



Factors Determining Outcome in Multivisceral Resection for Gastric Cancer – A South Indian Tertiary Care Centre Observational Study

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Background

Gastric cancer is one of the leading cause of cancer related deaths. In India, Chennai, has a very high incidence of 11.8/100000 among males and 5.9/100000 among females. The resectability rate for gastric cancer is about 40 – 50 %. The reason for inoperability are locally advanced disease involving other organs, peritoneal metastasis, liver metastasis and distant metastasis. Locally advanced gastric cancer and limited peritoneal disease can be taken for multivisceral resection with curative intent. But evidence for such a radical procedure is debatable. While some

studies indicate a trend towards increased perioperative mortality, others show a better long term outcome. In this background we have set out to analyse the outcome of patients with gastric cancer patients undergone MVR in our centre.

Aim of the Study

To analyse the factors influencing outcomes following multivisceral resection for gastric cancer. Secondary endpoint is to analyse the R status and N status and the extent of adjacent organ involvement in determining the outcome.

Materials and Methods

In this study, outcomes of 23 patients who underwent multivisceral resection for gastric cancer between August 2011 to Feb 2014 at the Institute of Surgical Gastroenterology and Coloproctology, Madras Medical College, Tamilnadu, was analyzed retrospectively. Standard D2 lymph node dissections were performed in these patients with curative intent. A distal subtotal gastrectomy or total gastrectomy was performed depending on the location of the primary tumor. The curative (R0) resection was defined as the complete removal of cancer tissue with no residual tumor macroscopically or microscopically and no evidence of distant metastasis. Patients with metastatic disease who had undergone palliative resection were excluded. Outcomes based on staging of cancer T3/T4, resection R0/R1, number of organs resected, perioperative complications were analyzed. It includes patients in whom adjacent organ involvement was discovered intraoperatively. Patients with metastatic involvement, and those in whom MVR was done following accidental/iatrogenic injury to neighbouring organs were excluded from the study. The seventh edition of the TNM staging system of the American Joint Committee on Cancer⁴¹ was used to stage the tumors. Patients with metastasis were not included in the study. 18 patients had undergone Total Gastrectomy while the rest had subtotal gastrectomy with multivisceral resection. Distal gastrectomy is selected when a satisfactory proximal resection margin (see above) can be obtained. No of adjacent organs involved varies from 1 to 3. Deaths within 30 days after surgery was considered as postoperative mortality. Surgical morbidity was defined as any complication that occurred in the 30-day postoperative period. Clinicopathological data were obtained from a prospectively constructed medical database. Survival duration was calculated from the time of surgery to death or the last follow-up date.

Results

Among the 23 patients, 16 were male and 7 were female. EG junction was the primary site of location of the cancer in 14 patients and 5 patients had cancers in the gastric body, while 4 patients had antral growths. Almost all the patients had significant loss of weight and loss of appetite. While the hemoglobin levels were less than 10 g% in 6 patients, it was more than 10 in the rest of the patients (17/23). 5 patients had T3 cancers while the rest had T4 cancers (18/23). Table 1 shows that 18 patients underwent total Gastrectomy and 5 patients underwent Distal Gastrectomy. Well differentiated adenocarcinoma was the histological subtype in 7 patients, while 9 patients had moderately differentiated tumors and 7 patients had poorly differentiated tumors. Three patients had no lymphnodal metastasis on pathological examination whereas, 3 patients had N1 staging, 7 had N2 staging and 10 patients were staged N3. 17 patients had one adjacent organ removal while 6 patients had 2 or more organs removed concomitantly (Fig :1).

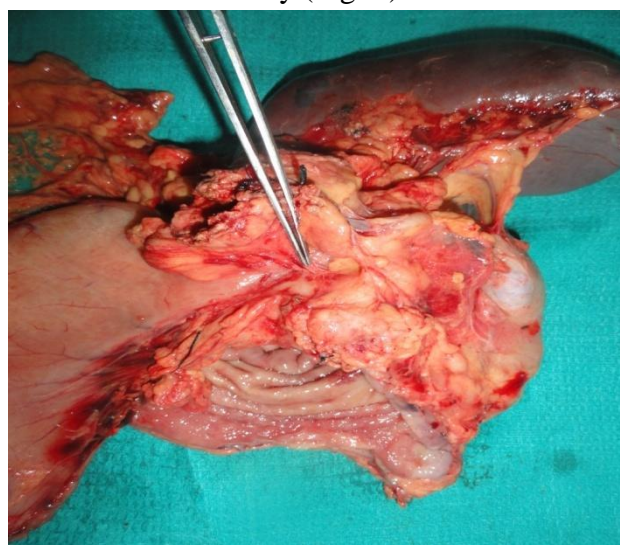


Fig 1 Multivisceral resection for gastric cancer including Pancreas, Spleen
Clinicopathologic characteristics of 23 Patients

Table 1: clinicopathologic variables of patients

Clinical variable	Mean	
Age (y)	51.4	
Gender		
Male	16	69.5%
Female	7	30.5%
Tumor diameter (cm)	7.2	4.2
Tumor location		
Upper	14	60.8%
Middle	5	21.7%
Lower	4	17.3%
Operation type		
Subtotal gastrectomy	5	21.2%
Total gastrectomy	18	78.2%
Borrmann type		
I and II	4	15.9%
III	11	49.2%
IV	8	34.9%
Differentiation		
Well	7	
moderate	9	
Poor-undifferentiated	7	
Depth of invasion		
T3	5	21.7%
T4	18	78.2%
N-stage		
N0	3	13%
N1(1~6)	3	13%
N2(7~15)	7	30.4%
N3(≥16)	10	43.4%
Number of organs resected		
1	17	73.9%
≥2	6	26.1%

Postoperative complications

Table 2: Incidence of postoperative complications Morbidity and Mortality

Complications	Number of Patients	Percentage
Pulmonary complications	2	8.6
Wound infection	8	34.7
Pancreatic leak	2	8.6
Duodenal blow out	1	4.3
Anastomotic leak	2	8.6
Mortality	2	8.6

Reported complications from the studies examining MVR has shown 3% anastomotic leaks, 2% pancreatic fistulas, and 10% perioperative death, with overall complications rates ranging from 11.8 to 90.5%. Perioperative

mortality ranged from 0 to 15%. In our study the morbidity rate was 69.5% and mortality rate was 8.6%. pulmonary complications and pancreatic leaks were observed in 2 patients. Table 2 shows the list of complications observed in our study. 2 patients who underwent Gastrectomy with multivisceral resection died in the post operative period. One death was due to Pneumonia and the other was due to anastomotic leak.

Results

Table 3: 1,3,5 yr survival based on T staging

T staging	1 year	3 years	5 years
T3 (n=5)	2/5	1/5	2/5
T4 (n=18)	8/18	2/18	1/18

The depth of tumor invasion was found to have significant impact on the survival of gastric cancer patients who underwent multi organ resection. While 2 out of the 5 patients who had T3 tumors had a 5 year survival, all but one of the 18 patients who had T4 tumors survived beyond 5 years.

Table 4: 1,3and 5 year survival based on N staging

N staging	1 year	3 years	5 years
N0 (n=3)	0/3	2/3	1/3
N1 (n=3)	1/3	0/3	2/3
N2 (n=7)	5/7	0/7	0/7
N3 (n=10)	4/10	1/10	0/10

Table 5 shows the 1,3 and 5 year survival of patients who underwent gastrectomy with enbloc multivisceral resection in respect to pathological nodal status. While 2 patients out of three with N0 status survived for more than 3 years , none of the 10 patients with N3 staging survived beyond 5 years and only one survived beyond 3 years.

Table 5: 1,3 and 5 year survival based on the number of organs resected.

No of organs resected	1 year	3 year	5 year
1 (n=17)	8/17	7/17	2/17
2 (n=4)	2/4	0/4	1/4
3 (n=2)	1/2	0/2	0/2

Table 5 shows the survival rates of patients who underwent gastrectomy with Multivisceral Resection depending upon the number of adjacent organs involved. Spleen was the most commonly involved organ, followed by pancreas. Other organs included transverse colon, liver, gall bladder and diaphragm (Fig:2). From the table it is

clearly seen that the increase in number of organs removed had a direct negative influence on the survival rates while most of the patients in whom only one additional organ was removed managed to have a reasonably good survival.

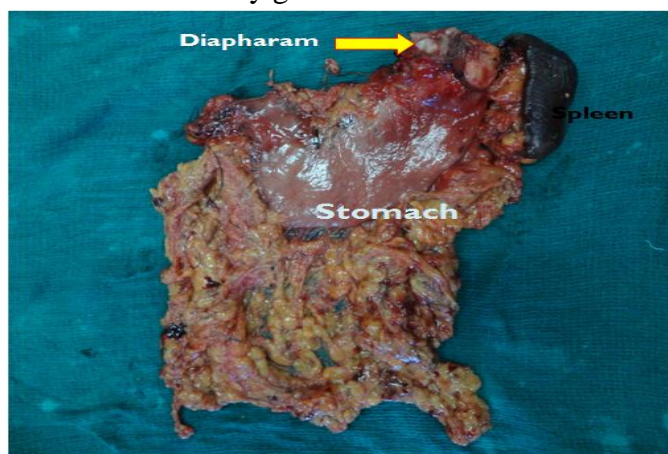


Fig 2 Multivisceral resection for gastric cancer including Diaphragm, Spleen

Table 6: survival at 1,3, and 5 yrs in relation to R status

R status	1 yr	2 yr	3 yr
R0 (n=16)	7	3	3
R1 (n=7)	1	0	0

An R0 resection was performed in 70% of patients. Four studies reported a statistically significant survival advantage when MVR was performed with an R0 resection compared to R1 resection^[22,38,17,18]. Two of four studies showed that an increasing number of organs involved or resected was associated with decreased survival at 5 years^[30,12]. However, an R0 resection resulted in 5-year survival of 32–35% for patients undergoing MVR, even when two or more organs were resected. In our study patients who had a R1 resection showed a dismal prognosis.

Discussion

Gastric cancer is a leading cause of cancer death throughout the world. Locally advanced gastric cancer carries a poor prognosis due to the possibility of simultaneous distant metastasis. A subgroup of patients with T4 tumors however, in the absence of distant metastasis can progress satisfactorily if a curative resection is performed,

albeit with a significantly increased morbidity and mortality rates. The morbidity and mortality rates following such procedures is reported to vary considerably between studies and stands at 11.8% to 90.5% and from 0 to 15%, respectively.^{4,5,6,7} In our study, the morbidity and mortality rates were 65 % and 8.6%, respectively, which were comparable to previous reports. Hence, aggressive surgical approach including multiorgan resection was still recommended for T4 gastric tumors. In our study there were 2 cases of postoperative Delayed Gastric emptying whereas the reported incidence of delayed gastric emptying (DGE) after gastrectomy ranged from 3.2 to 6.9%⁸⁻¹⁰

The median length of stay was 30 days in our series which is quiet higher than the international standards. This could be attributed to the fact that preoperative optimization of comorbid illnesses in these patients is usually done only after the patient gets admitted, combined with a stricter criteria for discharge in view of the difficulties of following up these patients at primary care level in our part of the world.

The 1-, 3-, and 5-year overall survival was 69.5%, 26.0%, and 13.0% respectively in our study. In a study by Kunisaki et al it was shown that curative resection performed for T4 gastric cancer with relatively small tumors and few lymph node metastases is associated with better outcomes.¹¹ Histologic type of poorly differentiated cancer cells was found to be associated with poor survival rates. Age and tumor sizes were also reported as independent poor prognostic factors.^{12,13,14,15,16} Such an association fail to show up in this study which may be attributable to the small sample size.

The number of metastatic lymphnodes has been shown to be an important indicator of prognosis for T4 gastric cancer.^{17,18} In the present study, lymph node metastasis was identified as an independent prognostic factor which significantly influenced the outcomes. While one patient out of 3 with no lymph nodal involvement survived beyond 5 years, none of the 10 patients with N3 nodal staging survived upto 5 years and had a

dismal 3 yr survival rate of 10% Dikken et al. demonstrated that postoperative chemotherapy could improve survival.¹⁹ For T4 gastric cancers aggressive chemotherapy was recommended after curative resection. Neoadjuvant chemotherapy is also a good choice if lymph node metastasis is diagnosed prior to surgery, Neoadjuvant chemotherapy can downstage the tumor and facilitate a complete resection. It can also eliminate systemic micrometastases and decrease distant recurrence and can also be used to assess tumor chemosensitivity to cytotoxic medications. The MAGIC trial showed that perioperative chemotherapy can extend the 5-year survival rate from 23 to 36%.²⁰ Lordick also stated that the neoadjuvant treatment could improve the rate of R0 resection and overall survival²¹. None of our patients received neoadjuvant chemotherapy

Curative resection is beneficial to patients with advanced gastric cancer and an R0 resection is significantly associated with improved survival.³⁴ MVR provide patients with the best chance of survival with a curative R0 resection. Eight studies have reported that achieving complete resection (R0) is possible with results ranging from 38 to 100%, suggesting that a significant proportion of patients have positive microscopic or macroscopic margins despite undergoing MVR^{1,12,17,18,22,27,28,39}. Survival in patients who underwent MVR without a complete resection was shown to be inferior when compared to those who had an R0 resection.^{17,18,22,38} Poor outcomes appear to be associated with both microscopic and macroscopic positive margins.^{13,32} There were no 5-year survivors in three studies that reported outcomes in patients undergoing MVR with residual tumor; however, for patients in whom an R0 resection was achieved, the 5-year survival was 11.1–45.0%.^{18,22,38} Saito and colleagues, found patients who underwent MVR and had positive microscopic or macroscopic margins had nearly the same outcomes as patients who did not undergo MVR.³⁸

Two studies reported decreased overall survival with MVR compared to gastrectomy alone^[24, 34]..

Martin et al.^[24] reported only 13.8% of patients who underwent MVR had pathologic T4 disease. There is no evidence that gastrectomy alone, when yielding an R1 or R2 margin, is appropriate when R0 resection with MVR is safe and feasible. However, resections involving the liver^{18,38} and the transverse colon¹⁸ were found to be associated with increased survival compared to MVR with resection of other adjacent structures.

The goal of R0 resection must be balanced against the challenges in identifying whether gastric cancer is truly invading adjacent organs. MVR ideally should be reserved for T4 lesions, with true histological invasion into adjacent organs.²⁸ Adhesions secondary to desmoplastic reaction can be mistaken for local invasion, especially when involving the pancreas.²² Distinction between T3 and T4 lesions may be facilitated by preoperative imaging, including computed tomography (CT) and endoscopic ultrasound (EUS), but they lack accuracy^[42]. Four studies examined the number of organs involved or resected as a predictor of survival.^{12,24,30,38} Ozer et al. found that patients who underwent MVR with 2 or more organs had a higher surgical morbidity, when adjusted for age, comorbidities, and stage, providing a possible explanation for the decreased survival for this group.¹² Martin et al. report an increase in surgical complications with a trend towards lower 5-year survival when comparing one-, two-, and three-organ resections in addition to gastrectomy.^{1,24} In none of the studies are operative details such as estimated blood loss given, nor is it clear whether differences in survival in patients with 2 or more organs involved are a result of operative mortality or a marker of aggressive biology. However, Saito et al. found that when an R0 resection was performed, there was no difference in survival when more than one organ was involved. They also found that when more than two organs adjacent to the stomach were involved, the patients who underwent an R0 resection had improved survival compared to those who did not undergo MVR³⁸. If resection of two or more

organs is necessary for achieving negative margins, MVR should be pursued despite possible operative risks.

Table 4 shows the survival data by extent of nodal involvement, and stage. Nodal status is highly predictive of survival in gastric cancer patients. Several papers show survival after an MVR to be dependent on the nodal status^{12,17,18,22,30}. Jeong et al reported that patients with N3 disease showed no improved survival in the MVR group versus the group treated with gastrectomy alone, thus suggesting that the benefit of MVR achieved in R0 resection may be limited by the burden of nodal involvement.¹⁷ Some studies conclude that extended MVR should not be done when macroscopic nodal disease is present.³³ Saito et al. showed a statistically significant difference in 5-year survival between patients with N3 disease who underwent an MVR with R0 resection compared to patients with positive pathological margins or patients who did not undergo MVR.³⁸ Thus, MVR in selected patients, is justified if negative histological margins can be achieved, even with extensive nodal involvement. Fukuda et al showed that Positive peritoneal washing cytology is the only independent poor prognostic factor for T4 gastric cancer patients who could be treated with potentially curative resection.⁶ In our study routine peritoneal washing cytological examination was not performed.

Conclusion

Our study showed that gastrectomy with additional organ resection can be done with acceptable morbidity and low mortality. Advancements in preoperative evaluation to differentiate T3 and T4 disease can avoid unnecessary organ resections. Depth of invasion and the presence and extent of lymph node metastasis are the most powerful determinants of survival following an R0 resection.

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