

Sentinel Lymph node biopsy in Carcinoma Stomach

Y.VKeshav Prasad¹, Shruthi Prabhu¹, A N Bhargava Vyas¹, Rajat Choudhari¹

¹Department of General Surgery, Kasturba Medical College, Manipal Academy of Higher Education, Mangalore – 575001

Corresponding author: A N Bhargava Vyas, Assistant Professor, Department of General Surgery, Kasturba Medical College, Manipal Academy of Higher Education, Mangalore – 575001, Phone number: (+91) 8197944666, Email: anbhargavvyas@gmail.com

Abstract

Background: Surgery is the mainstay of treatment in gastric carcinoma management with a longstanding controversy regarding the extent of lymphadenectomy. Recent studies have shown 88% sensitivity of Sentinel Node biopsy for patients with gastric cancer. There is a need for evaluation of this technique using cost effective alternative of methylene blue dye.

Methods: This was a prospective study which included all adults with diagnosis of carcinoma stomach planned for surgical resection. Intra-operatively, methylene blue dye was injected into the tumor and the stained lymph nodes were removed along with other visibly enlarged nodes.

Results: A total of 32 subjects were recruited in the study period. Mean age of the patients was 56.59 (± 12.02) years. Among all the specimens a total of 127 (35%) of 361 lymph nodes were found to be stained with methylene blue dye. Metastatic deposits were found in 132 of 361 lymph nodes. Bivariate analysis showed 79.52% of the lymph nodes stained with methylene blue were positive for metastases in contrast to 13.2% among those that remained unstained (p 0.001).

Conclusion: Sentinel lymph node mapping using methylene blue is a simple, cost and resource effective technique in all cases of gastric carcinoma undergoing resection, especially in early gastric carcinoma.

Keywords: gastric carcinoma, sentinel lymph node, methylene blue

Introduction

Gastric cancer is the 6th most common cancer in the world as per WHO and the 3rd leading cause for death due to cancer worldwide(1). Early diagnosis and treatment are the key to achieving better outcomes and prognosis. The treatment for gastric cancer is multimodal and encompasses endoscopic or surgical resection, radiation and chemotherapy based on tumour invasion and staging. Among the various prognostic factors, lymph nodal metastasis is significant and is reflected in the current American Joint committee on Cancer (AJCC) TNM staging system (2). There has been a longstanding controversy regarding the extent of lymph node dissection in gastric cancer and recommendations have been ever evolving.

Patients who undergo standard gastrectomy with D2 lymphadenectomy suffer a variety of complications, such as diarrhoea, reflux, dumping syndrome, termed postoperative syndrome associated with higher rate of mortality and a longer hospital stay than D1 lymphadenectomy (3). Lymph node metastasis in gastric cancer is proportionate to depth of infiltration of the primary and seen in less than 20% of T1 and T2 tumour and majority of these cases do not show nodal involvement (4).

Sentinel lymph node is the first lymph node to which cancer cells are likely to spread from the primary tumour. The technique of sentinel lymph node mapping (SLNM) and biopsy has been proven to be useful in breast cancer and malignant melanoma. The feasibility and

diagnostic reliability of sentinel node mapping of gastrointestinal (GI) cancers, however, are still unclear and controversial due to extensive interconnections between lymphatic channels and high incidence of skip metastases (5). Therefore the investigation of the validity of SLNM in patients with gastric cancer is justified in early stage tumours to avoid unnecessary lymph node dissection and spare the patient of the morbidity and allow faster recovery (6).

Dye-guided or radio-guided method can be used to identify the sentinel node (SN). Patent blue, lymphazurin, and Indocyaninegreen are preferably selected in intraoperative time. Dye-guided method has been widely used due to the cost effectiveness and has benefit to detect the lymphatic vessels as well as lymph nodes. However, it has been reported that the dye-guided method is not suitable for patients with a dense adipose tissue, which would cause a high false-negative rate (7). Recent studies have showed ICG dye is more suitable for SN due to its high accuracy rate without the added disadvantage of blue discoloration of the node (8). A recent meta-analysis by Ryu et al examined the sensitivity of SN biopsy for patients with gastric cancer (9). SN identification rate and sensitivity were 87.8% and 97.5%. By subgroup analysis, sensitivity of SN was shown to rely on the number of picked-up SN. They concluded SN mapping in gastric cancer is not clinically applicable for limited lymph node dissection due to its insufficient sensitivity and practical differences between surgeons.

There is a need for further evaluation of this technique to assess the incidence of sentinel node positivity among gastric cancer cases and its applicability in routine clinical practice at a resource limited centre using cost effective alternative of methylene blue dye. The aim of this study was to estimate the incidence of sentinel lymph node positivity in carcinoma stomach and determination of sensitivity of sentinel lymph node biopsy in carcinoma stomach at a tertiary care centre in South India.

Materials and methods:

Patients and Methods

All patients aged above 18 years diagnosed as malignant gastric lesions and planned for gastric resection procedures at the Hospitals affiliated to Kasturba Medical College, Mangalore during the study period November 2018- July 2020 were screened for inclusion. Those not willing to give consent for participating in the study, below 18 years of age, those with prior history of allergies to any dyes and pregnant women were excluded.

Sample size calculation

Kitagawa et al have previously studied the utility of sentinel node biopsy in gastric cancer and estimated the incidence of metastasis at around 38% (7). Using this as the baseline incidence, the study was powered at 80% and Confidence level of 95%. Accounting for a 10% non response rate, a sample size of 23 patients was calculated.

Data collection

A purposive sampling method was adopted and all eligible patients presenting with newly diagnosed or previously diagnosed carcinoma stomach during the study period were included and verbal and written consent was obtained from each of them. Demographic data was collected from patient records and stored in blinded patient proforma. Patients planned for total / subtotal or partial gastrectomy, transhiatal esophagectomy for gastroesophageal junction tumors and palliative gastrectomy or gastrojejunostomy with or without lymph node dissection were included in the study. The study was cleared by the Scientific and Ethical committee at Kasturba Medical College, Mangalore, Karnataka (affiliated to Manipal Institute of Higher Education).

Technique of Sentinel node mapping and biopsy

Intraoperative subserosal/perilesional injection of sterile methylene blue at 4-6 locations of the tumour was given and lymph node staining by dye was looked for (Fig 1). First lymph node to take the dye was considered as sentinel lymph node (Fig 2). Histopathological analysis of the lymph node was done along with other lymph nodes dissected during the procedure and number of lymph nodes with and without metastatic tumor deposits was correlated with presence or absence of staining.



FIG 1: Injection of methylene blue dye into the tumour (intralesional)

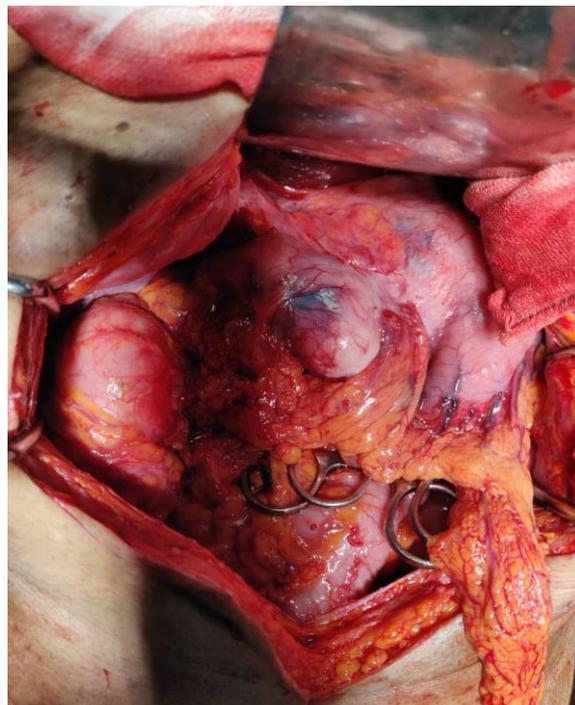


FIG 2: Staining of Sentinel lymph node by methylene blue dye



FIG 3: Gross specimen of the resected tumour and stained lymph nodes

Data analysis

The collected data was analyzed using SPSS Version 25. Qualitative data was expressed as frequencies and percentages and quantitative data as mean \pm Standard Deviation. Bivariate analysis was done by chi square test and student's t-test. The validity of the test was calculated using cross tabulation and sensitivity, specificity and predictive values.

Results

A total of 32 subjects were recruited in the study period. Accounting for loss to follow up and drop out, extra subjects were recruited but there was no loss and final analysis included all 32 patients. Among the total 32 patients, 23 (72%) were males and rest were females. Mean age of the patients was 56.59 (\pm 12.02) years.

The commonest location of tumor in the stomach was at the pylorus accounting for 56% (18 out of 32) cases with antrum and gastro-esophageal junction accounting for 22% (7/32) and 9% (3/32) respectively. The frequency of location of tumors is showed in Table 1. Fundus and body of stomach were the least common locations.

Among the cases, Distal Gastrectomy with D1 lymph node dissection was the commonest procedure done in 11 patients (34.3%) followed by Palliative gastrojejunostomy(7/32) and Subtotal Gastrectomy(7/32) with 21.8% each.(Table 2)

Among all the specimens a total of 361 lymph nodes were found at Histopathological examination and among these only 127 lymph nodes (35%) were found to be stained with methylene blue dye and remaining were unstained.

The presence of metastatic deposits was found in 132 of the total 361 lymph nodes and this was compared against the presence of methylene blue dye in the nodes (Table 3). The Bivariate analysis showed 79.52% of the lymph nodes stained with methylene blue were positive for metastases in contrast to only 13.2% among those that remained unstained. This difference was found to be statistically significant ($p < 0.001$).

Tumor site	Frequency
Pylorus	18
Antrum	7
Ge junction	3
Antrum & pylorus	2
Fundus	1
Body of posterior wall of stomach	1
Total	32

Table 1: Distribution of study subjects based on location of tumour

Surgical procedure performed	Frequency
Distal gastrectomy	11
Subtotal gastrectomy	7
Palliative gastrojejunostomy	7
D2 gastrectomy	2
Esophago - gastrectomy	2
Near total gastrectomy	1
Proximal gastrectomy	1
Transhiatal esophagectomy	1
Total	32

Table 2: Frequency of different types of surgeries performed.

Metastatic deposits	Stained (%)	Unstained (%)	Total
Positive	101(79.52)	31 (13.2)	132
Negative	26 (20.5)	203 (86.8)	229
Total (%)	127 (100)	234(100)	361

Table 3: Presence of metastatic deposits compared against staining of lymph nodes

DISCUSSION

Carcinoma stomach is the 6th most common cancer in the world. Surgery remains the mainstream therapeutic option for early, locally advanced as well as metastatic gastric carcinoma for palliation. Surgical options have evolved over the years and new recommendations are made as evidence becomes available. Previously, eastern Asian surgeons preferred a radical approach to gastric carcinoma with gastrectomy and extensive lymph node dissection labelled as the D2 lymphadenectomy (10). This outlook was changed by the Dutch and Italian studies that showed comparable outcomes and disease control with a limited D1 lymph node clearance and this was advocated for early cancers. Over the long term, however, increased rates of recurrence lead to development of D1+ lymphadenectomy that combined the radicality and conservativeness of the two techniques and provided justifiable outcomes with limited morbidity (10,11).

Developments in Histopathological analysis of gastric carcinomas and grading of tumours with studying of disease patterns suggested that low grade tumours tend to follow a linear path of lymphatic spread along a lymphatic channel primarily draining the tumour bed to a sentinel lymph node and then further on. Sentinel lymph node mapping (SLNM) is a known technique in malignancies involving the breast and skin such as melanoma. This thought combined with minimally invasive procedures for gastric resections lead to an increased interest in conservative lymphadenectomy in low grade and early gastric carcinoma. Metastasis to lymph nodes is commonly observed around the regional peri gastric lymph nodes and various techniques were developed to study lymph node mapping by radioactive tracer and dye injection techniques for stomach malignancies (11-15).

In our study, 23 out of the 32 patients were males (71.8%) showing the gender predominance in males for carcinoma stomach. The mean age of presentation was 56.3 years and majority of patients (43.7%) were above 60 years of age showing that carcinoma of the stomach is a disease of the elderly presenting after a long period of chronic inflammation and gradual dysplastic changes leading to development of malignancy. These findings of our study are in accordance with the known demographic data and risk factors from literature.

Among our patient population, pylorus was the most common involved site in the stomach with 18 out of 32 patients (56.3%) presenting with pyloric growth and 8 of these (25%) presented with gastric outlet obstruction. Pylorus is the area of maximum insult to the gastric mucosa and stasis due to the sphincter mechanism that prevents emptying into the duodenum rapidly. Hence, majority of gastric tumours present at the pylorus.

In our study majority of patients underwent distal gastrectomy (11 out of 32, 34%) as this is the treatment of choice for a distal or pyloric gastric malignancy. 7 out of 32 (21%) patients underwent a subtotal gastrectomy whereas 7 patients (21%) presented with an inoperable tumour and underwent a palliative drainage procedure in form of gastrojejunostomy. In our centre we commonly perform a D1 lymphadenectomy for all cases and any other visibly enlarged nodes along the rest lymph node stations are removed. Extensive D2 lymphadenectomy is routinely not performed due to the associated increased morbidity and availability of adequate post-operative adjuvant chemo and radiation therapy facilities.

During the study period for all included patients, sentinel lymph node mapping was done by injection of methylene blue dye intra operatively into the tumour and visible lymph nodes with staining were dissected along with any other grossly enlarged lymph nodes. All the lymph nodes removed were sent for histopathological analysis and total of 361 lymph nodes were identified in all the samples of which 127 (35.2%) of nodes were found to have been stained with methylene blue.

This overall percentage of dye uptake seems lower than expected but Bivariate analysis revealed 79.52% of the lymph nodes stained with methylene blue were positive for metastases in contrast to only 13.2% among those that remained unstained. This difference was found to be statistically significant ($p < 0.001$). These results are similar to the results of previous studies where the sensitivity of sentinel lymph node biopsy was found to be between 80-95% (5,6,16). The lower sensitivity in our study could be due to inexperience of our centre in this new technique and the result of excessive lymph node dissection as compared to the limited dissections in previous studies which lead to relatively lower percentage of positive nodes in the sample.

However, the finding that majority of nodes that were not stained by the dye were negative for metastasis, 203 out of 234(87%) shows that extensive lymph node dissection was not required in significant number of cases and patients could have been spared the excess surgical stress.

In our study, we note that the significant positivity of sentinel lymph node biopsy in identifying metastases among all cases of gastric cancer irrespective of location of tumour and presentation is a useful finding and will encourage use of the technique in all cases of gastric carcinoma to tailor the surgical technique to the actual patient disease status instead of a blanket radical lymphadenectomy. We believe that there is significant evidence to suggest the utility of SLNM in all cases of gastric resection where lymphadenectomy is planned especially in early T1 and T2 gastric carcinomas which will limit the extensive procedure and decrease morbidity to the patient by limiting the operative time, blood loss, injury to vessels and lymphatic channels and surrounding structures.

The limitation of the study was the relatively smaller number of patients and larger studies comparing the same are required for further validation of this technique. Also, we used the methylene blue dye method which relies on visual accuracy for identification of lymph node and may be prone to observer variation. Indocyanine green based assay maybe more reliable and accurate.

Conclusion

Sentinel lymph node mapping using methylene blue is a cost and resource effective technique with relatively easy procedure and should be practiced in all cases of gastric carcinoma undergoing curative or palliative resection and more importantly in cases of early gastric carcinoma.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The miscellaneous costs were borne by the authors themselves.

Conflict of Interest: The authors declare no conflicts of interest.

References

- 1) Brenner H, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. In: Verma M, ed. *Methods of Molecular Biology, Cancer Epidemiology*. Vol. 23. Totowa, NJ: Humana Press; 2009:467–477.(1)
- 2) Gastric cancer. In: *NCCN Clinical Practice Guidelines in Oncology*. V. 2. National Comprehensive Cancer Network; 2010(2)
- 3) Bonenkamp JJ, Hermans J, Sasako M, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ. Extended lymph-node dissection for gastric cancer. *New England Journal of Medicine*. 1999 Mar 25;340(12):908-14.(3)

- 4) Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric cancer*. 2000 Dec 1;3(4):219-25.(4)
- 5) Yashiro M, Matsuoka T. Sentinel node navigation surgery for gastric cancer: Overview and perspective. *World journal of gastrointestinal surgery*. 2015 Jan 27;7(1):1.
- 6) Kitagawa Y, Fujii H, Mukai M, Kubota T, Ando N, Watanabe M, Ohgami M, Otani Y, Ozawa S, Hasegawa H, Furukawa T. The role of the sentinel lymph node in gastrointestinal cancer. *Surgical Clinics of North America*. 2000 Dec 1;80(6):1799-809.
- 7) Kitagawa Y, Fujii H, Kumai K, Kubota T, Otani Y, Saikawa Y, Yoshida M, Kubo A, Kitajima M. Recent advances in sentinel node navigation for gastric cancer: a paradigm shift of surgical management. *Journal of surgical oncology*. 2005 Jun 1;90(3):147-51.
- 8) Tajima Y, Yamazaki K, Masuda Y, Kato M, Yasuda D, Aoki T, Kato T, Murakami M, Miwa M, Kusano M. Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. *Annals of surgery*. 2009 Jan 1;249(1):58-62.
- 9) Ryu KW, Eom BW, Nam BH, Lee JH, Kook MC, Choi IJ, Kim YW. Is the sentinel node biopsy clinically applicable for limited lymphadenectomy and modified gastric resection in gastric cancer? A meta-analysis of feasibility studies. *Journal of surgical oncology*. 2011 Nov 1;104(6):578-84.
- 10) Parkin DM. International variation. *Oncogene*. 2004;23:6329–6340.
- 11) Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol*. 2006;12(3):354–362
- 12) Maconi G, Manes G, Porro GB. Role of symptoms in diagnosis and outcome of gastric cancer. *World J Gastroenterol*. 2008;14(8):1149–1155
- 13) Bodger K, Eastwood PG, Manning SI, et al. Dyspepsia workload in urban general practice and implications of the British society of gastroenterology dyspepsia guidelines. *Aliment Pharmacol Ther*. 2000;14:413–420.
- 14) Abdalla EK, Pisters PW. Staging and preoperative evaluation of upper gastrointestinal malignancies. *Semin Oncol*. 2004;31(4):513–529.
- 15) Kwee RM, Kwee TC. Imaging in local staging of gastric cancer: a systematic review. *J Clin Oncol*. 2007;25(15):2107–2116
- 16) Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *The lancet oncology*. 2010 May 1;11(5):439-49.