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Pathological N3 Stage (pN3/ypN3) Gastric Cancer: Outcomes, Prognostic Factors and Pattern of Recurrences After Curative Treatment

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ABSTRACT

Background. pN3 or ypN3 stage gastric cancers (GCs) are known to have aggressive clinical behaviour. This study aimed to investigate factors affecting survival and pattern of recurrences of N3 stage GCs, treated with curative intent.

Methods. A total of 196 GC patients, operated on at the Tata Memorial Centre from 2003 to 2017 and reported as pN3 or ypN3 status on histopathology after D2 gastrectomy were included in this retrospective analysis.

Results. On multivariate analysis, use of NACT (neoadjuvant chemotherapy) and LN ratio (≤ 0.5/> 0.5) emerged as significant predictors for long-term survival. Patients who received NACT but were still harbouring N3 nodes (ypN3; $n = 102$) had a worse prognosis than those operated on upfront (pN3; $n = 94$), with a median survival of 19 months versus 24 months respectively ($p = 0.003$). The 5-year overall survival of the entire cohort was 16.3% (95% CI 12.8–19.8%), while 5-year disease-free survival (DFS) was 14.6% (95% CI 12.6–20%). Adjuvant chemoradiotherapy, though offered in a small number of patients (n = 38) resulted in improvement in DFS. Median DFS of adjuvant CT versus adjuvant CRT was 13 months versus 23 months ($p = 0.020$). The commonest site of relapse was the peritoneum (49.18%) and incidence of isolated loco-regional failure was 10.7%.

Conclusion. In GCs with N3 stage determined after radical D2 gastrectomy, LN ratio of > 0.5 and ypN3 status are predictors of poor prognosis. Considering the high incidence of peritoneal and loco-regional relapse in these patients, the role of more radical surgery, adjuvant chemoradiotherapy after upfront resection and intraperitoneal chemotherapy should be evaluated in prospective randomized clinical trials.

According to Globocan 2018 data, gastric cancer (GC) is the 4th most common cancer worldwide and 3rd most common leading cause of cancer-related deaths[1]. As per several cancer registry systems, lymph node (LN) positive GCs form more than 50% of all cases. As survival significantly decreases with increasing number of metastatic nodes, accurate categorization of lymph nodal status is most crucial. In the AJCC (American Joint Committee on Cancer) 8th edition, the number of positive LNs determines the nodal stage for GC. N3 nodal stage includes patients with 7 or more positive LNs, which is further sub-classified as N3a (7–15 positive LNs) and N3b (16 or more positive LNs). To accurately categorize patients in pN3 and ypN3

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(post neoadjuvant therapy) stage, radical resection and complete D2 lymphadenectomy along with thorough pathological evaluation are of paramount importance.[2]

Margin negative resection and D2 lymphadenectomy remain the prime determinants affecting outcome in localized GCs, apart from the stage and tumour biology, in the era of perioperative chemotherapy.[3,4] Although there remains some debate as regards the most optimum form of lymph node dissection, randomized control trials, and meta-analysis of these trials have clearly shown the survival benefit with D2 lymphadenectomy.[5,6] Hence, Japanese as well as several other international guidelines recommend D2 lymphadenectomy as a standard of care.[7,8] Also, there is some evidence suggesting benefit after extended lymphadenectomy (D2+) for selected indications.[9]

Despite curative resection with appropriate nodal dissection (D2 or D2+) along with neoadjuvant or adjuvant therapy, relapse at loco-regional, peritoneal and other distant sites is not uncommon. N3 disease characterized by a heavy burden of nodal metastasis is known to portend an extremely poor prognosis.[10] The recurrence rate in these patients, even with pT1 status, can be as high as 50% with N3a stage and reach up to 80% with N3b stage.[11]

This study aimed to identify factors affecting long-term survival in GCs after curative treatment for N3 stage disease. We also assessed patterns of relapse to explore and propose treatment options to minimize recurrences in these patients.

MATERIAL AND METHODS

Study Population

Data were retrospectively collected from a prospectively updated GC database, maintained by the Gastrointestinal and Hepato-Pancreato-Biliary (GI & HPB) surgery division, Department of Surgical Oncology at Tata Memorial Centre, Mumbai, India. The study period was from January 2003 to December 2017.

Inclusion Criteria All patients with resectable GC, who underwent distal-subtotal/total/proximal gastrectomy with D2 lymphadenectomy with curative intent and pathologically proven N3 disease (positive LN 7 or more) according to AJCC 8th edition, and without distant metastasis, were included in the study, i.e. stages IIB, IIIA, IIIB and IIIC.

Exclusion Criteria

- Any other histology apart from adenocarcinomas such as gastric lymphoma, sarcoma, or carcinoma in situ
- pN0, pN1, or pN2 disease (post resection)
- Metastatic disease diagnosed on CECT (contrast-enhanced computed tomography) or diagnostic laparoscopy, or detected intraoperatively
- Recurrent GC
- Palliative resections for symptoms
- Lymphadenectomy less than D2

Preoperative Assessment

A multidisciplinary team, comprising a GI & HPB surgical oncologist, a radiologist, a medical oncologist, a radiation oncologist, and a pathologist was involved in planning management. All the patients were evaluated with upper GI endoscopy, CECT thorax, abdomen and pelvis. Locally advanced GC patients (cT3/T4 and/or cN+) underwent staging laparoscopy to exclude peritoneal metastasis. Peritoneal fluid was collected for cytological assessment during laparoscopy.

Treatment

After a thorough evaluation, the management plan for all patients was discussed in the multidisciplinary tumour board. Patients with locally advanced disease were offered neoadjuvant chemotherapy (NACT) and the most commonly used regimen was EOX (epirubicin/oxaliplatin/capecitabine) or ECF (epirubicin/oxaliplatin/5flurouracil),[12,13] while those who were suspected of having early disease or presented with significant gastric outlet obstruction, tumour perforation, or significant bleeding (more than 3 transfusions in a week or significant drop in haemoglobin and inability to control bleeding with angioembolization) were offered upfront surgery. Also, patients with advanced age and poor general condition were offered upfront surgery as they were unfit to receive neoadjuvant chemotherapy at that point in time. The surgical procedures performed were proximal gastrectomy, distal/subtotal gastrectomy, or total gastrectomy along with D2 or D2+ lymphadenectomy (stations 12, 13, 14a, 14v, and/or 15, 16a1, 16a2, 16b1) on an individual case basis (in addition to the standard D2 dissection) depending on location and extent of the primary lesion, baseline and/or post-chemotherapy imaging and intraoperative assessment of nodal disease. Distal pancreatosplenectomy (DPS) or splenectomy alone, was performed selectively when deemed necessary to achieve complete nodal clearance. Adjuvant chemotherapy (ECF/EOX in those who received NACT and CAPOX—capecitabine/oxaliplatin, in those operated upfront) or chemoradiotherapy (CRT) was offered after discussion in the multidisciplinary tumour board.[14] Patients who had prolonged postoperative recovery due to

complications or those who denied/defaulted for any reason, could not receive any form of adjuvant therapy.

Follow-Up

All the patients were kept under follow up with physical examination, tumour marker (carcinoembryonic antigen-CEA, carbohydrate antigen-CA 19.9), and abdominal ultrasound at regular intervals of 3 months for the first 2 years and 6 months for the next 3 years. Imaging (CECT of chest, abdomen and pelvis) or upper GI endoscopy were also used when clinically indicated.

Recurrence

First reporting of recurrence on imaging or presence of ascitic or pleural fluid (confirmed for the presence of malignant cells of GC origin on cytology evaluation) with or without the presence of symptoms or rise in tumour marker levels, was considered as the date of first recurrence. All the sites of recurrences on imaging were noted. Recurrences were categorized into 3 main categories: (a) loco-regional recurrences, including recurrences at the anastomotic site and regional lymph nodes in the post-gastrectomy bed, (b) distant recurrences, including visceral organs (liver, lung, cytology positive pleural effusion), distant organs (skin, brain, bone) and nonregional nodes, (c) peritoneal recurrences, including peritoneal deposits, cytology positive ascites, ovarian deposits (Krukenberg tumours) and serosal deposits on abdominal viscera. Recurrences were categorized as early or late depending on duration from completion of treatment to detection of recurrence being either less than or more than 1 year. Patients detected with recurrence were discussed in a multidisciplinary tumour board and planned for treatment depending on type of recurrence and the patient's general condition. Loco-regional recurrences amenable to re-resection were planned for salvage surgery after preoperative chemotherapy. EBRT (external beam radiotherapy) was considered for localized disease not amenable to surgery, along with chemotherapy. Patients who were not candidates for any type of salvage treatment were treated with palliative intent (palliative chemotherapy). Best supportive care was offered to patients who were not fit for any type of cancer-directed therapy.

Survival and Statistical Analysis

OS (overall survival) was defined as the time elapsed between date of diagnosis (date of registration, if diagnosis was established before presenting to our institute) and death or date of last contact. DFS (disease-free survival) was calculated from the date of surgery to the date of first recurrence. OS and DFS were plotted by Kaplan Meier estimates. Statistical analysis was performed with SPSS v23 software: univariate analysis was conducted using a log-rank test. Multivariate analysis was conducted on significant variables of univariate analysis by using Cox's proportional hazard model. Log-rank tests were applied to find the cut-off values of continuous variables [i.e. age, lymph node yield, lymph node ratio (LNR)—number of positive nodes/total nodes dissected] to define 2 subgroups of significantly different outcomes.

RESULTS

A total of 1796 patients underwent radical gastrectomy (distal subtotal/total/proximal) during the study duration, out of which 228 patients had N3 stage on final histopathology. Thirty patients were identified as having metastatic disease either preoperatively or intraoperatively, or underwent less than a D2 dissection, hence were excluded. Additionally, 2 more patients were excluded as they had other known malignancies apart from GC. Hence, 196 patients were eligible for final analysis.

Median age (± SD) of the study population was 53 years (± 12.8) (range 18–83 years), with a male to female ratio of 2.5:1. Demographic characteristics, treatment details, perioperative outcomes and pathological outcomes are highlighted in Table 1.

DPS was required in 4 patients and 3 required splenectomies alone, to achieve complete nodal clearance. D2+ lymphadenectomy was performed in 4 patients depending on preoperative imaging or intraoperative findings. Postoperative major complications developed in 8.2% of cases and there was one postoperative mortality due to intra-abdominal sepsis secondary to duodenal stump blowout. The median hospital stay was 9 days. Seventeen (8.6%) patients could not receive any adjuvant therapy due to delayed postoperative recovery or mortality. Data on planned treatment completion was available for 115 patients, and of these, 74.8% completed adjuvant treatment.

Of the total, 102 patients (52.04%) received NACT, while 94 patients (47.96%) were operated on upfront. The median LN yield was 22 (SD ± 9.86) and the median positive LN per patient was 11 (SD ± 6.53). The 5-year OS of the entire cohort was 16.3% (95% CI 12.8–19.8%), while the median survival was 20 months (SE 1.748) (95% CI). The 5-year DFS was 14.6% (95% CI 12.6–20%) while the median DFS was 14 months (SE 1.732) (95% CI). The median follow-up duration was 17 months (mean 23 months).

TABLE 1. Demographic characteristics, treatment details and perioperative & pathological outcomes

Patient demographic profile			
1	Age	Mean (range)	53.48 years (18-83)
2	Gender	Male	141 (71.9%)
		Female	55 (28.1%)
3	Ethnicity	Asian (Indian subcontinent)	196 (100%)
4	ECOG performance status	0	24 (12.25%)
		1	164 (83.67%)
		2	8 (4.08%)
5	BMI	Mean (range)	21.39 (13.1-31.6)
6	ASA	I	106 (54.1%)
		II	51 (26.0%)
		III	8 (4.1%)
		NA	31(15.8%)
Treatment details			
1	Neoadjuvant	NACT	102(52.04%)
		No NACT	94 (47.96%)
2	Surgery	Proximal gastrectomy	13(6.63%)
		Subtotal gastrectomy	130(66.33%)
		Total gastrectomy	53(27.04%)
3	Lymphadenectomy type	D2	192(97.96%)
		D2+	4 (2.04%)
4	Adjuvant	Adjuvant chemo	141(71.93%)
		Adjuvant Chemoradiotherapy	38(19.39%)
		No adjuvant treatment	17(8.67%)
Perioperative outcomes			
1	Blood loss	Median (range)	600ml (150-2650 ml)
2	Postop hospital stay	Median (range)	9 days (3-56 day)
3	Elective/emergency	Elective	181 (92.3%)
		Emergency	15 (7.6%)
4	Complications - Clavien Dindo grade	Grade I and II	34 (17.3%)
		Grade III and IV	16 (8.2%)
		Grade V	01 (0.51%)
Pathological outcomes			
1	pT Stage	ypT0	1 (0.51%)
		pT1/ypT1	3 (1.53%)
		pT2/ypT2	11 (5.61%)
		pT3/ypT3	96 (48.98%)
		pT4/ypT4	85 (43.37%)
2	pN stage	pN3a/ypN3a	150 (76.53%)
		pN3b/ypN3b	46 (23.47%)
3	LVI	Present	112 (57.14%)
		Absent	84 (42.86%)
4	PNI	Present	67 (34.18%)
		Absent	129 (65.82%)
5	PNE	Present	28 (14.29%)
		Absent	168 (85.71%)
6	Signet ring pathology	Present	85 (43.37%)
		Absent	111 (56.63%)
7	Histological grade	Poorly differentiated	167 (85.20%)
		Moderately differentiated	29 (14.80%)

TABLE 1. continued

8	Resection (R) status	R0	172 (87.76%)
		R1	24 (12.24%)
9	Tumour regression grade (TRG) (only for those patients who received NACT $n = 102$)	TRG 1	1 (0.98%)
		TRG 2	4 (3.92%)
		TRG 3	21 (20.59%)
		TRG 4	26 (25.49%)
		TRG 5	19 (18.63%)
		Not available	31 (30.39%)

ECOG Eastern Cooperative Oncology Group, *BMI* body mass index, *ASA* American Society of Anaesthesiologists, *NACT* neoadjuvant chemotherapy, *pT stage* pathological tumour stage, *pN stage* pathological nodal stage, *LVI* lymphovascular invasion, *PNI* perineural invasion, *PNE* perinodal extension

By applying log-rank tests, on univariate analysis, the total LN yield (≤ 20 or > 20), LN ratio (≤ 0.5 or > 0.5), ECOG (Eastern Cooperative Oncology Group) performance status, and use of NACT were factors significantly affecting long-term survival (Table 2). On multivariate analysis including factors that were significant on univariate analysis (Table 2), only NACT and LN ratio retained their significance as predictors for long-term survival.

The 5-year OS of patients with LN ratio ≤ 0.5 was 26.6% (SD $\pm$ 6.7) while for an LN ratio of > 0.5 it was 9.7% (SD $\pm$ 3.4%) ($p < 0.001$). Survival curves according to LN ratio and NACT are shown in Fig. 1.

Adjuvant CT was administered in 141 patients, while 38 patients received adjuvant CRT. The median OS in the adjuvant CT group was 21 months versus 24 months in the adjuvant CRT group ($p = 0.170$). Median DFS in the adjuvant CT group was 13 months versus 23 months in the adjuvant CRT group ($p = 0.020$). In the subgroup analysis of patients who received NACT followed by adjuvant treatment ($n = 94$), the median DFS in the adjuvant CT group was 10 months as against 8 months in the adjuvant CRT group ($p = 0.429$). Similarly, in patients who underwent upfront surgery and received adjuvant treatment ($n = 85$), median DFS in the adjuvant CT group was 18 months versus 49 months in those who received adjuvant CRT ($p = 0.052$) (Fig. 2).

Recurrence

There were 122 (62.25%) relapses and the recurrence patterns of patients, with their relative numbers, are described in Table 3 and Fig. 3. Loco-regional relapse was observed in 10.7%, distant relapse in 20.9% and peritoneal metastasis in 30.6% of patients.

DISCUSSION

Outcomes of GC, especially with locally advanced disease, have improved over the past two decades with standardization of surgery and utilization of multimodality treatment in the form of adjuvant and neoadjuvant therapy. Although in Europe perioperative chemotherapy forms the standard of care, either using a 3-drug (ECF) regimen or newer 4-drug (FLOT) regimen,[13,15] postoperative chemoradiation remains the mainstay of treatment in America.[16] In Asia, the practice varies in different regions and mainly includes postoperative or perioperative chemotherapy.[14,17,18]

Optimal treatment strategies for N3-stage GC are yet to be established, as most of the studies either do not include these patients separately, or the number of patients analysed is smaller; hence, they are treated in the same manner as other localized GCs. These patients are considered potentially for curative treatment, but achieving R0 resection (especially clearance of complete nodal disease) can be challenging. Also, they are likely to require extended resections with associated higher perioperative morbidity and hence the treatment completion rate can be low. In the MAGIC and CRITIC trials, patients with N3 disease were reported to have a lower percentage of their planned treatment completion rate.[13,19] In the present study, data on treatment completion was not available in 81 (41.3%) patients, because the study covered a long period of time with inconsistent documentation on treatment completion in the early period. In the remaining 115 patients, 29 (25.2%) either could not receive or complete the planned adjuvant therapy due to various reasons.

In an Asian study, the 5-year OS rate for patients with stages N3a and N3b were 40.1% and 24.7%, respectively,[20] while another older study showed 5-year survival rates for N3a and N3b patients as 23.1% and 5.4%, respectively, after D2 lymphadenectomy.[21]

TABLE 2. Factors predicting long-term survival

Variable	Group	*N* (%age)	5 Year OS (SE)	*p* value	5 Year DFS (SE)	*p* value
Age (years)	< 60	132 (76.35%)	12.8% (SE 3.9%)	0.409	12.3 (4.1)	0.025
	≥ 60	64 (32.65%)	25.4% (SE 6.7%)		25.2 (7.6)	
Sex	Male	141 (71.9%)	17.4% (SE 4.2%)	0.210	19.3 (4.5)	0.68
	Female	55 (28.1%)	16.0% (SE 5.6%)		9.9 (6.0)	
ECOG	0	24 (12.25%)	24.3% (SE 9.4%)	0.047	26 (10.9)	0.027
	1	164 (83.67%)	16.2% (SE 3.9%)		15.4 (4.1)	
	2	8 (4.08%)	NA		NA	
Tumour size	≤ 5 cm	100 (51.02%)	18.9% (SE 4.8%)	0.546	16.9 (5.2)	0.891
	> 5 cm	96 (47.96%)	14.5% (SE 4.9%)		16.2 (5.3)	
Tumour location (epicentre)	Proximal	11 (5.61%)	NA	0.315	NA	0.243
	Body	115 (58.67%)	15.1% (SE 4.1%)		15.1 (4.3)	
	Distal	70 (35.72%)	20.5% (SE 6.5%)		17.5 (6.9)	
Extent of gastric resection	Proximal	13 (6.63%)	16.9% (SE 10.9%)	0.080	17.9 (11.3)	
	Subtotal	130 (66.33%)	22.8% (SE 4.6%)		22.1 (5.1)	0.025
	Total	53 (27.04%)	NA		NA	
Signet ring histology	Present	85 (43.36%)	15.7% (SE 4.9%)	0.257	17.4 (5.5)	0.250
	Absent	111 (56.63%)	18.0% (SE 4.7%)		16.0 (5.0)	
p N stage	N3a (7–15)	150 (76.53%)	18.7% (SE 4.2%)	0.220	16.3 (4.2)	0.695
	N3b (≥ 16)	46 (23.47%)	10.6% (SE 5.3%)		18.8 (7.6)	
LN retrieved	≤ 20	83 (42.35%)	13.0% (SE 4.5%)	0.021	13.0 (5.9)	0.261
	> 20	113 (57.65%)	18.8% (SE 4.9%)		18.4 (4.8)	
LN ratio	≤ 0.50	82 (41.84%)	26.6% (SE 6.7%)	0.0003	19.7 (5.7)	0.099
	> 0.50	114 (58.16%)	9.7% (SE 3.4%)		13.7 (4.8)	
Tumour differentiation	Moderate	29 (14.80%)	29.4% (SE 11.6%)	0.107	18.3 (9.2)	0.217
	Poor	167 (85.20%)	14.5% (SE 3.5%)		16.6 (4.1)	
NACT	Yes	102 (52.04%)	3.3% (SE 2.8%)	0.003	NA	0.000026
	No	94 (47.96%)	30.7% (SE 5.8%)		30.8 (6.2)	
LVI	Yes	112 (57.14%)	11.8% (SE 4.6%)	0.269	14.3 (5.2)	0.799
	No	84 (42.86%)	21.6% (SE 5.2%)		18.6 (5.3)	
PNI	Yes	67 (34.18%)	22.6% (SE 6.4%)	0.661	20.1 (6.2)	0.915
	No	129 (65.82%)	13.6% (SE 4.0%)		14.3 (4.6)	
PNE	Yes	168 (85.71%)	14.2% (SE 3.5%)	0.156	14.1 (3.9)	0.119
	No	28 (14.29%)	31.7% (SE 9.2%)		29.8 (10.3)	
Margin status	R0	172 (87.76%)	15.2% (SE 3.6%)	0.425	15.1 (3.8)	0.608
	R1	24 (12.24%)	25.8% (SE 10.6%)		31.0 (12.7)	
Adj treatment (n = 179)	Adj CRT	38 (19.39%)	22.1% (SE 8.1%)	0.170	37.7 (9.5)	0.020
	Adj CT	141 (71.94%)	12.3% (SE 4.3%)		7.6 (4.2)	
Positive LN stations	D1	75 (38.27%)	22.7% (SE 6.0%)	0.167	21.7 (6.7)	0.550
	D2	121 (61.73%)	14.4% (SE 3.9%)		13.9 (4.3)	
pT stage	T1–T2	15 (7.65%)	NA	0.455	NA	
	T3	96 (48.98%)	15.9% (SE 4.5%)		17.3 (4.9)	0.872
	T4	85 (43.37%)	16.2% (SE 6.2%)		14.9 (5.8)	

Variable	HR	SE	Significance
Multivariate analysis of significant variables in the equation			
ECOG	**1.499**	**.235**	**0.085**
NACT	1.631	.179	0.006
LN ratio	1.777	.192	0.003
Total LN yield	0.890	.188	0.535

SE standard error, *OS* overall survival, *DFS* disease free survival, *ECOG* Eastern Cooperative Oncology Group, *NA* not applicable, *LN* lymph node, *NACT* neoadjuvant chemotherapy, *LVI* lymphovascular invasion, *PNI* perineural invasion, *PNE* perinodal extension, *pT stage* pathological tumour stage, *pN stage* pathological nodal stage, *Adj CT* adjuvant chemotherapy, *Adj CRT* adjuvant chemoradiotherapy, *HR* hazard ratio

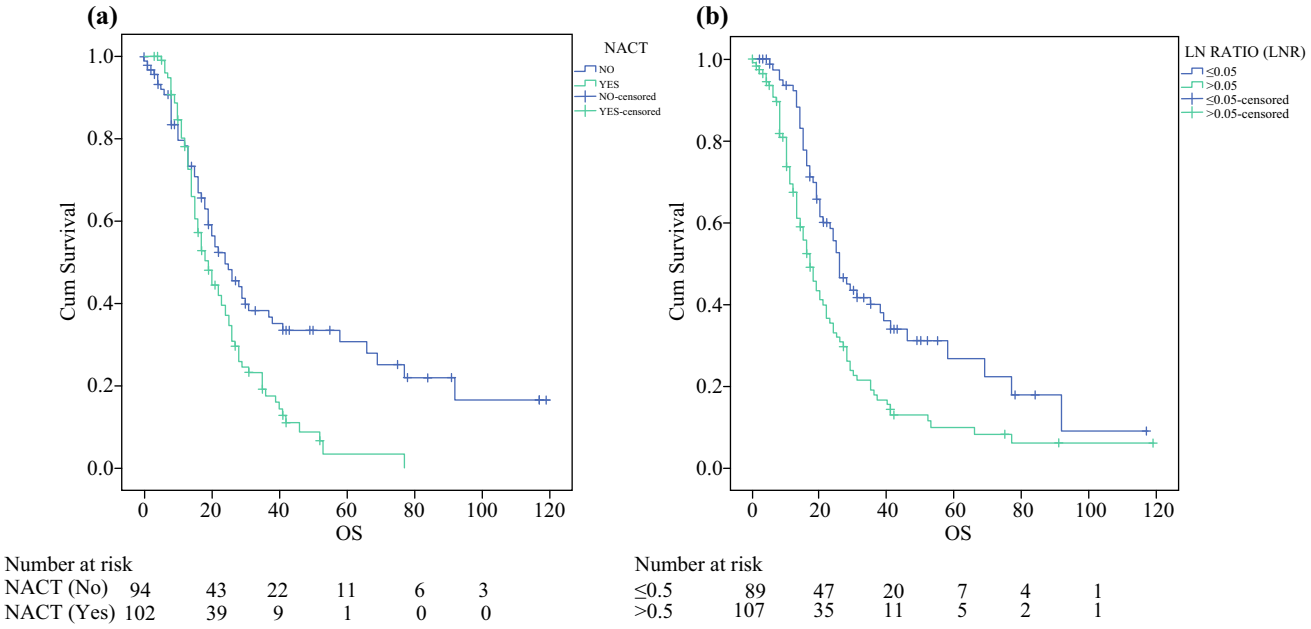

FIG. 1. Survival curves according to **a** NACT, **b** LNR (*NACT* neoadjuvant chemotherapy, *LNR* lymph node ratio)

In the present series, 5-year OS for N3a and N3b nodal stages were 18.7% and 10.6%, respectively. The 5-year OS of the entire cohort was 16.3% (95% CI 12.8–19.8%), which is less than that reported by Li et al.[22] in his study (22.8%), and can be attributed to the different types of neoadjuvant and adjuvant treatments used in our study population.

The current study observed that LN ratio of > 0.5 and ypN3 status (post NACT) are the only factors having an adverse impact on long-term survival in pathological N3 stage. The prognostic importance of the LN ratio has also been reported previously by other studies.[10,23] The median survival of patients operated on without NACT (upfront surgery), i.e. pN3, was 24 months, as against 19 months in patients with NACT, i.e. ypN3 ($p = 0.003$). In the AJCC 8th edition, yp stage (post neoadjuvant pathological stage) was designated considering that the estimated survival of these patients is likely to be different from those who were operated on upfront, because p stage is significantly affected by neoadjuvant treatment. So far, only one study has compared survival of patients with pTNM against ypTNM with stage matching for GC, and concluded that ypTNM stage had a worse prognosis when compared with those with a similar pTNM stage.[24] Also, ypN stage, but not the graded histological response after chemotherapy, is known to predict survival more accurately in patients undergoing curative resections after NACT.[25,26] Because the nodal stage is the primary determinant of TNM stage in the absence of metastatic disease, GC patients in whom N3 status persisted even after NACT (owing either to a very high burden of positive LNs at presentation or due to poor response to NACT) are thus expected to have an even worse prognosis and survival compared with those operated on upfront with a similar stage. These results should never be interpreted as upfront surgery being better in N3 stage GC. All patients who present with cN3 status should receive NACT before resection, as per the current guidelines.

Evaluating the pattern of recurrences in our study, in the 122 patients who relapsed, 21 (17.22%) failed at a loco-regional site alone, either at the anastomotic site or in regional nodes. The remaining developed distant metastasis with the most frequent site of relapse being the peritoneum, observed in 60 patients (49.18%). Isolated peritoneal relapse occurred in 35 (28.69%) patients. Most peritoneum alone and loco-regional recurrences occurred within the 1st year of treatment completion (Fig. 4), suggesting a possible role of additional therapy in these patients. Metastasis to distant and visceral organs or non-regional nodes was the second most common site of metastasis, affecting 41 patients (33.61%). In a study evaluating treatment strategies for N3 GC, the isolated loco-regional relapse rate was 16.9% which is comparable to our study.[27] There remains incongruity in the reporting of recurrence patterns by various studies, which can be attributed to differences in patient populations, neoadjuvant and adjuvant treatment protocols used, and evaluation methods used for recurrence detection. In another study that specifically evaluated recurrence patterns of stage III GC, the most common relapse site was peritoneum (33.2%), followed by loco-regional failure (23.8%) and distant failure (19.9%).[28]

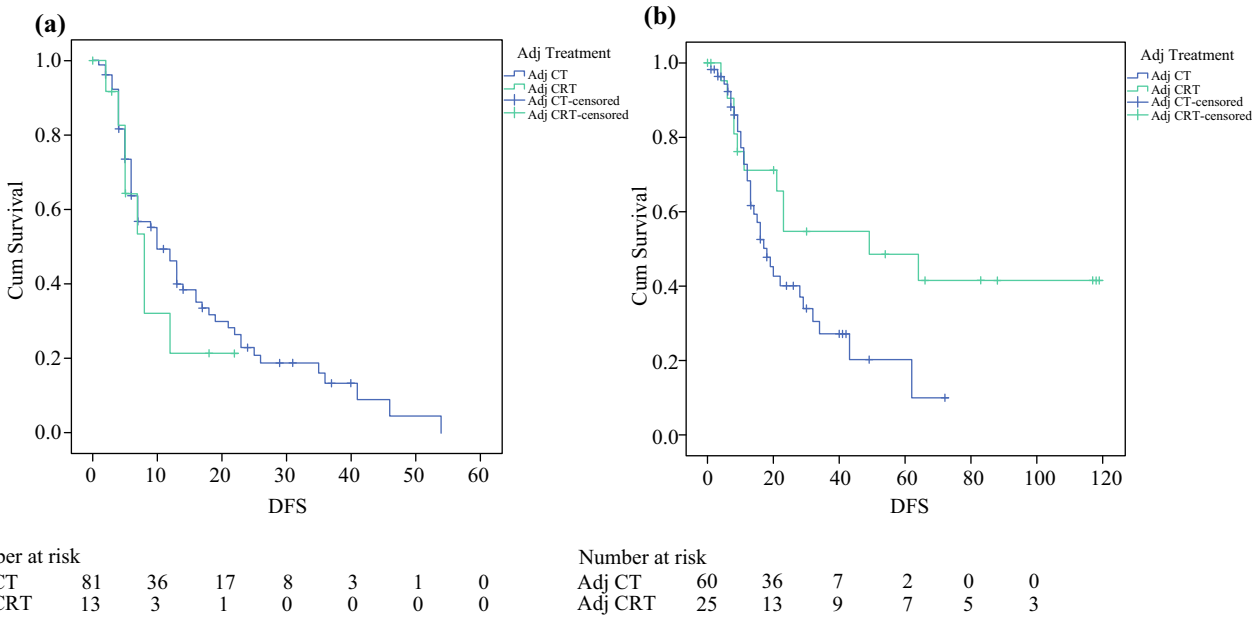

FIG. 2. Disease-free survival curves comparing adjuvant CRT versus adjuvant CT in **a** Post NACT, **b** upfront surgery (*CRT* chemoradiotherapy, *CT* chemotherapy, *NACT* neoadjuvant chemotherapy)

TABLE 3. Pattern of recurrences

S. no	Categories of recurrences	Site of recurrences	*n*	% Of total	% Of relapse	Total
1	Loco-regional only (LR)	Anastomotic site	13	6.63%	10.66%	21
		Regional node	08	4.08%	6.56%	
2	Distant metastasis (DM)	Visceral and distant organs	21	10.71%	17.21%	41
		Nodal	14	7.14%	11.48%	
		Both	6	3.06%	4.91%	
3	Peritoneal	Only peritoneal	35	17.86%	28.69%	60
		Peritoneal + DM	13	6.63%	10.66%	
		Peritoneal + LR	12	6.12%	9.84%	
	Total	All recurrences	122	62.25%	–	

An approach to minimize loco-regional recurrences in N3 stage GC could involve adoption of more radical surgery by performing aggressive LN dissection. In a Chinese study of N3 stage GC, the extent of lymphadenectomy was one of the independent prognostic factors affecting long-term survival (HR = 1.725, 95% CI 1.111–268, $P = 0.015$). The authors concluded that at least 30 LNs should be removed and examined for N3 stage patients and extended lymphadenectomy, i.e. D2 LN dissection plus PAND (para-aortic node dissection), may improve overall survival for GC patients in N3 stage.[29] The present study could not assess the impact of extended lymphadenectomy and PAND on outcomes, as very few patients underwent D2+ dissection.

To mitigate the problems of loco-regional recurrences after radical surgery, adjuvant chemoradiotherapy (CRT) has been evaluated as an option. The INT-0116 trial demonstrated a clear survival benefit of adjuvant CRT; however, adjuvant CRT was compared against observation, which is not the present standard of care. Also, since 90% of the patients underwent D1 resection in this trial, adjuvant CRT probably neutralized the negative impact of suboptimal lymphadenectomy.[16] The ARTIST trial, which investigated the role of adjuvant CRT versus CT alone in patients who underwent D2 lymphadenectomy showed that addition of RT to CT did not significantly improve survival; however, in the subgroup of patients with node-positive disease, combined treatment was superior to CT alone ($P = 0.0365$), and the statistical significance was retained at multivariate analysis ($P = 0.0471$).[30] In both these studies, prior therapy (NACT) was not administered. The results of the CRITICS trial, comparing adjuvant CRT with adjuvant CT in patients who received NACT and adequate surgical resection, did not show any benefit with adjuvant CRT, although 51% of patients in the trial had LN positive disease.

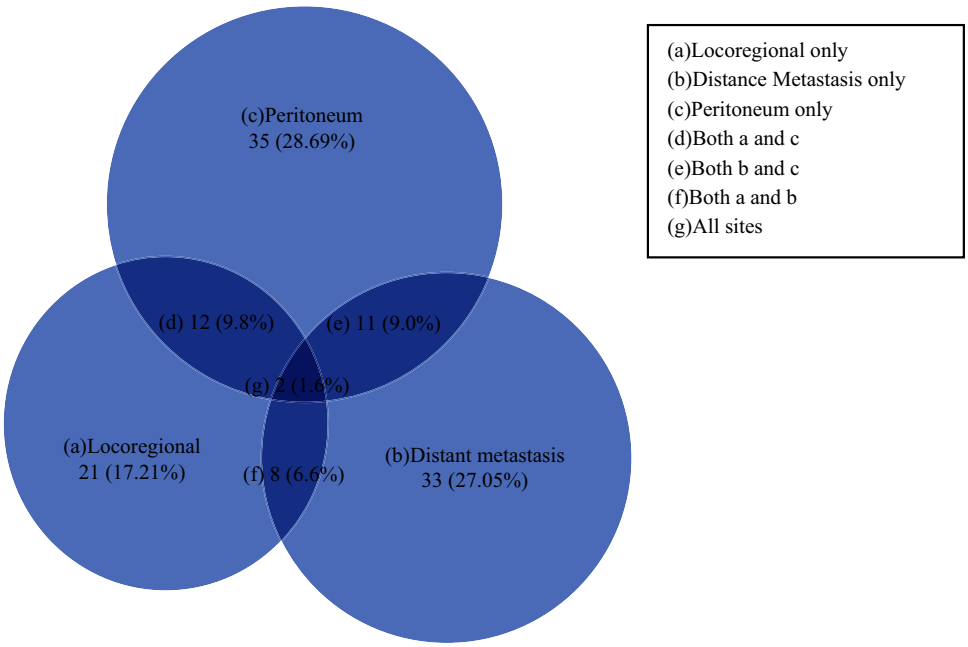

FIG. 3. Pattern of recurrences (% within the relapses)

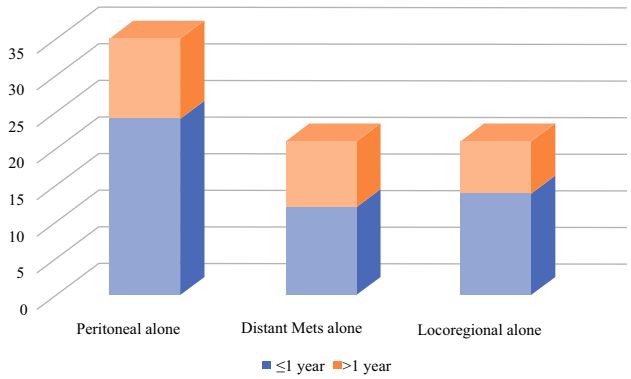

FIG. 4. Early and late recurrences as per recurrence site

The recently published Artist 2 trial, including node positive stage II and stage III GC patients, failed to show any survival advantage of adjuvant CRT (SOXRT) over adjuvant CT (SOX) after upfront D2 resection.[31] Adjuvant CT and CRT were equally effective in prolonging DFS, when compared with S-1 monotherapy. However, the median LN ratio was 0.1 in the CT arm and 0.15 in the CRT arm, indicating that the majority of the included patients had an early stage nodal disease. Adjuvant CRT might still be beneficial in N3 stage GC where the LN ratio is high.

In the present study (with a median LN ration of > 0.5), only 38 (19.3%) patients received CRT as adjuvant therapy, either because of N3 stage ($n = 28$) or R1 resection ($n = 10$). Although the OS was comparable, DFS was significantly better in patients receiving adjuvant CRT ($p = 0.020$). In subgroup analysis, adjuvant CRT provided DFS benefit specifically in the upfront surgery group, while no benefit was observed in the post NACT group. Based on this observation in our study, albeit with a small number of patients receiving adjuvant CRT, together with the results of subgroup analysis of the ARTIST 1 trial with node-positive disease, adjuvant CRT can be considered as a potentially effective option for patients with N3 stage GC who have undergone upfront resection. However, in view of the fewer numbers of patients who received CRT in the present study, a definitive conclusion cannot be drawn. Hence, adjuvant CRT in patients with a high number of positive nodes (N2/N3) needs to be explored further in prospective trials.[31] The toxicities associated with adjuvant CRT can be reduced with the help of several techniques like IMRT (intensity-modulated radiotherapy) and 3D CRT.[32]

Peritoneal metastasis is the most common and dreaded form of recurrence, as observed in this, as well as other, studies,[33] especially in the early period after treatment completion (within 1st year). Hence, measures to reduce the risk of peritoneal recurrence may prove most beneficial. In a randomized case-control study involving locally advanced GC, more favourable 3-year DFS (76.9% vs 60.5%) and a lower peritoneal recurrence rate (5% vs 30%) were seen in patients who received prophylactic HIPEC (heated intraperitoneal chemotherapy) at the time of surgery, compared with the control group (without HIPEC).[34] Another method used to deliver intraperitoneal chemotherapy is by surgically placing a peritoneal access port. Multiple studies have shown the feasibility of this approach along with delivery of weekly intraperitoneal paclitaxel chemotherapy after radical gastrectomy in patients with a high risk of peritoneal recurrence.[35,36]

Further prospective randomized control trials are required to define the role of these strategies for prevention of peritoneal disease in this subgroup of GC patients with a high risk of peritoneal relapse.

There are a few limitations to this study owing to its retrospective nature. First, this study spans over a long period of time, with different regimens used as neoadjuvant and adjuvant chemotherapy. The data on treatment completion was not available in 41.2% of patients. Also, the heterogeneity in the adjuvant therapy used may have had an impact on long-term survival. Nonetheless, the study presents a focused analysis on a larger number of sheer N3-stage GCs after curative treatment and has identified important prognostic factors.

CONCLUSION

In gastric cancers with N3 stage determined after radical D2 gastrectomy, an LN ratio of > 0.5 and ypN3 (post neoadjuvant chemotherapy) status are predictors of poor prognosis. Knowing the recurrence patterns with higher peritoneal and loco-regional sites of failure in these patients, the role of more radical surgery, adjuvant chemoradiotherapy after upfront resection, prophylactic HIPEC, or adjuvant intraperitoneal chemotherapy should be evaluated in prospective randomized clinical trials.

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