Conversion Therapy in Gastric Cancer – Curative Intent in Stage IV Patients is Beneficial

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Abstract

Background

Stage IV Gastric cancer is associated with a poor prognosis and is often managed with palliative chemotherapy. Conversion therapy in gastric cancer is a growing concept in the treatment of stage IV gastric cancer, wherein an R0 resection is attempted following neoadjuvant chemotherapy. The present study aimed to evaluate the role of conversion therapy in gastric cancer.

Methods

Retrospective analysis of a surgical database was performed. Clinically stage IV patients who received chemotherapy were divided into Group 1 with R0 resection (conversion surgery group) and Group 2 without R0 resection (Stage IV noncurative). Upfront operated stage III patients were identified as Group 3. The primary endpoint was overall survival.

Results

The database included 212 gastroesophageal patients, of which 47 patients were eligible for conversion therapy. Group 1 included 26 patients, Group 2 21 patients and Group 3 43 patients. The overall survival of Group 1 was significantly higher when compared with Group 2 (p-value: 0.03; HR: 2.14 with 95% CI: 1.04 -4.39). The overall survival in Group 3 was higher when compared to Group 1 but did not attain statistical significance (p-value: 0.30; HR: 1.44 with 95% CI: 0.71 – 2.90).

Conclusion

Stage IV gastric cancer has improved survival and offers a chance at potential cure if R0 resection is achieved after neoadjuvant chemotherapy. This group of patients have similar survival to upfront resected stage III gastric cancer patients treated with curative intent.

Introduction

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related mortality worldwide.[1] Surgical resection is the mainstay of treatment and offers the only hope of a cure. However, unlike in Japan, the absence of screening protocols for gastric cancer in various countries leads to a delayed presentation where surgical resection may not be feasible, and chemotherapy is often offered as palliative chemotherapy.[2, 3] Presentation with non-specific symptoms and delays in referral for endoscopy further contribute to delayed diagnosis and advanced stage on presentation.[4, 5]

According to the National Cancer Database, the median survival of clinical-stage IV (T4b and M+) gastric cancer patients is 6-7 months.[6] An analysis of Shizuoka Cancer Centre data has shown that the median survival of clinical-stage IV patients increases to 13.3 months after curative or palliative surgery.[6] The REGATTA trial studied the role of gastrectomy in the presence of metastasis but found no advantage over chemotherapy alone. The trial, however, did not perform an R0 resection, and lymphadenectomy was restricted to D1.[7] This has led to the development of the concept of conversion therapy in gastric cancer. It is defined as the use of chemotherapy followed by surgical resection of a tumour that was previously considered unresectable or metastatic.[8]

The present study aimed to evaluate the benefit of conversion surgery in stage IV gastric cancer patients at a tertiary care centre.

Methodology

A retrospective analysis of the gastro-oesophageal cancer surgical oncology database at a single institute was performed. Patients with histologically proven stage IV, adenocarcinoma of the stomach, clinically unresectable (T4b) or with limited metastasis (M1), who received neoadjuvant chemotherapy and underwent surgery with a preoperative curative intent were considered eligible as conversion therapy. Stage IV patients that underwent R0 resection were identified as conversion surgery population (Group 1), and stage IV patients who underwent R1, R2 or no resection were identified as Group 2. Patients with histologically proven adenocarcinoma of the stomach operated upfront without neoadjuvant chemotherapy and pathologically stage III was identified as curative stage III population (Group 3). Limited metastasis included para-aortic node involvement, resectable liver metastasis and resectable focal peritoneal involvement. Curative surgery was defined as gastrectomy (Distal, Subtotal, Proximal or Total) with D2 lymphadenectomy and resection of other involved sites achieving an R0 resection.

The primary study endpoint was overall survival. Secondary endpoints included disease-free survival and factors influencing survival in the conversion surgery population. Overall survival was defined as the period from the date of diagnosis to the last follow-up or death date. Disease-free survival was defined as the period from the date of surgery to the date of last follow-up, recurrence or death. Mortality was defined as death due to any cause.

Statistical analysis was performed using STATA software Version 11 (StataCorp LP, TX). Survival data were analysed using Kaplan-Meier survival estimates. The overall survival was compared using the cox proportional hazards. Factors influencing overall survival in the conversion surgery population was analysed using the log-rank test.

The institutional ethics committee approved the study protocol. The study was conducted per the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline.

Results

From April 2016 to May 2021, 212 gastro-oesophageal cancer patients underwent surgical intervention. Forty-seven patients were diagnosed as clinically stage IV, advised neoadjuvant chemotherapy and planned for surgery with a preoperative curative intent. Among these, 26 patients achieved R0 resection (55.3%) and were identified as Group 1, and 21 patients (44.7%) were identified as Group 2. Group 3 included 43 patients. **[Figure 1]**

The median age of the conversion surgery population (n=26) was 53 years (Range: 23 – 70) with a male to female ratio of 1.6:1. Pancreatic involvement (61.5%) was the most common cause of classifying as clinically stage IV. EOX (Epirubicin, oxaliplatin and capecitabine) and DOX (Docetaxel, oxaliplatin and capecitabine) regimens were used most commonly as the neoadjuvant regimen (38.5% each). **[Table 1]** Post-surgery, most patients were staged as ypStage III (50%). **[Table 2]** One patient (3.8%) had postoperative mortality.

In Group 1, after a median follow-up of 17.4 months, 15 patients (57.7%) had died. The median overall survival was 18.4 months, with a 3-year overall survival rate of 28.5%. **[Table 3]** The overall survival of Group 1 was significantly higher when compared with Group 2 (p-value: 0.03; HR: 2.14 with 95% CI: 1.04 -4.39). **[Figure 2A]** The overall survival in Group 3 was higher when compared to Group 1 but did not attain statistical significance (p-value: 0.30; HR: 1.44 with 95% CI: 0.71 – 2.90). **[Figure 2A]** The disease-free survival was also higher in Group 3 when compared to Group 1 but did not attain statistical significance (p-value: 0.09; HR: 1.76 with 95% CI: 0.90 – 1.76). **[Figure 2B]**

The median overall survival in Group 1 on using DOX and EOX regimen was 29.7 and 17.7 months, respectively, which was significantly better compared to the 9.6 months with FLOT regimen (p-value: 0.004). Age, gender, histological differentiation, lymphovascular invasion, perineural invasion, lymph node ratio and perinodal extension were not found to influence survival in the conversion surgery population. **[Table 4]**

Discussion

The study included 47 patients eligible for conversion surgery. Most of the patients had pancreatic involvement (55.3%) followed by para-aortic node involvement (21.2%). R0 resection was achieved in 26 patients (55.3%). The overall survival in stage IV patients with R0 resection was significantly higher than those who did not have an R0 resection with a 3-year survival rate of 28.5% and 5.9%, respectively (p-value: 0.03). The overall and disease-free survival of stage IV patients with R0 resection was not statistically different from stage III upfront curative patients.

Stage IV gastric cancer is associated with a dismal prognosis, and the treatment is limited in most cases to palliative chemotherapy.[9] Several chemotherapy regimens have been studied in advanced gastric cancer, and based on the SPIRITS trial, S1 plus cisplatin is now considered the first-line option in Japan. [10] Despite the advances in chemotherapy protocols, the median overall survival in stage IV gastric cancer remains less than one year, with the intent of treatment still being considered palliative.[11,12] Surgery is the only modality that can offer a chance to cure gastric cancer but is often not feasible in advanced gastric cancer. The addition of targeted agents to chemotherapy has shown benefits, but it is still not a curative option.[13,14]

Surgery in advanced gastric cancer is usually recommended for symptom palliation, palliative resections for bleeding or bypass procedures for outlet obstruction.[15] Surgery as a means to decrease the tumour burden has been studied. The REGATTA trial evaluated the role of upfront gastrectomy in patients with a single non-curative factor without addressing the metastatic lesions and adequate lymphadenectomy. No survival benefit was seen in performing gastrectomy prior to chemotherapy compared to chemotherapy alone.[7] This has led to the development of conversion therapy, a novel approach to treat advanced gastric cancer patients. Patients are subjected to neoadjuvant chemotherapy followed by surgery to attain R0 resection.

Several investigators have evaluated the role of conversion therapy in advanced gastric cancer. **[Table 5]** The median overall survival in patients undergoing conversion therapy has ranged from 11 months to as high as 62 months.[8,16] The studies have included a heterogeneous group of patient populations, including T4b lesions, para-aortic nodes, limited peritoneal metastasis, positive peritoneal cytology, resectable hepatic metastasis and ovarian metastasis. The focus of these studies has been to achieve an R0 resection and has consistently shown a significant survival benefit over patients treated with chemotherapy alone.[8,17–19]

Yoshida et al. have classified advanced gastric cancer into four categories. Categories one and two include technically resectable metastasis and marginally resectable metastasis, respectively. These categories of patients are suitable to be considered as candidates of conversion therapy and advised neoadjuvant chemotherapy. Category three and four include potentially unresectable and non-curative metastasis involving peritoneum and other organ metastases. Categories 3 and 4 are usually not considered as candidates for conversion surgery.[20]

Attaining R0 resection is the single most important prognostic factor in conversion therapy.[18] The R0 resection rates in patients undergoing surgical intervention after neoadjuvant chemotherapy has been reported to range from 24 – 100%.[8,17,21–26] The presence of a single noncurative factor is associated with higher rates of R0 resection.[16] The R0 resection rate in the present study was 55.3 % which was similar to several other studies.[17,19,26]

The median overall survival of patients with a successful conversion surgery in the present study was 18.4 months, significantly higher than the patients treated with chemotherapy alone. Though the median overall survival was less when compared to the stage III population, the difference was not statistically significant. This indicates that the conversion surgery cohort is a group of patients with good biology that behaves similar to the stage III population. Clinic-pathological characteristics did not significantly correlate with survival outcomes of stage IV patients with R0 resection in the present study. Along with R0 resection, several studies have identified tumour size less than 5cm, downstaging of the nodal stage, complete or partial response of metastatic sites, one noncurative factor and a decrease in CEA levels to be associated with good prognosis in patients undergoing conversion therapy.[16,27–30]

The choice of a chemotherapy regimen in conversion therapy has not been uniform in most studies. As most of the studies have been reported from Japan, S1 has been a component of most trials.[16,19,24,28,31] Few investigators have studied the role of specific chemotherapy regimens, but there is no head to

head comparison of different regimens.[22,32,33] The present study showed a significant survival advantage of EOX and DOX regimen over FLOT, but this could be biased due to the small sample size. Institutional guidelines may be followed in deciding the optimal chemotherapy regimen for conversion therapy.

The present study carries several limitations. The study is a retrospective analysis of the surgical oncology database and does not include data pertaining to patients that did not respond to neoadjuvant chemotherapy. The cohort is a biologically heterogeneous group, and the small sample size limits the evaluation of surgical protocol. Patient treatment decisions were made on a case by case basis after discussion in the institutional tumour board and therefore had a lack of uniformity in chemotherapy regimens, number of cycles and timing of surgery.

In conclusion, stage IV gastric cancer, after neoadjuvant chemotherapy, if R0 resection is achieved, confers an improved survival and offers a chance at a potential cure. This group of patients have similar survival to upfront resected stage III gastric cancer patients treated with curative intent. Further studies are required to consolidate the optimal chemotherapy regimen and identify the patient population that would benefit most from conversion therapy.

Declarations

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Tables

Table 1: Patient characteristics of study groups

Characteristic	Group1 n=26	Group 2 n=21	Group 3 n=43
Age (Median)	53 years (Range: 23 – 70)	55 years (Range: 35 – 74)	57 years (Range: 30 – 80)
Gender (Male: Female)	16:10	14:7	28:15
ECOG			
0	3 (11.5%)	2 (9.5%)	4 (9.3%)
1	18 (69.2%)	14 (66.7%)	35 (81.4%)
2	1 (3.8%)	4 (19.0%)	1 (2.3%)
Unknown	4 (15.4%)	1 (4.8%)	3 (6.9%)
Co-morbidities			
Hypertension	3 (11.5%)	2 (9.5%)	13 (30.2%)
Coronary artery disease	2 (7.7%)	1 (4.8%)	2 (4.6%)
Diabetes Mellitus	1 (3.8%)	1 (4.8%)	1 (2.3%)
Hypothyroidism	1 (3.8%)	-	4 (9.3%)
Clinical stage			
IVA	22 (84.6%)	11 (52.4%)	-
IVB	4 (15.4%)	10 (47.6%)	
Stage IV features			
Pancreatic involvement	16 (61.5%)	10 (47.6%)	
Diaphragm involvement	5 (19.2%)	1 (4.8%)	
Liver involvement	4 (15.3%)	2 (9.5%)	
Aorta involvement	1 (3.8%)	-	-
Transverse colon	-	1 (4.8%)	
Para-aortic nodes	3 (11.5%)	7 (33.3%)	
Liver metastasis	1 (3.8%)	1 (4.8%)	
Peritoneal metastasis	-	1 (4.8%)	
Neoadjuvant regimen ^a			
EOX	10 (38.5%)	6 (28.6%)	
DOX	10 (38.5%)	9 (34.6%)	-
FLOT	5 (19.2%)	5 (19.2%)	
PC	1 (3.8%)	1 (4.8%)	
Procedure			
Distal gastrectomy	4 (15.4%)	3 (14.3%)	20 (46.5%)
Subtotal gastrectomy	6 (23.1%)	1 (4.8%)	8 (18.6%)
Proximal gastrectomy	2 (7.7%)	-	1 (2.3%)
Total gastrectomy	14 (53.8%)	1 (4.8%)	14 (32.5%)
Gastro-jejunostomy	-	6 (28.6%)	-
Feeding jejunostomy	-	2 (9.5%)	-
Exploration alone	-	8 (38.1%)	-
Operative duration	265 min (SD: +/- 53 min)	129 min (SD: +/- 95 min)	272 min (SD: +/- 85 min)
Blood loss	271 ml (SD: +/- 148ml)	116 ml (SD: +/- 104ml)	306 ml (SD: +/- 172ml)
30-day Postop-mortality	1 (3.8%)	-	2 (4.6%)

^aDOX: Docetaxel, oxaliplatin and capecitabine; EOX: Epirubicin, oxaliplatin and capecitabine; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; PC: Paclitaxel and carboplatin

Table 2: Histopathological characteristics of group 1 and group 3

Characteristic	Group1 n=26	Group 3 n=43
Differentiation		
Well differentiated	3 (11.5%)	7 (16.3%)
Moderately differentiated	5 (19.2%)	7 (16.3%)
Poorly differentiated	15 (57.7%)	25 (58.1%)
Unknown	3 (11.5%)	4 (9.3%)
Lymphovascular invasion		
Yes	15 (57.7%)	37 (88.1%)
Unknown	3 (11.5%)	1 (2.3%)
Perineural invasion		
Yes	18 (69.2%)	29 (69.0%)
Unknown	3 (11.5%)	1 (2.3%)
Lymph node ratio	Median 0.15 (Range: 0 – 0.92)	Median 0.3 (Range: 0.02 – 0.89)
Extra-nodal extension		
Yes	6 (23.1%)	27 (62.7%)
Unknown	16 (61.5%)	2 (4.6%)
pT		
T1	-	1 (2.3%)
T2	5 (19.2%)	-
T3	16 (61.5%)	15 (34.5%)
T4	5 (19.2%)	27 (62.8%)
pN		
N0	4 (15.4%)	-
N1	8 (30.8%)	3 (6.9%)
N2	4 (15.4%)	6 (13.9%)
N3	10 (38.5%)	34 (79.1%)
pStage		
I	2 (7.7%)	-
II	8 (30.8%)	-
III	13 (50.0%)	43 (100%)
IV	3 (11.5%)	-

Table 3: Comparison of survival data of different groups

	Group 1 Conversion surgery n=26	Group 2 Noncurative Stage IV n=21	Group 3 Curative Stage III n=43
Median follow up	17.4 months (4-59)	9.3 months (4-29)	15 months (1-62)
Mortality	15 (57.7%)	16 (76.2%)	17 (39.5%)
Recurrence	8 (30.7%)	-	8 (18.6%)
Median Overall survival	18.4 months	11.5 months	31.4 months
3 year overall survival	28.5%	5.9%	36.8%
Median Disease-free survival	12.4 months	-	28.6 months
3 year Disease-free survival	22.3%	-	28.8%

Table 4: Factors influencing overall survival in the conversion surgery group (log-rank test)

Factor	n	Mortality	Median overall survival (months)	p-value
Age (n=26)				0.89
Age<50	10	5	17.7	
Age≥50	16	10	18.4	
Gender (n=26)				0.86
Male	16	9	20.8	
Female	10	6	17.7	
Neoadjuvant regimen (n=26)				0.004
EOX	10	4	17.7	
DOX	10	5	29.7	
FLOT	5	5	9.6	
PC	1	1	NR*	
Differentiation (n=23)				0.93
Well	3	2	29.7	
Moderate	5	3	17.1	
Poor	15	7	18.4	
Lymphovascular invasion (n=23)				0.18
Yes	15	10	NR	
No	8	3	17.1	
Perineural invasion (n=23)				0.83
Yes	18	10	18.4	
No	5	3	15.2	
Lymph node ratio (n=24)				0.78
<0.5	21	12	18.4	
≥0.5	3	2	15.2	
Perinodal extension (n=10)				0.55
Yes	6	4	18.4	
No	4	1	17.7	

*NR: Not reached

Table 5: Review of studies on conversion surgery in gastric cancer

Author, Year	Country	No. of patients ^a	Unresectability characteristics					Neoadjuvant Chemotherapy	D2 dissection (%) ^b	R0 resection (%)	Median OS (months)
			T4b	Para-aortic nodes	Peritoneal metastasis	Liver metastasis	Others				
Yano et al. 2002[26]	Japan	33	12 (36.4%)	10 (30.3%)	26 (78.8%)	4 (12.1%)	1 (3.0%)	5-FU + epirubicin + methotrexate + cisplatin (or) pirarubicin +5-FU + leucovorin + cisplatin + mitomycin C.	NR	24.2%	NR
Ishigami et al. 2008[18]	Japan	18	-	8 (44.4%)	9 (50%)	5 (27.8%)	-	S1 + Paclitaxel	83.3%	77.8%	25.7
Suzuki et al. 2009[34]	Japan	20	3 (15%)	9 (45%)	6 (30%)	6 (30%)	1 (5%)	S-1 + Docetaxel	NR	45%	28.5
Satoh et al. 2012[35]	Japan	44	2 (4.5%)	7 (15.9%)	15 (34.1%)	4 (9.1%)	1 (2.3%)	S1 + Cisplatin	82%	59%	19.2
Kanda et al. 2012[28]	Japan	28	9 (32.1%)	15 (53.6%)	7 (25%)	4 (14.3%)	-	S1 alone (or) S1 + cisplatin (or) S1 + paclitaxel (or) S1 + irinotecan	60.7%	92.9%	29.0
Han et al. 2013[27]	Korea	34	-	15 (44.1%)	5 (14.7%)	4 (11.8%)	1 (2.9%)	5-FU + Platinum (or) Taxane + 5-FU + Platinum	100%	76.5%	22.9
Kim et al. 2014[36]	Korea	18	-	-	18 (100%)	-	-	5-FU + cisplatin (or) Titanium silicate1 + cisplatin.	100%	55.6%	37.0
Saito et al. 2014[31]	Japan	13	2 (15.4%)	4 (30.8%)	3 (23.1%)	-	4 (30.8%)	S1 + Cisplatin	100%	81.2%	53.0
Ito et al. 2015[30]	Japan	14	-	2 (14.3%)	12 (85.7%)	-	2 (14.3%)	S1 alone (or) S1 + cisplatin (or) S1 + docetaxel (or) Paclitaxel	NR	100%	24.8
Fukuchi et al. 2015[16]	Japan	40	6 (15%)	14 (35%)	11 (27.5%)	5 (12.5%)	-	S1 + cisplatin (or) S1 + paclitaxel	NR	80%	62.0
Sato et al. 2017[24]	Japan	33	7 (21.2%)	18 (54.5%)	9 (27.3%)	6 (18.2%)	5 (15.2%)	Docetaxel + cisplatin + S-1 therapy	100%	85%	47.9
Mieno et al. 2017[32]	Japan	31	8 (25.8%)	18 (58.1%)	8 (25.8%)	5 (16.1%)	-	Docetaxel + cisplatin + S-1 therapy	61.3%	74%	56.1
Yamaguchi et al. 2018[19]	Japan	84	72 (85.7%)	28 (33.3%)	35 (41.7%)	20 (23.8%)	-	Docetaxel + cisplatin + S-1 therapy	NR	51%	41.3
Einama et al. 2017[37]	Japan	10	1 (10%)	5 (50%)	2 (20%)	1 (10%)	1 (10%)	S-1 alone (or) S-1 + cisplatin (or) S-1 + docetaxel	100%	100%	29.0
Morgagni et al. 2018[23]	Italy	33	8 (24.2%)	11 (33.3%)	2 (6.1%)	2 (6.1%)	-	ECF (or) DOX	91.9%	66.7%	38.0
Beom et al. 2018[17]	Korea	101	2 (1.9%)	35 (34.6%)	55 (54.5%)	11 (10.9%)	20 (19.8%)	Platinum + fluoropyrimidine (or) Taxane + fluoropyrimidine (or) Platinum + Taxane + fluoropyrimidine	75.2%	56%	26.0
Solaini et al. 2019[38]	Italy	45	-	3 (6.7%)	38 (84.4%)	4 (8.9%)	-	Cisplatin + 5-FU (or) ECF (or) DOX	91.1%	67%	15.0
Li et al. 2019[39]	China	81	-	60 (74.1%)	8 (9.8%)	4 (8.8%)	3 (3.7%)	Oxaliplatin + 5-FU or DOX	NR	81.4%	15.9
Ramos et al. 2019[8]	Brazil	16	10 (62.5%)	4 (25%)	1 (6.2%)	1 (6.2%)	-	Capacetabine + Platinum (or) mFLOX (or) Capacetabine + oxaliplatin (or)	81.3%	81.3%	11.3

								paclitaxel + carboplatin			
Present study	India	26	26 (100%)	3 (11.5%)	-	1 (3.8%)	-	DOX (or)EOX (or) FLOT	100%	55.3%	18.4

^aNo of patients undergoing surgical intervention after neoadjuvant chemotherapy. ^bPercentage represents the number of patients undergoing D2 dissection among curative surgeries. ^cMedian overall survival (OS) of patients undergoing R0 resection. NR: Not reported; ECF: Epirubicin + Cisplatin + 5-FU; DOX: Docetaxel + Oxaliplatin + Capacetabine; EOX: Epirubicin + Oxaliplatin + Capacetabine; FLOT: 5-FU + Leucovorin + Epirubicin + Oxaliplatin + Docetaxel.

Figures

Figure 1

Consort flow of study groups.

Figure 2

Kaplan-Meier survival curves. **A:** The overall survival in Stage IV R0 resection (Group 1) is significantly higher than Stage IV noncurative (Group 2) with a p-value of 0.03. No statistical difference was seen in Stage IV R0 resection (Group 1) and Stage III Curative (Group 3) with a p-value of 0.30. **B:** No statistical difference was seen in the disease-free survival of Stage IV R0 resection (Group 1) and Stage III Curative (Group 3) with a p-value of 0.09.