

Gastrectomy with D2 Lymphadenectomy for Carcinoma of the Stomach in a Stand-alone Cancer Centre in Rural India

Nizamudheen Mangalasseri Pareekutty¹ · Sachin Kadam² · Basavaraj Ankalkoti¹ · Satheesan Balasubramanian¹ · Bindu Anilkumar³

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Abstract

Context The therapeutic role of D2 lymphadenectomy in the management of gastric cancer is an ongoing controversy.

Aims To examine the morbidity and oncological outcomes of D2 lymph node dissection for gastric cancer patients treated in a stand-alone cancer center in rural India and to compare it with international data.

Settings and Design Retrospective study on patients treated for gastric cancer from June 2009 to December 2014.

Methods and Material All patients underwent subtotal or total gastrectomy with modified D2 lymph node dissection preserving spleen and pancreas. The Clavien-Dindo model was used to stratify the severity of morbidity.

Statistical analysis Descriptive statistics was used for data exploration. Chi-square test was used to compare the association of various factors with survival. Kaplan-Meier method was used to calculate the survival rates (RFS and DFS). Log-rank test was used to compare the survival of different subgroups.

Results Fifty-four patients (41 males and 13 females) were included in the study. Four (7.4%) patients had significant postoperative morbidity. The 5-year OS and DFS respectively were 34.9% and 37.6%. Female sex was associated with poorer survival. Lymph node ratio of more than 0.2 and advanced stage at presentation showed strong tendency towards lower OS and DFS.

Conclusions An R0 resection with D2 lymphadenectomy for gastric cancer carries acceptable morbidity and mortality in Indian patients with survival rates comparable with the western studies. Lymph node ratio more than 0.2 and female gender and advanced stage were associated with poorer oncological outcomes.

Keywords D2 lymphadenectomy · Stomach cancer · Gastrectomy · Lymph node ratio

Introduction

Stomach cancer is the fourth largest killer among all cancers worldwide [1]. It is the fifth most common malignancy in the

world, preceded by cancers of the lung, breast, colorectum, and prostate. More than 70% of cases occur in developing countries. The highest estimated mortality rates are found in Eastern Asia (24 per 100,000 among men and 9.8 per 100,000

Statement by all authors

We hereby affirm that the manuscript is the original work of the above-mentioned authors and has been read and approved by all. The authorship criteria as mentioned above have been met. We hereby agree to transfer the publication right to the Journal.

✉ Satheesan Balasubramanian
gabas9@rediffmail.com

Nizamudheen Mangalasseri Pareekutty
dmizamudheen@gmail.com

Sachin Kadam
kool_sachin555@yahoo.com

Basavaraj Ankalkoti
basuhvr@yahoo.co

Bindu Anilkumar
binduanilkumarmcc@gmail.com

¹ Department of Surgical Oncology, Malabar Cancer Center, Thalassery, Kerala 670103, India

² Ruby Hall Clinic, Pune, India

³ Department of Cancer Registry, Malabar Cancer Center, Thalassery, Kerala 670103, India

in women) while the lowest rates are seen in Northern America (2.8 and 1.5, respectively among men and women) [2].

In India, the incidence of gastric cancer is approximately 34,000 per year, with a male preponderance (male-to-female ratio, 2:1). As per a recent survey of cancer-related mortality in India, gastric carcinoma was the second most common cause among men and women alike [3] with the highest incidence reported from the North East [3].

Radical gastrectomy with systematic regional lymphadenectomy remains the primary modality of treatment for non-metastatic gastric cancer. East Asian surgeons, especially Japanese and Korean surgeons, routinely perform D2 lymph node dissection. However, the western counterparts have not accepted D2 lymphadenectomy as standard procedure and continue to perform D1 dissection. Some trials from the west have shown mixed results of morbidity and survival [4–8]. The higher morbidity and uncertain oncological benefit had been bone of contention for accepting D2 lymphadenectomy as a standard surgical procedure in several centres in the west.

In this retrospective study, we examined the oncological outcome and morbidity associated with gastrectomy with D2 lymph node dissection in a tertiary cancer centre in South India.

Materials and Methods

This is a retrospective study of patients with stomach cancer who were treated with radical gastrectomy and D2 lymph node dissection in a tertiary cancer centre from June 2009 to December 2014. All patients with operable gastric cancer were included. Patients with metastatic disease and those who were not fit for radical surgery were excluded.

Surgery and Adjuvant Treatment

Distal subtotal gastrectomy, total gastrectomy and proximal gastrectomy were the procedures performed for gastric cancer. An open approach with midline incision was used. All patients underwent standard D2 lymph node dissection with clearance of nodal stations required as per the location of the tumour within the stomach. For distal tumours, nodal stations 1, 3, 4d, 5, 6, 7, 8a, 9, 11 and 12a were cleared. For proximal cancer stations 1, 2, 3, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 10, 11 and 12a, nodes were removed. Elective splenectomy was avoided.

The reconstruction was done in all patients using Roux-en-Y loop of the jejunum. Gastrojejunal anastomosis was done using lineal cutter stapler in antecolic, side to side fashion. Circular stapler of size 25 mm was used for performing esophagojejunal anastomosis in patients with total gastrectomy. Feeding jejunostomy was routinely performed. Duodenal stump was oversewn over the staple line regularly.

Adjuvant combination chemotherapy with epirubicin (50 mg/M²), oxaliplatin (130 mg/M²) and capecitabine (1000 mg/M² twice daily for 14 days) was administered within 4 weeks in patients with >T2 or N+ disease. Adjuvant radiotherapy was additionally given in the case of margin positivity.

The Clavien-Dindo model was used to express post-operative morbidity. Significant morbidity was defined as any grade above IIIA. Procedure-related mortality was defined as death within 1 month of the surgical procedure.

Histopathological reports were analysed carefully and pertinent pathological variables were collected.

Follow-up

Patients were followed at intervals of 3 months until 2 years, six monthly until 5 years and yearly thereafter. At each visit, a detailed history and clinical examination was performed. Body weight was documented. Complete blood count and serum biochemical evaluation were obtained whenever clinically indicated. Imaging and/or endoscopy was done based on symptomatology or clinical suspicion of tumour recurrence.

Data Collection and Statistical Analysis

Data regarding demographic profile, comorbidities, details of surgery and follow-up was retrieved from case records. Descriptive statistical analysis was used for data exploration. Chi-square test was used to compare the association of various factors with survival. Kaplan-Meier method was used to calculate the survival rates (overall survival [OS] and disease-free survival [DFS]). Log-rank test was used to compare the survival of different subgroups under study. OS was defined as the period from date of surgery until death due to any cause or last follow-up (whichever was earlier). DFS was defined as the period from the date of surgery to the development of recurrent disease or last follow-up. Lymph node ratio (LNR) was calculated by dividing the number of lymph nodes positive for metastasis with the total number of lymph nodes dissected. A *p* value of < 0.05 was considered significant.

Results

The total number of patients included was 54. The patient profile and histological variables are mentioned in Table 1. The numbers of patients who had undergone distal subtotal, total and proximal gastrectomy were 37 (68%), 15 (28%) and 2 (4%) respectively. The average lymph node yield was 25.1 and a median of 23.

Margin positivity was seen in five patients (9.26%): two patients with tumour of the distal stomach had positive distal margin from sub-mucosal spread in the duodenal end; two

Table 1 Demographics and tumor characteristics

VARIABLES		NUMBER	PERCENTAGE
Gender	Males	41	76
	Females	13	24
Age groups	< 60 years	27	50
	60-70 years	20	37.03
	> 70 years	07	12.96
Comorbidities	Diabetes	05	9.25
	Hypertension	03	5.55
	Pulmonary	01	1.85
	Multiple	05	9.25
	Others	03	5.55
Stage	IA	5	9.25
	IB	8	14.81
	IIA	8	14.81
	IIB	11	20.37
	IIIA	10	18.52
	IIIB	8	14.81
	IIIC	4	7.41
Tumour location	Pylorus and distal body	39	72.22
	Proximal body, fundus,cardia	11	20.37
	Linitis plastica	4	7.40
pT category	T1	05	9.25
	T2	20	37.03
	T3	19	35.18
	T4	10	18.51
pN category	N0	21	38.89
	N1	8	14.81
	N2	11	20.37
	N3	14	25.93
Histology	WDAC-MDAC	27	50
	PDAC	18	33.33
	Mucin secreting adenocarcinoma	4	7.41
	Signet ring cell type	5	9.26
Invasion	Lymphovascular	13	24.07
	Perineural	15	27.77
	Both	10	18.51
	No invasion	37	68.51

patients had linitis plastica and one patient with proximal gastric cancer had deposits of tumour at the resected margins which could not be improved even after re-resection. Adjuvant radiation therapy was offered to these patients.

Postoperative 30-Day Morbidity and Mortality

Four (7.4%) patients had significant postoperative morbidity. The details are depicted in Table 2.

Table 2 Postoperative morbidity and thirty day mortality

CLAVIEN-DINDO	NUMBER (n=8)	DETAILS
IIIA	4	Wound infection requiring drainage and dressing
IIIB	1	Burst abdomen, re-suturing under GA
IV	1	Internal bleeding from left gastric vein. Re-exploration and successful control of haemorrhage.
V	2	- Duodenal stump leak with sepsis. Patient died of multi-organ failure. - Severe resistant pulmonary infection in the postoperative period leading to septicemia and death.

Recurrences

Twenty-six (48.15%) patients were diagnosed with recurrent disease: twelve had peritoneal recurrences while 14 had recurrences in the liver, lung, adrenals, brain, umbilicus, subcutaneous sites or multiple sites.

Survival and Factors Predicting Cumulative Long-term Survival

The estimated mean OS was 52.88 ± 6.75 months (95% CI = 39.65–66.10 months) and estimated mean DFS was 53.43 ± 7.01 months (95% CI = 39.69–67.16 months). The corresponding 5-year OS was 34.9% and DFS was 37.6%. The median follow-up was 48.3 months.

The influence of age, gender, disease stage, site of disease and LNR were analysed for the influence on OS and DFS. Our findings are shown in Table 3. It was noted that patients with LNR above 0.2 had a significantly worse DFS ($p = 0.037$) and tendency towards lower OS ($p = 0.058$) (Fig. 1). Female patients also had a significantly worse oncological outcome (Fig. 2). Stage III disease showed a lower OS and DFS, but statistical significance could not be achieved. Likewise, the site of disease did not show statistically significant effect on survival.

Discussion

Radical gastrectomy with D2 lymphadenectomy has been the standard of surgical management in Japan and South Korea for decades. Several Japanese and Korean retrospective studies have demonstrated low morbidity and high survival rates with D2 lymphadenectomy [9–11].

Two large-scale RCTs performed in the west to assess the role of D2 lymphadenectomy in the management of gastric cancers were the Dutch Gastric Cancer trial [4, 12–14] and the

Table 3 Various factors influencing survival

VARIABLE	SUBGROUPS	MEAN OS (MONTHS)	p VALUE	MEAN DFS (MONTHS)	p VALUE
Age	≤50 (n=8)	42.00 +/-9.87	0.982	39.03+/-10.53	0.896
	>50 (n=46)	53.22+/-7.43		53.95+/-7.71	
Gender	Male (n=41)	59.96+/-7.94	0.040	61.26+/-8.18	0.020
	Female(n=13)	27.48+/-7.21		24.33+/-7.31	
Site of disease	Distal (n=37)	50.26+/-7.47	0.406	51.30+/-7.80	0.460
	Proximal (n=17)	62.85+/-14.73		63.20+/-14.65	
Stage	Early stage (I&II)(n=32)	60.24+/-9.24	0.229	62.36+/-9.61	0.170
	Advanced stage (Stage III) (n=22)	37.16+/-6.67		35.86+/-6.79	
Lymph node ratio	≤0.2 (n=32)	62.56+/-8.964	0.058	64.54+/-9.31	0.037
	>0.2 (n=22)	37.04+/-8.96		35.41+/-9.07	
Adjuvant chemotherapy	Received (n=28)	53.07+/-9.75	0.937	55.21+/-10.33	0.786
	Not received (n=26)	52.39+/-9.27		52.01+/-9.45	

Medical Research Council Gastric Cancer Surgical trial [5, 15]. Both trials showed higher morbidity and mortality with D2 lymph node dissection and failed to show a clear survival advantage in D2 lymphadenectomy over D1 lymphadenectomy. However, both trials have been criticised for lack of standardisation of the procedure and inadequate surgeon experience. High rate of surgical morbidity and mortality overshadowed possible advantage from D2 dissection.

Despite the lack of definite survival advantage with randomised trials, several nonrandomised studies from the west have shown acceptable morbidity and survival benefit in D2 lymphadenectomy [16–18]. Fifteen-year follow-up results of Dutch Gastric Cancer trial also concluded that there is an improvement in DFS and cancer-related

death following D2 lymphadenectomy compared with D1 dissection. They recommended spleen-preserving D2 lymphadenectomy as standard surgical procedure for gastric cancer [14]. A recent Italian paper also showed possible benefit with D2 dissection in patients with high nodal burden even though statistically significant difference in survival could not be demonstrated [19]. A 2015 Cochrane review showed improved disease-specific survival with D2 lymphadenectomy. However, the therapeutic effect was reduced by increased mortality associated with D2 dissection [20]. A meta-analysis from Australia, based on 6 RCTs with three large studies from the western world, showed no difference in 5-year survival for D2 compared with D1 lymphadenectomy [21].

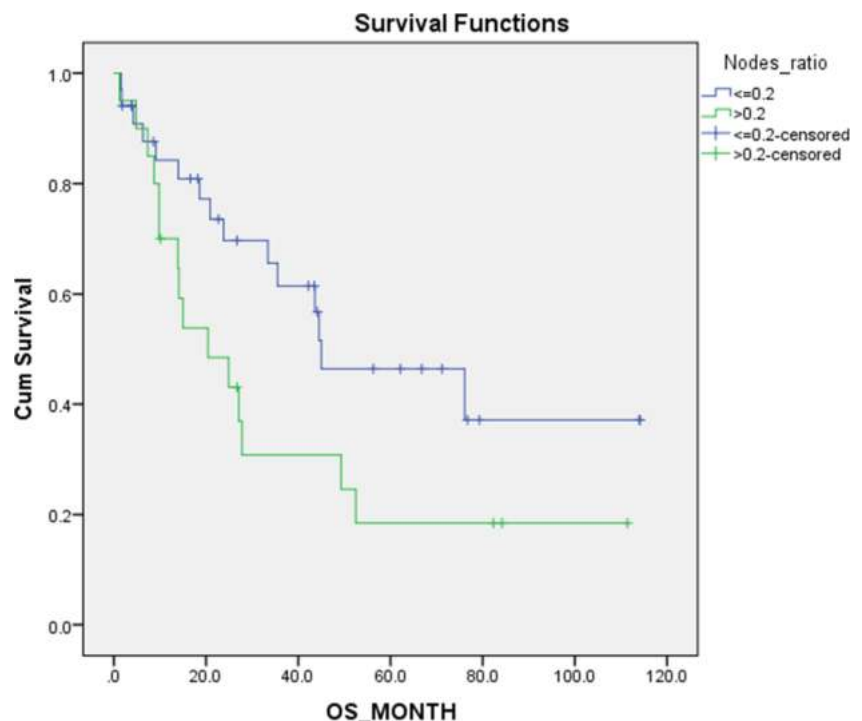
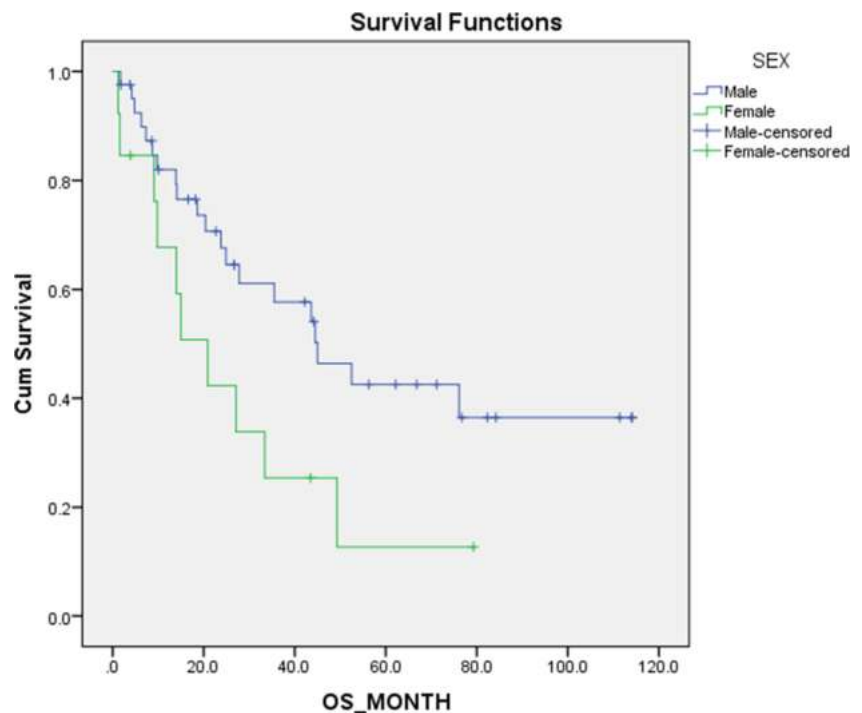
Fig. 1 Cumulative survival

Fig. 2 Comparison of survival against gender

We have adopted D2 lymphadenectomy as standard surgical procedure for stomach cancer in our institute. All the gastric cancer surgeries were performed by single specialised unit and the techniques were standardised. In our series, significant postoperative morbidity (Clavien-Dindo IIIB or more) was encountered in 4 (7.4%) patients and there were two deaths (3.7%). Table 4 compares the morbidity and mortality of the major international trials on D2 lymphadenectomy with our study.

It has been suggested that the reason for difference in survival after treatment for gastric cancer between the eastern patients and their western counterparts is multifactorial. Higher patient age, higher body mass index, higher stage of the disease, more of proximal tumours for the western patients and stage migration with more nodal examination in the east are some of the factors which are pointed out [22]. In the presence of confounding factors like the difference in adjuvant practices and difference in tumour biology between the east

and west, it is difficult to commend on the real benefit of D2 lymphadenectomy.

Lymph node ratio (LNR) has been found to be an independent prognostic factor for gastric cancers and gastro-oesophageal junction tumours [23, 24]. Female patients were found to have worse survival.

Advanced stage (stage III) was associated with worse survival compared with those with stages I and II even though statistical significance could not be achieved. We believe that this was due to small number of patients. Age and site of disease in the stomach were not found to have significant correlation with survival.

Overall survival rate of the patients in our study is comparable with that of western patients [25, 26], but inferior to their Japanese and Korean counterparts. The probable reasons for reduced survival include advanced tumour with higher node positivity and lower rate of completion of adjuvant treatment.

Table 4. Comparison of morbidity and mortality of major published studies

STUDY	COUNTRY	n (D1/ D2)	MORBIDITY (%) (D1/D2)	MORTALITY (%) (D1/D2)
Dutch study (1989–1993) (5,12)	Netherlands	380 / 331	25 / 43	4 / 10
MRC trial (1987–1994) (5)	UK	200 / 200	28 / 46	6.5 / 13
Italian study (1999–2002) (18)	Italy	NA/ 191	NA/ 20.9	NA/ 3.1
Taiwanese trial(1993–1999) (27)	Taiwan	D1/D3 110/111	D1/D3 7.3/17.1	D1/D3 0/0
Shrikhande SV et al (2002–2006) (28)	India	NA/ 159	NA/4.4	NA/1.25
Present study (2009 –2014)	India	NA/ 54	NA/ 7.4	NA/ 3.7

Conclusion

R0 resection with gastrectomy and D2 lymphadenectomy for gastric cancer is feasible in a stand-alone cancer centre in rural India. The low morbidity and mortality associated with D2 dissection along with potential survival benefit justify accepting it as the surgical standard of care in experienced hands. Lymph node positivity ratio and female sex are found to have significant adverse influence on survival in our series.

Authors' Contribution Nizamudheen Mangalasseri Pareekutty: concept, study design, write up

Sachin Kadam: data collection, write up

Basavaraj Ankalkoti: data collection, contributed to study

Satheesan Balasubramanian: Concept, supervised the project, editing

Bindu Anilkumar: statistical analysis

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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