Identification of the Lymphatic Drainage Pattern of Esophageal Cancer with Near-Infrared Fluorescent Imaging

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Abstract

Objective: Nodal status is one of the most important long-term prognostic factors for esophageal cancer. The aim of this study was to evaluate the ability of near-infrared (NIR) light fluorescent imaging to identify the lymphatic drainage pattern of esophageal cancer.

Methods: Patients with distal esophageal cancer or esophagogastric junction cancer scheduled for esophagectomy were enrolled in this study. Before surgery, an endoscopy was performed with submucosal injection of 2 cc of indocyanine green (ICG) around the tumor. Real-time NIR images from the surgical field were obtained for each patient to visualize the lymphatic ICG drainage.

Results: A total of nine patients were included in this study. Ivor Lewis esophagectomy was performed in all cases. ICG drainage was visualized to first drain along the left gastric nodes in eight patients (88.9%) and toward the diaphragmatic nodes in one patient (11.1%). The median number of resected nodes was 32. Three patients (33.3%) presented nodal involvement. All of them had positive nodes in the first nodal station identified with ICG.

Conclusions: Evaluation of the lymphatic drainage pattern with real-time NIR light fluorescent technique is feasible. Distal and esophagogastric junction tumors showed to drain first in the left gastric nodes in most of the cases.

Keywords: esophageal cancer, lymphatic drainage, near-infrared imaging

Introduction

ESOPHAGEAL CANCER SPREADS in a multidirectional way through the submucosal lymphatics to regional nodal stations. Lymph node (LN) metastasis is one of the most important prognostic factors, especially for esophageal adenocarcinoma. Taking into account that an increased number of metastatic LNs are predictive of poor survival, the 2010 American Joint Committee on Cancer (AJCC) staging system markedly changed the N classification of esophageal carcinoma and recommended a more extensive lymphadenectomy to achieve accurate N staging.¹

Nodal disease after esophagectomy is often found in multiple locations, in the abdomen, the chest, or both, and a two-field lymphadenectomy is recommended in the United States.² The application of a lymphatic mapping could increase detection of nodal stations most likely to harbor metastasis, micrometastasis, or isolated metastatic cells. Targeted lymphadenectomy rather

than extensive nodal dissection has the potential of decreasing surgery time and postoperative complications.

The use of radioactive agents and lymphoscintigraphy to determine the lymphatic spread of esophageal cancer is not new. Lymphatic mapping by injecting radioactive sulfur colloid around the tumor to visualize mediastinal LNs was first described by Terui et al. in 1982.³ The authors concluded that visualized nodes with preoperative lymphoscintigraphy indicated a high percentage probability of metastatic nodes. In subsequent studies, lymphatic mapping was performed using radiocolloid tracers such as Technetium 99m or a combination of radioactive colloid and blue dye. These methods, however, have shown some limitations for routine application.^{4,5}

Near-infrared (NIR) light fluorescent imaging has been recently proven to be a safe technology for lymphatic mapping offering improved visibility without the use of radioactive tracer and potentially better accuracy.⁶

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FIG. 1. Endoscopic injection of ICG around the tumor. ICG, indocyanine green.

We performed a pilot study to evaluate the feasibility of NIR method in visualizing lymphatic drainage pattern of known esophageal cancer in patients undergoing esophagectomy.

Materials and Methods

In this retrospective study, a consecutive series of patients with distal esophageal cancer or esophagogastric junction cancer scheduled for esophagectomy were included. Pre-operative work-up included endoscopic ultrasound (EUS) and positron emission tomography (PET-CT) in all patients. Patients underwent induction chemotherapy and radiation followed by surgery or upfront surgery as indicated by the stage of their tumor.

Using a standard adult endoscope and an endoscopic needle, patients were injected with 2 cc of indocyanine green (ICG; Novadaq Technologies, Bonita Springs, FL) doubly diluted in sterile water (1.25 mg/mL) into the esophageal submucosa at the four quadrants (0.5 cc for each injection) around the tumor before initiating the laparoscopic phase of the esophagectomy (Fig. 1).

Upon entering the abdomen with the Novadaq PINPOINT® 10-mm 45° camera, real-time NIR fluorescence images were obtained from the surgical field. This system has the ability to collect simultaneously standard visible light images, black and white NIR image, and a merged image with the NIR

signal shown in green in the context of a visible light image. Qualitative assessment by color visualization only was available. Pattern of ICG drainage was recorded in each patient. The first nodal station where the ICG drained to was dissected and sent separately to pathology. The patients then underwent standard esophagectomy with two-field lymphadenectomy as previously described.⁷ Nodal stations were classified according to the American Joint Committee on Cancer 7th Edition.⁸

Surgical esophageal specimen and LNs were fixed in formalin solution and then embedded in paraffin. Tissue sections were stained with hematoxylin and eosin for routine histological examination. All resected specimens were evaluated by one experienced GIA pathologist.

Results

A total of nine patients with esophageal cancer were included in this study. Five patients (55.6%) received chemoradiation therapy before surgery. The Ivor Lewis approach was performed in all cases, with a minimally invasive approach in eight of them (88.9%). The in-hospital and 90 days mortality was 0%.

The ICG highlighted the lymphatic drainage within 15–20 minutes from the injection and was detected with NIR imaging to drain first in the nodal station along the left gastric artery (station 17) in eight patients (88.9%) and in the diaphragmatic nodes (station 15) in only one (11.1%) (Figs. 2 and 3). The median number of resected nodes was 32 (IQR 18–45). A total of three patients (33.3%) had LN involvement on the final pathology. The first nodal station identified with ICG contained positive nodes in all of these patients.

The pathologic findings of all nine patients are shown in Table 1.

Discussion

LN status is one of the most important long-term prognostic factors for esophageal adenocarcinoma.^{9,10} Unfortunately, preoperative imaging to evaluate the extent of LN involvement with PET-CT has several limitations and EUS has been associated with high rates of inaccuracy.^{11,12} Intraoperative identification of the anatomical lymphatic drainage of esophageal tumors may help surgeons to avoid unnecessarily

FIG. 2. NIR imaging with detection of ICG along the left gastric artery. ICG, indocyanine green; NIR, near-infrared.

FIG. 3. NIR imaging with detection of ICG in diaphragmatic nodes. ICG, indocyanine green; NIR, near-infrared.

extended lymphadenectomies. In this pilot study, we aimed to evaluate the feasibility of a novel *in vivo* NIR imaging technique to identify the lymphatic nodal drainage pattern of distal esophageal tumors. We found that most of the patients presented lymphatic drainage toward the left gastric artery nodes as the first site of drainage.

Previously, lymphatic spread was intraoperatively identified by either radiation techniques with a gamma probe or observing blue dye. In esophageal cancer, lymphatic mapping with radioactive tracer was first described by Kitagawa et al. in 2000 with encouraging results.¹³ Recently, Boone et al.¹⁴ showed an intraoperative lymphatic drainage identification rate of 38% with the use of gamma probe. They found that the main cause of failure was the accumulation of the radioactive tracer in periesophageal nodes in direct proximity to the tumor, with the tumor radioactivity surpassing the radioactivity of surrounding nodes. They concluded that the intraoperative gamma probe would be beneficial only in detecting cervical nodes or for exploring the abdominal and thoracic cavities after resection. As to dye-guided dissection, Burian et al.¹⁵ showed discouraging results in distal esophageal tumors with difficulties to differentiate blue colored LNs. It is difficult to recognize LN with dye until the medi-

astinal pleura is opened and/or mediastinal nodes are black due to anthracosis. Coordinating preoperative lymphoscintigraphy after endoscopic peritumoral injection and same-day surgery is also often not practical. The radioactive tracer and the dual tracer methods may also carry some radiological hazard, and special equipment is necessary to detect the radioisotope intraoperatively.¹⁴ The development of new optical imaging techniques may provide surgeons with an extra tool to identify lymphatic drainage in real-time during surgery. In our small series, ICG was easily detected intraoperatively and the lymphatic drainage pattern was identified in all patients. After 15–20 minutes from the ICG injection, we were able to follow the dye from the tumor migrating toward the left gastric artery nodal station (station 17) in 88.9% of the patients with distal esophageal cancer or esophagogastric junction cancer. Hachey et al.⁶ reported NIR + regional nodes in 6 of the 10 patients with esophageal adenocarcinoma included in their study. They reported that in five of those six patients (83.3%) ICG was first identified in pericardial nodes. However, the aim of the authors was different from ours as they wanted to find one specific sentinel node and we were looking at patterns of drainage, rather than a single sentinel node. The clinical impact of this

TABLE 1. CHARACTERISTICS OF THE PATIENTS ENROLLED IN THE STUDY

Patient	Cancer type	Induction	pT	pN	No. of nodes removed	First nodal station identified	No. of N+	Location of N+
1	Adeno	Yes	1b	2	32	Left gastric nodes	6	Left gastric and lower paraesophageal nodes
2	Adeno	Yes	0	0	18	Left gastric nodes	0	
3	Adeno	No	1a	0	70	Left gastric nodes	0	
4	Adeno	No	1a	0	16	Left gastric nodes	0	
5	Adeno	No	1a	0	45	Left gastric nodes	0	
6	Adeno	Yes	3	3	48	Left gastric nodes	26	Left gastric, lower and middle paraesophageal, subcarinal, and right lower paratracheal nodes
7	Adeno	Yes	3	1	26	Left gastric nodes	2	Left gastric nodes
8	SCC	Yes	1b	0	40	Left gastric nodes	0	
9	Adeno	No	1a	0	15	Diaphragmatic nodes	0	

Adeno, adenocarcinoma; N+, metastatic lymph nodes; pN, pathological nodal metastasis; pT, pathological tumor depth of invasion; SCC, squamous cell carcinoma.

finding is promising as it may lead to identify the lymphatic pathway of distal esophageal tumors, with the potential benefit of sampling critical regional LNs for better staging. Further experience in endoscopic peritumoral ICG injection and timing for intraoperative detection is needed to accurately detect lymphatic drainage routes in patients with esophageal cancer.

Lymphatic drainage of the esophagus consists in a complex system of network of lymph capillaries in the lamina propria and muscularis mucosae, and metastatic lymphatic spreading may occur longitudinally upward or downward and transversally through the muscularis propria. For this reason, it may be difficult to compare cancer of the esophagus with other types of neoplasms such as breast cancer or melanoma where a sentinel node can be pursued to predict nodal status. In fact, previous studies have failed to demonstrate the clinical value of sentinel node in esophageal cancer.^{14,16} In contrast, identification of the first nodal stations of cancer drainage may be more valuable, and the presence of nodal metastasis in this station may be better at predicting the overall nodal status. Interestingly, we found that all of the three patients with nodal disease presented nodal involvement in the first nodal station identified with ICG and no one had nodal disease elsewhere without involvement of the primary station. This finding suggests that histopathological examination of the first nodal station may lead to avoid unnecessary extensive lymphadenectomy with the potential of reducing operative time and surgical morbidity. Moreover, it would allow to select early stage esophageal cancer patients with real N0 for esophageal preservation with endoscopic resection. Although these are only few cases, the results are encouraging.

This study has several limitations. First, a small number of patients were included in the analysis, and therefore, the clinical value of our findings is still uncertain. Second, as a consecutive series of distal or esophagogastric junction tumors were enrolled in the study, no inclusion criteria as regards to histologic type or clinical stage was determined. Thus, both squamous cell carcinoma and adenocarcinoma were included as well as patients with and without induction therapy. This, however, was meant to be a feasibility study only, and further investigation will follow to better understand the value of real-time lymphatic mapping in esophageal cancer.

Conclusions

Lymphatic mapping with ICG and near-infrared light fluorescent imaging is feasible. Lymphatic spread in patients with tumors of the distal esophagus and esophagogastric junction appears to follow a specific pattern, and the left gastric nodes seem to be the most likely first nodal station involved.

Disclosure Statement

Dr. Molena has been a speaker for the educational meeting organized by Novadaq, Inc. For all other authors, no competing financial interests exist.

References

1. Yuan F, Qingfeng Z, Jia W, et al. Influence of metastatic status and number of removed lymph nodes on survival of patients with squamous esophageal carcinoma. *Medicine* 2015;94:1–5.
2. Peyre CG, Hagen JA, DeMeester SR, et al. The number of lymph nodes removed predicts survival in esophageal cancer: An international study on the impact of extent of surgical resection. *Ann Surg* 2008;248:549–556.
3. Terui S, Kato H, Hirashima T, et al. An evaluation of the mediastinal lymphoscintigram for carcinoma of the esophagus studied with 99mTc rhenium sulfur colloid. *Eur J Nucl Med* 1982;7:99–101.
4. Arima H, Natsugoe S, Uenosono Y, et al. Area of nodal metastasis and radioisotope uptake in sentinel nodes of upper gastrointestinal cancer. *J Surg Res* 2006;135:250–254.
5. Kato H, Miyazaki T, Nakajima M, et al. Sentinel lymph nodes with technetium-99m colloidal rhenium sulfide in patients with esophageal carcinoma. *Cancer* 2003;98:932–939.
6. Hachey KJ, Gilmore DM, Armstrong KW, et al. Safety and feasibility of near-infrared image-guided lymphatic mapping of regional lymph nodes in esophageal cancer. *J Thorac Cardiovasc Surg* 2016;152:546–554.
7. Mungo B, Lidor AO, Stem M, et al. Early experience and lessons learned in a new minimally invasive esophagectomy program. *Surg Endosc* 2016;30:1692–1698.
8. American Joint Committee on Cancer (AJCC). *AJCC Cancer Staging Handbook 7th Edition*. Chicago: Springer, 2010.
9. Cabau M, Luc G, Terrebbonne E, et al. Lymph node invasion might have more prognostic impact than R status in advanced esophageal adenocarcinoma. *Am J Surg* 2013;205:711–717.
10. Bhamidipati CM, Stukenborg GJ, Thomas CJ, et al. Pathologic lymph node ratio is a predictor of survival in esophageal cancer. *Ann Thorac Surg* 2012;94:1643–1651.
11. Little SG, Rice TW, Bybel B, et al. Is FDG-PET indicated for superficial esophageal cancer? *Eur J Cardiothorac Surg* 2007;31:791–796.
12. Crabtree TD, Yacoub WN, Puri V, et al. Endoscopic ultrasound for early stage esophageal adenocarcinoma: Implications for staging and survival. *Ann Thorac Surg* 2011; 91:1509–1515.
13. Kitagawa Y, Fujii H, Mukai M, et al. The role of the sentinel lymph node in gastrointestinal cancer. *Surg Clin North Am* 2000;80:1799–1809.
14. Boone J, Hobbink MG, Schipper ME, et al. Sentinel node biopsy during thoracoscopic esophagectomy for advanced esophageal cancer. *World J Surg Oncol* 2016; 14:117.
15. Burian M, Stein HJ, Sendler A, et al. Sentinel node detection in Barrett's and cardia cancer. *Ann Surg Oncol* 2004;3: 255S–258S.
16. Nagaraja V, Eslick GD, Cox MR. Sentinel lymph node in oesophageal cancer—A systematic review and meta-analysis. *J Gastrointest Oncol* 2014;5:127–141.

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