

SIGNIFICANCE OF LYMPH NODAL METASTASES IN TREATMENT OF ESOPHAGOGASTRIC ADENOCARCINOMA

T. Aikou, H. Shimazu, T. Takao, M. Baba, S. Natsugoe, M. Simada

Department of Surgery, First Department of Surgery, Kagoshima University School of Medicine, Kagoshima, Japan

ABSTRACT

Between 1973 and 1990, 104 patients with adenocarcinoma of the esophago-gastric junction (EGJ) (i.e., primary tumor within 2-3cm of and including the EGJ) were operated upon. Preoperatively, all were deemed potentially resectable. In 70, the esophagogastric resection was combined with en-bloc resection, that is, wide excision of the primary mass in conjunction with radical lymph node dissection of the posterior mediastinum and upper abdomen. Postoperative staging was done using the WNM system [i.e., wall penetration (W), lymph node involvement (N), and systemic metastases (M)]. Sixty-four patients or 62% had lymph nodes positive for metastases and these neoplastic nodes were most common in the area between the lower mediastinum and the celiac axis. Of the 70 patients undergoing radical en-bloc resection, paracardiac lymph nodes had the highest rate of metastatic involvement (40%) while gastric lesser curvature lymph nodes had 29%, and distal splenic/pancreatic lymph nodes 11%. Overall, the frequency of intrathoracic lymph nodal metastases was 7%. Those patients who had intrathoracic lymph nodal metastasis also had intraabdominal lymph nodal secondary tumor involvement. Among postoperative survivors, the percent of 5 year survival with N0 (no positive node) and N1 (1 to 3 positive nodes) stage of disease was 38.6%

and 28.9%, respectively, compared to only 11.5% in those with N2 (4 or more positive nodes) staging. Because long-term survival is dismal in patients with multiple lymph nodal metastasis, preoperative and intraoperative staging is desirable to avoid morbidity of radical resection for EGJ adenocarcinomas. With less than 3 positive nodes, en bloc resection is worthwhile.

How extensive should lymph nodal dissection be to eradicate adenocarcinoma arising at the esophago-gastric junction (EGJ)? On the one hand, an incomplete removal of lymph nodes involved with secondary implants is not curative. On the other hand, unnecessary and radical dissection may be associated with considerable postoperative morbidity. Adenocarcinomas of non-Barrett's epithelium originates in the EGJ and arises from the intraabdominal distal esophagus and gastric cardia. Commonly, intrathoracic and intraabdominal lymph nodes are involved with secondary malignancy, as seen after radical en-bloc resection (1-3).

In this report, we retrospectively examined 104 consecutive patients operated upon for adenocarcinoma of the EGJ. We determined the anatomic and pathologic spread of these malignancies and specifically the pattern of lymph nodal involvement and its relationship to potential curability.

Clinical Studies

Adenocarcinoma of the esophagogastric junction (EGJ) is defined as an epithelial neoplasm in which the main tumor mass is centered at the EGJ with an origin from the subdiaphragmatic esophagus (about 2 to 3cm in length), or the true EGJ, or the first 2 to 3cm of the gastric cardia. For purposes of this report, adenocarcinomas arising in the upper one-third of the body of the stomach, the gastric fundus, diffuse infiltrative carcinoma (i.e., linitis plastica), squamous cell carcinoma of the distal esophagus, and adenocarcinoma arising in Barrett's epithelium are excluded.

The medical records were reviewed of 104 consecutive patients with adenocarcinoma of the EGJ at the Department of Surgery at the Kagoshima University Hospital over 18 years (1973-1990). The male to female ratio was 4.7:1 (86 men and 18 women). The mean patient age was 65.0 years, with an age range of 36-88 years. All 104 patients were operated upon as the initial step of either a planned radical resection or a palliative procedure. Only one was found to have unresectable disease because of multiple hepatic metastases and peritoneal implants. The remaining 103 patients underwent esophagogastrectomy. Resection was classified as en-bloc (i.e., curative) in 70 patients, and palliative in 33 patients by virtue of hepatic metastasis (12 patients), extensive nodal involvement beyond radical resection (9 patients), peritoneal implants (9 patients), and associated cardiovascular disease precluding a prolonged and extensive operation (3 patients). The technique of radical en-bloc resection of the tumor-bearing cardia was carried out as described by the senior author (16). Among 103 patients who underwent esophagogastrectomy, resection was performed through a left thoracoabdominal incision in 54 patients and via a laparotomy alone in 49.

The 103 resected specimens were classified according to the staging system proposed by Skinner and associates (1,2) on

the basis of operative and pathology reports. This staging system is based on wall penetration (W), lymph node involvement (N), and systemic metastases (M). W0 designates a neoplasm limited to the mucosa, W1 tumor penetration through the submucosa and into but not through the muscle, and W2 for primary tumor penetrating full wall thickness. Lymph nodes were classified as N0 when all were negative for metastasis. In this patient series, 30 were N0, W0 or W1, M0 (29%), 17 were N1, W0 or W1, M0 (17%), and 20 were N2, W1 or W2, M0 disease (19%).

Nomenclature and Statistical Methods

Different terminologies have been proposed for lymph node designations in the mediastinum and abdomen removed for treatment of carcinoma of the esophagus and stomach (4,5). For purposes of statistical analysis, we divided the lymph nodes according to the following nomenclature—mid-paraesophageal, left pulmonary, and subcarinal lymph nodes were designated as *middle mediastinal lymph nodes*. *Lower mediastinal nodes* included the distal paraesophageal and paradiaphragmatic nodes. Paragastric cardia, lesser curvature, and lymph nodes along the left gastric artery were included together as *superior gastric lymph nodes*. Lymph nodes at the splenic hilum and those at the celiac axis were also removed. After exploration, the patients first underwent lymph node sampling and if middle mediastinal and/or para-aortic nodes were found on frozen section histopathology to be positive for carcinoma, only a palliative resection was done.

Survival curves were computed using the Kaplan-Meier method. General Wilcoxon test was used to quantify statistical differences. Patients were followed until either the time of death or April 31, 1991.

Pathologic Findings

1. Positive lymph nodes

Lymph nodes obtained from all 103

patients who underwent esophago-gastrectomy were pathologically examined and 64 or 62% had metastatic involvement. Thirty-four of 70 patients or 49% who underwent en-bloc radical resection had lymph node metastases (Table 1). The mean number of lymph nodes examined in the radically resected specimens was 32 with a maximum of 102. A total number of 2269 lymph nodes were examined histologically and 150 were found to be positive for metastasis, a rate of 6.6%.

2. Site of positive lymph nodes

Table 2 shows the metastatic status of the lymph nodes in 103 patients undergoing esophagogastrectomy and in 70 patients who underwent curative en-bloc radical resection. In the latter group, paragastric cardiac lymph nodes had the highest rate of metastases (40%) with lesser curvature lymph nodes having the next highest tumor positivity (29%). The prevalence of intrathoracic and intraabdominal lymph node tumor involvement in the specimens after esophagogastrectomy was 7%. All 7 patients who had intrathoracic lymph node tumor involvement also had intraabdominal lymph node metastatic disease.

3. Survival of lymph node metastases relating to depth invasion of the primary tumor

Among all the patients, lymph node metastases were observed in 32 (55.2%) of 58 patients with W1, and in 31 (79.5%) of 39 patients with W2. No patient with W0 had lymph nodal metastases. The frequency of nodal metastases significantly increased as depth of the tumor advanced. The incidence with N1 (1 to 3 positive nodes) was 36.2% in W1 tumors, and 38.5% in W2 tumors. On the other hand, the incidence with N2 (4 or more positive nodes) was 19.0% in W1 tumor, and 41.0% in W2 tumor.

4. Survival

Follow-up information was available in 104 patients (100%). Thirty-three of the 70 who had undergone en-bloc resection died

from recurrent carcinoma. Seven patients died of other disease including complications of the operation. Thirty patients are still alive. The long-term result shown in Fig. 1 are for 103 patients who underwent en-bloc (70 patients) and palliative resection (33 patients). Survival curves are determined by actuarial method excluding postoperative mortality (7 patients). Five year actuarial survival rates for the 70 patients undergoing en-bloc resection was 39.3% (Fig. 1). Twenty-nine of 33 patients who had a palliative resection died within 2 years (61% survival), but with a 1 year actuarial survival rate of 48% (Fig. 1). Based upon WNM staging, the 103

TABLE 1
Lymph Node Metastases (LNM) in Patients Undergoing Resection for Esophagogastric Junction (EGJ) Adenocarcinoma

Patients n=103	Overall n=70	En-Bloc
(+) LNM	64 (62%)	34 (49%)
(-) LNM	39 (38%)	36 (51%)

TABLE 2
Incidence (%) of Lymph Node Metastasis After Resection for EGJ Adenocarcinoma

Node Location	Overall (n=103)	En-Bloc (n=70)
Cardia (gastric)	55 (53%)	28 (40%)
Lesser curvature	40 (39%)	20 (29%)
Left gastric artery	12 (12%)	6 (9%)
Celiac axis	7 (7%)	2 (3%)
Splenic/pancreatic	15 (14%)	8 (11%)
Abdominal para-aortic	7 (7%)	0 (0%)
Lower para-esophageal	4 (4%)	1 (1%)
Middle para-esophageal	0 (0%)	0 (0%)

EGJ - esophagogastric junction

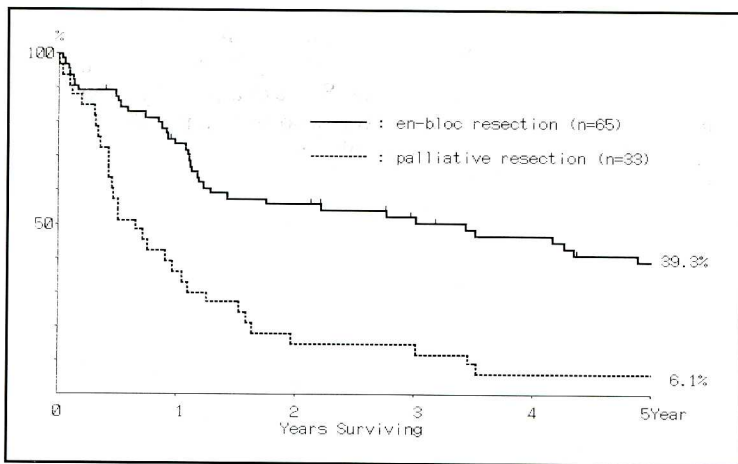


Fig. 1. Comparison of survival after en-bloc versus palliative esophagogastrrectomy during 1973-1990. Survival curves have been determined by actuarial method excluding postoperative mortality. The curves diverge significantly, $p < 0.05$.

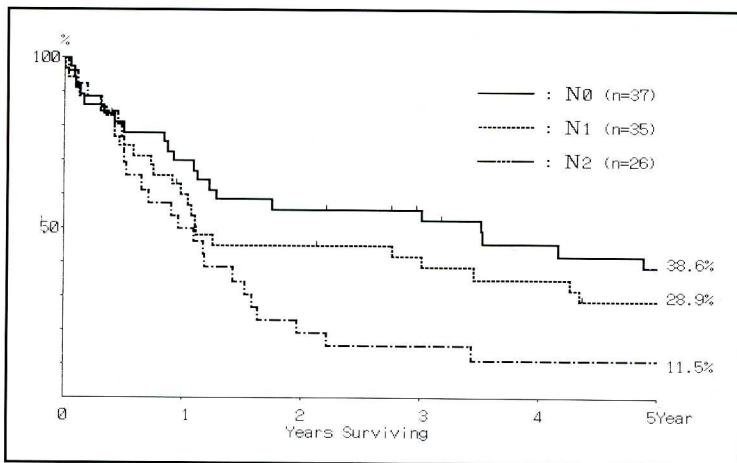


Fig. 2. Comparison of survival after esophagogastrrectomy; N0 (no positive nodes) or N1 (1 to 3 positive nodes) versus N2 (4 or more positive nodes). Survival curves have been determined by actuarial method. The curves diverge significantly, $p < 0.05$.

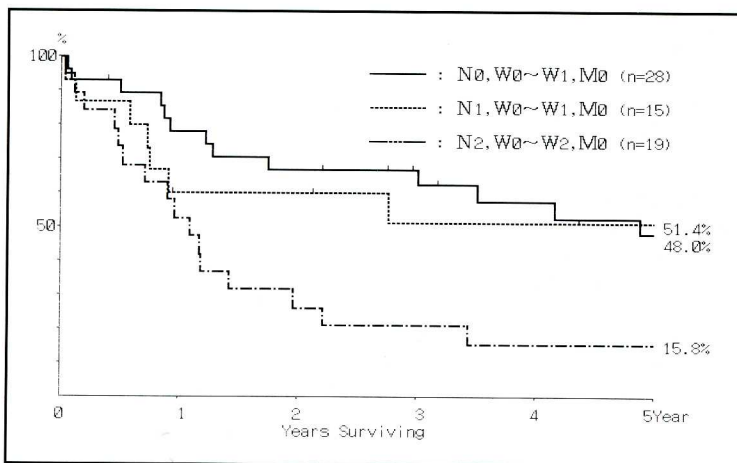


Fig. 3. Comparison of survival after esophagogastrrectomy based upon WNM staging. Among the patients with N0 versus N1 disease, W0 and W1 of the primary site have been combined. Survival curves have been determined by actuarial method. The upper curves do not differ significantly.

patients were divided into two groups—N0, N1, and N2 disease (*Fig. 2*). Among the patients with W0 and W1, a five year survival of the patients with N0 was 48.0% or almost equal to patients with N1 (*Fig. 3*) with 4 or more positive nodes (N2), however, survival was only 15.8% (*Fig. 3*). As for the relationship between anatomic location of metastatic nodal disease and patient survival, 6 of 11 patients with only upper gastric nodal tumor involvement were alive after 5 years.

DISCUSSION

Adenocarcinoma arising at the esophago-gastric junction (EGJ) still remains one of the most difficult malignant neoplasms to treat. Standard operative therapy usually consists of removal of a segment of the distal esophagus and upper stomach and adjacent lymph nodal tissue from the mediastinum and abdomen (6-9); nonetheless, long-term patient survival is poor (10-12). To shed light on this dismal outlook, we focused on the pattern of lymph nodal metastases in this disease. Based on these 104 patients, one of whom had far advanced disease and 103 who underwent resection, it is clear that EGJ adenocarcinoma shows early tumor spread to cardiac, lesser curvature, and distal paraesophageal lymph nodes. This pattern of nodal spread confirms reports of DeMeester (13), Akiyama and associates (4), Castrini and Rappalardo (14). Early metastases to both upper abdominal and lower mediastinal lymph nodes relates to the rich interconnecting anastomotic channels of lymphatics draining the distal esophagus and the cardia of the stomach. In previous work (15,16), we examined the intramural lymphatic system of the distal esophagus and gastric cardia in mongrel dogs using dye injection techniques. When colored dye was injected into the esophageal or gastric mucosa within 2cm of the EGJ, an extensive network of intercommunicating lymphatics was displayed both superior and inferior to the EGJ along the muscularis mucosa. Transmission electron microscopy demonstrated

that the gastric channels filled with dye were lymphatic capillaries with open gaps and overlapping or interdigitating endothelial cell processes. Some dye-filled lymphatic capillaries were also seen in the distal esophageal submucosa. If the anatomic situation is similar in humans, then it is understandable that even early adenocarcinomas arising at the EGJ spread quickly to lymph nodes adjacent to the gastric cardia and distal esophagus.

In 1983, Skinner (1) described a modified technique and patient outcome for using a radical en-bloc resection for treatment of adenocarcinoma of EGJ. The en-bloc resection outlined was based on the concept that the distal half of the esophagus originally had a mesentery in the embryo which governed the development of the blood vascular and lymphatic circulation in this region. In our series, 64 of 103 patients or 62% had lymph nodes positive for secondary tumor. The distribution of these positive lymph nodes was centered between the middle mediastinum and the celiac axis. In the 70 patients undergoing en-bloc resection, paracardiac lymph nodes had the highest rate of metastatic involvement (40%), lesser curvature lymph nodal metastases was 29% and splenic/pancreatic lymph nodal metastases was 11%. The frequency of tumor involvement for both intrathoracic and intraabdominal lymph nodes was 7% with all patients having intrathoracic lymph nodal metastases also displaying intraabdominal lymph node tumor involvement. Accordingly, if radical resection is undertaken, it's imperative that nodal dissection include both the posterior mediastinum and the upper abdomen.

As depth of the tumor advances, not only the frequency of the lymph node metastases but also the number of positive nodes significantly increases. In a previous study, Skinner and his associates (1,2) found that metastases to regional lymph nodes and the depth of tumor penetration into the muscle were independent variables affecting survival after resection for malignancies at the EGJ. Siewert (17) also reported that patients with fewer than 5 tumor infiltrated

lymph nodes have a better prognosis in patients with carcinoma of the esophagus. In our series, we confirmed that 5 year survival in N0 and N1 disease was 38.6% and 28.9%, compared to a dismal 11.5% for N2 disease. Important determinants of survival were both the presence of lymphatic metastases and the number of nodes involved.

In conclusion, the presence of peritumoral lymph node metastases is compatible with long-term patient survival if the nodes are removed as part of an en-bloc resection. Furthermore, operative dissection for eradication of adenocarcinomas arising at the EGJ even if "early" should include radical removal of lymph nodes superiorly from the lower paraesophageal region in the mediastinum to the celiac axis inferiorly. Nonetheless, because long-term patient survival is very poor in patients with multiple lymph nodal metastases (greater than 4), preoperative and intraoperative nodal staging is desirable to avoid morbidity of radical en-bloc resection.

REFERENCES

1. Skinner, DB: En bloc resection for neoplasms of the esophagus and cardia. *J. Thorac. Cardiovasc. Surg.* 85 (1983), 59.
2. Skinner, DB, MK Ferguson, A Soriano, et al: Selection of operation for esophageal cancer based on staging. *Ann. Surg.* 204 (1986), 391.
3. Skinner, DB: Staging for esophageal cancer operation. *Ann. Surg.* 204 (1986), 390.
4. Akiyama, H, M Tsurumaru, T Kawamura, et al: Principle of surgical treatment for carcinoma of the esophagus. *Ann. Surg.* 94 (1981), 438.
5. Japanese Research Society for Gastric Cancer: The General Rules for the Gastric Cancer Study in Surgery and Pathology. *Jap. J. Surg.* 11 (1981), 1275.
6. Sefton, GF, DJ Cooper: Assessment and resection of carcinoma at the gastroesophageal junction. *Surg. Gyn. Obst.* 144 (1977), 563.
7. Paolini A, F Tosato, M Cassese, et al: Total gastrectomy in the treatment of cardia. *Am. J. Surg.* 151 (1986), 238.
8. Mishima, Y, R Hirayama: The role of lymph node surgery in gastric cancer. *World J. Surg.* 11 (1987), 406.
9. Hans, US, B Franz: Cancer of the distal esophagus and cardia. *Ann. Surg.* 203 (1983), 188.
10. Calan, L, G Portier, P Ozoux, et al: Carcinoma of the cardia and proximal third of the stomach. *Am. J. Surg.* 155 (1988), 481.
11. Gatzinsky, P, E Berglin, L Dernevil, et al: Resectional operation and long-term results in carcinoma of the esophagus. *J. Thorac. Cardiovasc. Surg.* 89 (1985), 71.
12. Jackson, JW, DK Cooper, Guvendik, et al: The surgical management of malignant tumours of the oesophagus and cardia. *Br. J. Surg.* 66 (1979), 98.
13. DeMeester, TR, G Zaninotto, KE Johansson: Selective therapeutic approach to cancer of the lower esophagus and cardia. *J. Thorac. Cardiovasc.* 95 (1985), 42.
14. Skinner, DB, KD Dowlatsahi, TR DeMeester: Potentially curable cancer of the esophagus. *Cancer* 50 (1982), 2571.
15. Aikou, T, S Natsugoe, G Tanabe, et al: Lymph drainage originating from the lower esophagus and gastric cardia as measured by radioisotope uptake in the regional lymph nodes following lymphoscintigraphy. *Lymphology* 20 (1987), 145.
16. Aikou, T, H Shimazu: Difference in main lymphatic pathways from the lower esophagus and gastric cardia. *Jap. J. Surg.* 19 (1989), 145.
17. Siewert, JR, AH Hoelsher, HJ Dittler: Preoperative staging and risk analysis in esophageal cancer. *Hepato-gastroenterol.* 37 (1990), 382.

Dr. Takashi Aikou
Department of Surgery
First Department of Surgery
Kagoshima University School of Medicine
1208-1 Usuki Cho
Kagoshima 890, JAPAN