in clinical practice. The 2-year survival documented in the MAGIC trial was 50% and 41% among the neoadjuvant and adjuvant groups, respectively, whereas in our study, it was 81% and 77%, respectively. This could be due to

Table 3: Distribution of median survival and overall survival among the locally advanced gastric cancer patients who underwent neoadjuvant and adjuvant chemotherapies during 2015-2017

Estimate	Adjuvant chemotherapy (*n*=67)	Neoadjuvant chemotherapy (*n*=70)
Overall survival		
Median overall survival time (months)	8.3	18.6
Number of deaths	8	12
Duration followed (months)	919.5	1440.7
Incidence rate for overall survival	8.47/1000 person-months	8.33/1000 person-months
HR	Reference	0.97 (95% CI: 0.39-2.37)
Disease-free survival		
Median disease-free survival (months)	10.3	13.3
Number of recurrence	15	26
Duration followed (months)	780.2	1014
Incidence rate for disease-free survival	19.2/1000 person-months	25.6/1000 person-months
HR	Reference	1.25 (95% CI: 0.66-2.37)

CI – Confidence interval; HR – Hazard ratio

Table 4: Disease-free survival of the locally advanced gastric cancer patients who underwent neoadjuvant and adjuvant chemotherapies during 2015–2017

Variables	Categories	HR^	95% CI	*P*	HR^^	95% CI	*P*
Group	Adjuvant	Reference			Reference		
	Neoadjuvant	1.25	0.66-2.37	0.49	1.46	0.64-3.32	0.372
Sex	Male	Reference			Reference		0.100
	Female	0.58	0.28-1.22	0.15	0.44	0.17-1.17	
Stage	2	Reference					
	3	1.55	0.6-4.0	0.36	-	-	-
	4	2.73	0.57-10.4	0.23	-	-	-
Lymph node involvement	Nil	Reference			2.30	0.31-17.08	0.418
	Regional nodes	2.04	0.40-8.5	0.33	63.65	2.76-1465.90	0.009
	Nonregional lymph nodes	26.6	3.1-225.5	0.003*	Reference		
Adjacent organ involvement	No	Reference			-	-	-
	Yes	0.92	1.3-6.8	0.94	-	-	-
Radiological response	Complete response	Reference			-	-	-
	Partial response	1.67	0.57-4.90	0.35	-	-	-
	Progressive disease	1.58	0.29-8.77	0.6	-	-	-
	Stable disease	1.44	0.45-4.62	0.54	-	-	-
Node dissection	D1	Reference			Reference		
	D2	0.14	0.02-1.18	0.07	0.99	0.05-21.59	0.998
Surgical stage#		1.29	0.79-2.12	0.3			
Pathological nodal stage	pN0	Reference			Reference		
	pN1	0.83	0.31-2.25	0.72	0.76	0.18-3.26	0.711
	pN2	0.86	0.33-2.25	0.77	0.76	0.17-3.41	0.722
	pN3	1.33	0.53-3.30	0.54	1.29	0.29-5.67	0.735
Surgical response	R0	Reference			Reference		
	R1	1.34	0.48-3.83	0.56	3.66	0.95-14.12	0.059
	R2	8.66	1.1-6.70	0.04*	-	-	-
Grade of tumor#		1.67	0.98-2.85	0.06	-	-	-
Number of chemotherapy cycles	<6	Reference					
	>6	0.69	0.32-1.51	0.35	-	-	-
	<4	Reference			-	-	-
	>4	0.87	0.34-2.24	0.78	-	-	-

^Unadjusted risk ratio; **P*<0.05; ^^Adjusted HR; #Risk progression from Stage 1/Grade 1 to one unit increase in subsequent categories. CI – Confidence interval; HR – Hazard ratio; pT1 – Tumor invades the lamina propria, muscularis mucosae or submucosa; pT2 – Tumor invades the muscularis propria; pT3 – Tumor invades adventitia; pT4 – Tumor invades adjacent structures; pN0 – No regional lymph node metastasis; pN2 – Metastases in one or two lymph nodes; pN2 – Metastases in three to six lymph nodes; pN3 – Metastases in seven or more regional lymph nodes; R0 – No residual disease postsurgery; R1 – Microscopic residual disease postsurgery; R2 – Macroscopic residual disease postsurgery

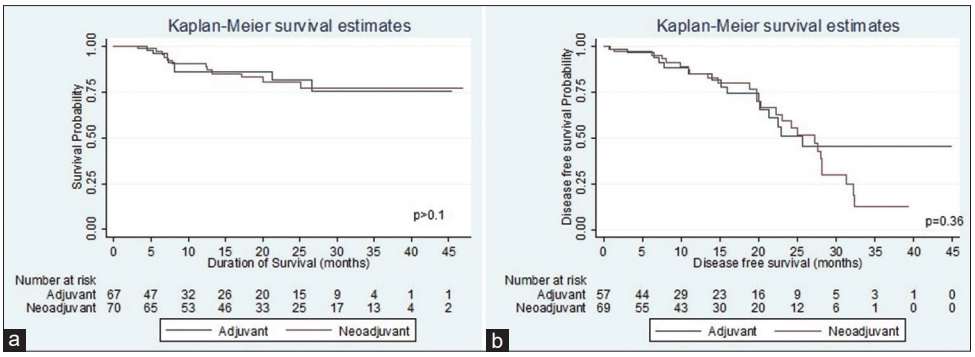

Figure 2: (a) Comparison of overall survival between neoadjuvant and adjuvant chemotherapies in locally advanced gastric carcinoma, South India 2015–2017. (b) Comparison of disease-free survival between neoadjuvant and adjuvant chemotherapies in locally advanced gastric carcinoma, South India 2015–2017

Table 5: Overall survival of the locally advanced gastric cancer patients who underwent neoadjuvant and adjuvant chemotherapies during 2015-2017

Variables	Categories	HR^	95% CI	*P*	HR^^	95% CI	*P*
Group	Adjuvant	Reference			Reference		
	Neoadjuvant	0.97	0.39-2.372	0.94	1.05	0.36-3.00	0.933
Sex	Male	Reference			Reference		
	Female	0.25	0.06-1.07	0.06	0.12	0.01-1.06	0.056
Stage	2	Reference					
	3	0.73	0.24-2.23	0.59	-	-	-
	4	1.07	0.19-5.83	0.94	-	-	-
Lymph node involvement	Nil	Reference			Reference		
	Regional nodes	1.12	0.15-8.5	0.9	0.72	0.09-5.87	0.757
	Nonregional lymph nodes	20.8	2.18-197.9	0.008*	9.14	0.71-117.4	0.089
Adjacent organ involvement	No	Reference			Reference		
	Yes	5.75	1.67-19.8	0.006*	0.19	0.05-0.80	0.023
Radiological response	Complete response	Reference			-	-	-
	Partial response	1.54	0.34-7.04	0.58			
	Progressive disease	4.1	0.57-29.4	0.16			
	Stable disease	0.64	0.09-4.53	0.653			
Node dissection	D1	Reference			-	-	-
	D2	0.36	0.05-2.78	0.3			
Surgical stage	pT1	Reference			Reference		
	pT2	0.19	0.03-1.15	0.07	0.44	0.05-3.58	0.441
	pT3	0.15	0.03-0.70	0.02*	0.32	0.04-2.79	0.302
	pT4	0.23	0.04-1.18	0.08	0.24	0.03-1.98	0.184
Pathological nodal stage	pN0	Reference			-	-	-
	pN1	0.14	0.03-0.66	0.01*			
	pN2	0.48	0.18-1.34	0.16			
	pN3	0.23	0.06-0.87	0.03*			
Grade of tumor#		0.61	0.29-1.30	0.2			
Number of chemotherapy cycles	<6	Reference	-		-	-	-
	>6	0.19	0.08-0.46	0.001*	-	-	-
	<4	Reference			Reference		
	>4	0.28	0.11-0.70	0.006*	0.36	0.10-1.35	0.130

^Unadjusted risk ratio; **P*<0.05; ^^Adjusted HR; #Risk progression from Grade 1 to one unit increase in subsequent categories. CI – Confidence interval; HR –Hazard ratio; pT1 – Tumor invades the lamina propria, muscularis mucosae or submucosa; pT2 – Tumor invades the muscularis propria; pT3 – Tumor invades adventitia; pT4 – Tumor invades adjacent structures; pN0 – No regional lymph node metastasis; pN2 – Metastases in one or two lymph nodes; pN2 – Metastases in three to six lymph nodes; pN3 – Metastases in seven or more regional lymph nodes; R0 – No residual disease postsurgery; R1 – Microscopic residual disease postsurgery; R2 – Macroscopic residual disease postsurgery

better compliance with chemotherapy in our study. Further, in their study, the proportion of patients completing six cycles was 48%, whereas in the present study, 67% had completed all six cycles. From the Indian context, Ostwal *et al*. and Chawla *et al*. had reported the tolerability of newer neoadjuvant chemotherapy regimen (EOX/ECF)

in gastric cancers. The study report by Ostwal *et al*. had reported the median DFS and overall survival to be 31 and 37 months, respectively, in the neoadjuvant group. The survival reported in the current study is less compared to other studies reported from India. This could be due to difference in the distribution of tumor sites and attrition rate.

Our study results are in congruence with other studies like FNCLCC[15-17] which followed the path of the MAGIC trial, testifying favorable survival outcomes for adjuvant and neoadjuvant therapies in gastric cancer.[18] Although the FAMTX trial[19] could not demonstrate better outcomes for neoadjuvant chemotherapy, a meta-analysis on chemotherapy concluded that chemotherapy was advantageous in advanced gastric cancer.[20]

In India, there has been a long-existing disparity in gastric cancer research in general and specifically in the context of therapeutics compared to other Western and Asian countries, as reported by review articles.[18,21] Studies have reported neoadjuvant therapy to be reliable in LAGC and improving outcomes such as resectability rate and survival while reducing recurrence.[22-25] In the recent randomized controlled trial comparing two chemotherapy regimens in the neoadjuvant setting, the median OS at 2 years was 52% and 44% for both the groups.[22] Kushwaha and Vidyarthi reported an improvement in resectability rate following neoadjuvant chemotherapy after 4–6 cycles.[26] In our study, patients receiving at least four cycles of chemotherapy had a reduction in the mortality rate. Our study also found that patients receiving neoadjuvant chemotherapy had statistically insignificant longer median DFS (18.6 vs. 8.3 months) than those receiving adjuvant chemotherapy.

The treatment of LAGC is not uniform in India and varies across centers due to several patient- and health-care provider-related factors. D2 dissection is the standard surgery in gastric carcinoma among the Indian population, and in our study population, more than 80% underwent D2 dissection.[27] In our study, patients with tumors in the cardia received neoadjuvant therapy more often than patients with pylorus tumors. As the prognosis and survival from the proximal site of gastric cancers are inferior, more representation of patients with the cardia site of gastric cancers in the neoadjuvant chemotherapy group could have precluded the statistical significance. This can be explained by the fact that most pyloric tumors present with obstructive features necessitating upfront surgery instead of neoadjuvant chemotherapy and vice versa for the patients with tumor in the cardia.[28,29] Hence, the future randomized control trial has to plan the enrollment with adequate representation from various sites of gastric cancers such as stratified randomization techniques. Due to short follow-up and smaller sample size, the number of adverse events observed was smaller, and there was a nonuniform representation of patients in the type of nodal dissection. Furthermore, as this was a retrospective study, missing data were to the extent of 8%–10%.

Conclusion

In locally advanced gastric carcinoma, perioperative chemotherapy has shown to improve the survival in comparison with surgery alone. The neoadjuvant chemotherapy showed a better median overall and disease-free survival compared to the adjuvant group. Nonregional lymph node involvement and adjacent organ involvement had independently increased the risk of death.

The major limitation of the study was the small sample size which could have contributed to the statistical insignificance. However, the study has contributed important findings to the already existing global and regional evidence. In this study, we have excluded the patients who received few cycles of neoadjuvant chemotherapy but did not undergo surgery due to various reasons including loss to follow-up, disease progression, and worsening performance status. This may give rise to selection bias. However, the number excluded was minimal. Hence, this limitation is unlikely to change the survival estimates. Furthermore, in this study, a higher proportion of patients from neoadjuvant chemotherapy had a tumor at the cardiac site compared to adjuvant chemotherapy. As the prognosis of proximal site gastric cancers is expected to result in a poor survival, this could have precluded the statistical significance. Adverse events due to neoadjuvant chemotherapy can influence the survival pattern. However, this study did not account for any adverse events that occurred during the course of treatment. Despite the limitations, the current retrospective study shows a promising trend toward using neoadjuvant chemotherapy in LAGC patients. The researchers recommend similar studies in larger settings with robust randomization based on the influencing factors. High-quality evidence is the need of the hour to bring about changes in the current guidelines of gastric cancer management.

Acknowledgments

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by the Special Program for Research and Training in Tropical Diseases at the World Health Organization. The training model is based on a course developed jointly by the International Union Against Tuberculosis and Lung Disease (The Union) and Medécins sans Frontières (Doctors Without Borders). The specific SORT IT program which resulted in this publication was jointly developed and implemented by Fenivi Research Solutions Private Limited, Chennai, India; The Union South-East Asia Office, New Delhi, India; and the Center for Operational Research, The Union, Paris, France. Mentorship and the coordination/facilitation of this particular SORT IT program were provided through

Fenivi Research Solutions Private Limited, Chennai, India; The Union South-East Asia Office, New Delhi, India; the Center for Operational Research, The Union, Paris, France; Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; All India Institute of Medical Sciences, Nagpur, India; and Velammal Medical College Hospital and Research Institute, Madurai, India. The specific SORT IT program which resulted in this publication was based on the data shared by the members of Collaborative Medical Oncology Group, India. Dr. Jegan Niwas Kannan and S. Mahalakshmi provided support in data extraction/analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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