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HOW TO DO IT

Application of the HyperEye Medical System for esophageal cancer surgery: a preliminary report

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Abstract The HyperEye Medical System is a newly developed device that allows for the visualization of the fluorescent image of indocyanine green enhanced by near-infrared light among the surrounding vivid color images. We recently applied this system to confirm the blood flow of an esophageal substitute, and for sentinel node navigation during esophagectomy. Five consecutive patients with thoracic esophageal cancer who underwent a subtotal esophagectomy between June 2010 and May 2011 were enrolled in the study. The esophageal substitute used for reconstruction was the stomach and ileocecum in four and one cases, respectively. In all cases with a reconstructive stomach, fine arterial blood flow and venous perfusion were observed. The blood flow of the reconstructive colon was poor before microvascular anastomosis, however, it dramatically increased after anastomosis. Concerning the sentinel node navigation, the fluorescence of lymph nodes, lymphatic vessels, and the tumor site were detected. The postoperative courses of all cases were uneventful, with no mortalities or anastomotic leakage occurring.

Keywords HyperEye Medical System · Esophagectomy · Indocyanine green

Introduction

The HyperEye Medical System (HEMS; Mizuho Ikakogyo Co., Ltd., Tokyo, Japan) is a new device consisting of an ultra-high sensitive color camera with a charge-coupled device (CCD), which captures indocyanine green (ICG) fluorescence illuminated with light emitting diodes (LED) (Fig. 1). As this system can simultaneously detect colored visible light and near-infrared rays, and can be used under bright room light, an operation can be performed under the guidance of ICG fluorescence under normal surgical suite lighting. The HEMS was developed by Handa and his group at Kochi University [1, 2] and was first used for coronary artery bypass graft (CABG) surgery. It is also applied in sentinel node navigation surgery (SNNS) for head and neck cancer or breast cancer [3], because the surgical field is superficial, and application of this device is relatively easy.

We previously tested the HEMS in swine and found that it was suitable for deep-layer, prolonged and back table observations [4, 5]. We recently applied the HEMS to confirm the blood flow in the esophageal substitute after esophagectomy and for SNNS during surgery for esophageal cancer. We herein report the results of this preliminary experience.

Methods

Five consecutive subjects with thoracic esophageal cancer who underwent subtotal esophagectomy between June 2010 and May 2011 were enrolled in this study. This study was approved by the local ethics committee of the International University of Health and Welfare Mita Hospital, and written informed consent was obtained from all subjects. Table 1 shows the clinicopathological data on these patients. Their stages of disease ranged from IIB to IV according to the 2010 7th edition AJCC TNM classification [6]. Patient #5, who had neuroendocrine carcinoma (NEC),

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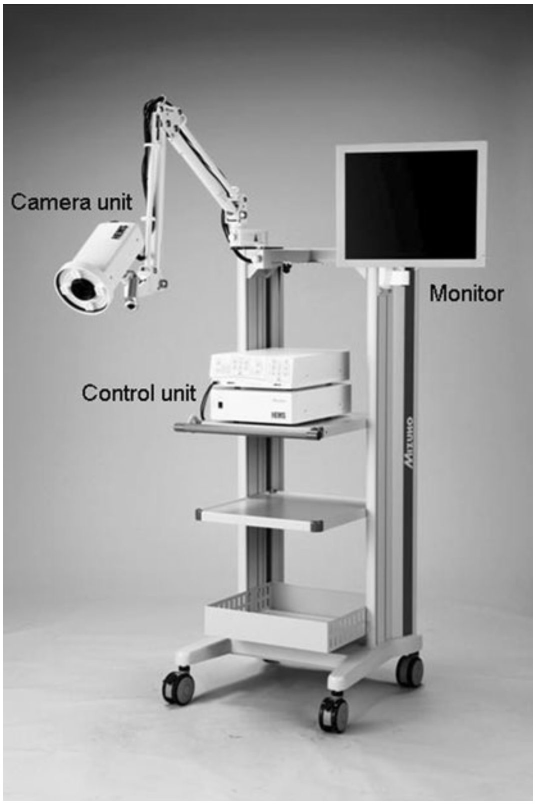

Fig. 1 The HyperEye Medical System. This system can visualize the fluorescent image of ICG enhanced by near-infrared light among the surrounding vivid color images

was staged using the classification for squamous cell carcinoma (SCC) [6, 7]. All patients were administered two courses of neo-adjuvant chemotherapy consisting of 5-fluorouracil (800 mg/m^2/day, continuous infusion on days 1–5) and cisplatin (80 mg/m^2 on day 1) [8, 9]. Subtotal esophagectomy with three-field lymphadenectomy was performed in all five patients. Digestive continuity was reestablished in all patients by end-to-side anastomosis using a curved intraluminal stapler (Proximate® ILS, Johnson & Johnson Co., Ltd., Tokyo, Japan) that was 25 mm in diameter. The substitution used for reconstruction was the stomach through the retrosternal route in four cases (Patients #1–#4), and the ileocecum through the subcutaneous route in one case (Patient #5). This latter patient had a history of gastrectomy, and microvascular anastomosis of the iliocolic artery and internal thoracic artery was additionally performed (the 'supercharge' technique).

The blood flow and perfusion of the reconstructive substitute were examined using the HEMS in all patients. Among the four subjects with reconstruction using the stomach, the blood flow and perfusion were examined before dissection of the area of the left gastric artery in one case (Patient #1) and after dissection of the same area in the other three cases (Patients #2–#4). In Patient #5, the blood flow of the reconstructive colon was examined before and after arterial microvascular anastomosis.

After preparation of the substitute, the camera was positioned above the operating area of interest at a distance of 50–70 cm. ICG dye (0.5 g/kg body weight) was then injected. The images were simultaneously stored in AVI formatted files. The feasibility of HEMS was examined by comparing the results of blood flow and perfusion estimated by HEMS in relation to the postoperative courses of the patients and the development of complications, such as anastomotic leakage and stenosis.

The feasibility SNNS was tested in one case (Patient #1). For SNNS, 0.2 ml of ICG dye (0.05 mg/ml) was injected at four points under the mucosal layer of the esophagus near the tumor site using an endoscope on the day before the surgery, in line with the method of SNNS used for gastric surgery [5]. At the time of thoracotomy and after esophageal mobilization, the HEMS was used to detect the ICG fluorescence for intraoperative image acquisition. The feasibility of HEMS was examined by comparing the results obtained using the HEMS with the results of the preoperative evaluation by CT and the pathological results of lymph node involvement [10].

Results

In all cases with reconstruction using the stomach, sufficient arterial blood flow and venous perfusion were observed by the HEMS. The arterial blood supply provided via a marginal artery was much more abundant than the direct blood flow in the gastric tissue. Before the dissection along the region of the left gastric artery in the lesser curvature, greater blood flow was supplied via the route from the right gastric artery to the left gastric artery than via the right gastroepiploic artery. After dissection along the region of the left gastric artery in the lesser curvature, the blood supply was alternatively delivered via the right gastroepiploic artery, which was almost equal in quantity, but flowed at a slower rate than that via the right gastric artery (Fig. 2a, b). Venous blood perfusion was observed about 15–20 s after the arterial blood supply began (Fig. 2c). Although the arterial blood supply was equally good throughout the substitute, the venous blood perfusion was relatively poor in the top area of the substitute (Fig. 2d). An abundant blood flow in the remnant esophageal stump was also observed by the HEMS.

The blood flow in the reconstructive colon as determined by the HEMS in Patient #5 was poor before the arterial microvascular anastomosis; therefore, the substitute was dark in color, and venous congestion was observed macroscopically (Fig. 3a). After micro-arterial anastomosis, the arterial blood flow via the ileocolic artery

Table 1 Clinicopathological findings of the enrolled subjects

No	Age	Gender	Histology	T	N	M	Grade	Location	Stage
1	71	Female	SCC	3	2	0	G2	Middle	IIIB
2	64	Male	SCC	3	3	1	G2	Lower	IV
3	69	Male	SCC	3	1	0	G2	Lower	IIIA
4	68	Male	SCC	2	0	0	G2	Middle	IIB
5	64	Male	NEC	2	2	0	G3	Middle	IIIA

SCC squamous cell carcinoma, *NEC* neuroendocrine carcinoma

Stage grouping, according to the 7th AJCC [6]; G2, moderately differentiated; G3, high mitotic rate according to the 4th WHO [7]

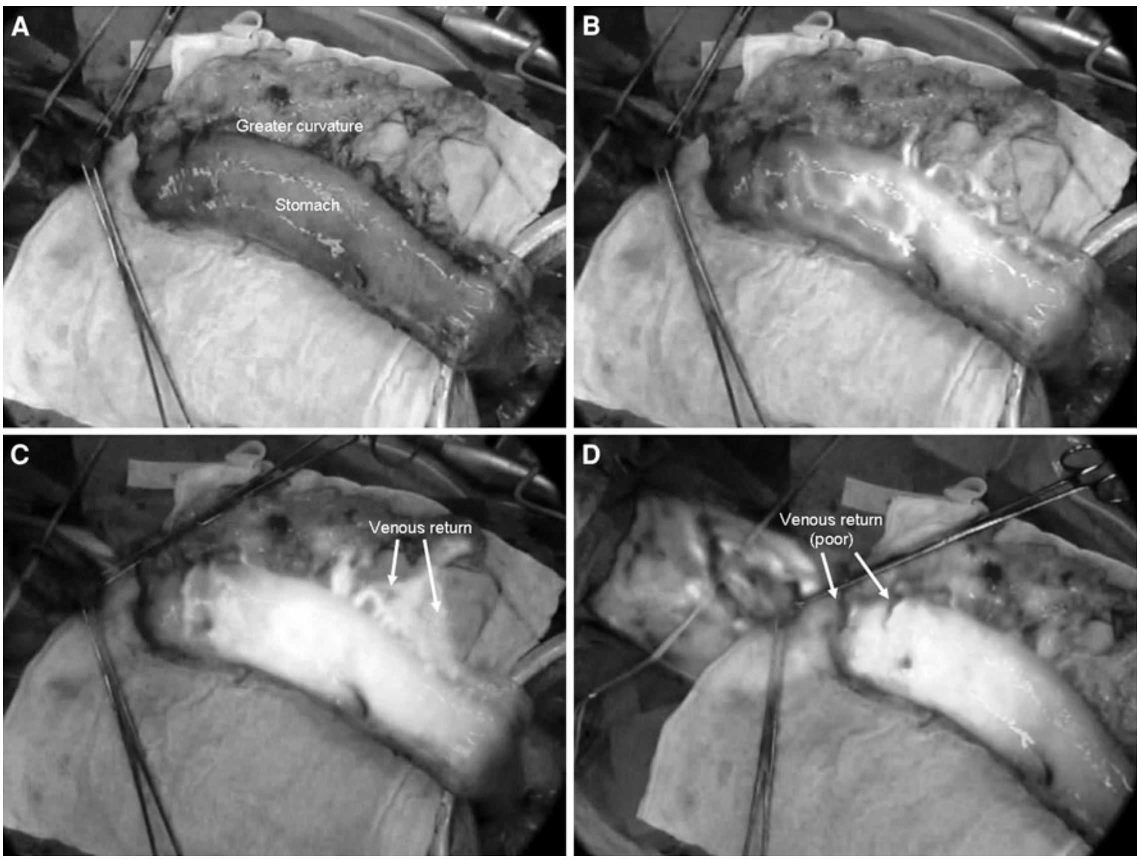

Fig. 2 **a**, **b** After dissection along the region of the left gastric artery in the lesser curvature, the blood supply was alternatively delivered via the right gastroepiploic artery. **c** Venous blood perfusion was observed about 15–20 s after the arterial blood supply began. **d** Although the arterial blood supply was equally well distributed, the venous blood perfusion was relatively poor in the top area of the substitute

dramatically increased (Fig. 3b) and the macroscopic color and congestion were improved. It took a slightly longer time from the appearance of arterial blood flow to the observation of venous blood perfusion in the colon than in the stomach, about 20–30 s.

Concerning SNNS, many lymph nodes suspected of being metastatic and intrametastatic lymphatic vessels were fluorescent in the paraesophageal and lower mediastinal region, especially in the area along the left recurrent nerve (Fig. 4). The ICG-injected site in the esophagus was also intensely fluorescent. This finding was compatible with the preoperative diagnosis by CT scanning and the pathological results of the resected specimen (metastasis was present in #101R, right cervical paraesophageal; #106recL, left recurrent nerve; #108, middle thoracic paraesophageal; #1, right cardiac; #3: along the lesser curvature) [10], although the fluorescence was too intense in all of the fields to provide useful information because some cancer-free lymph nodes and normal vessels were also fluorescent.

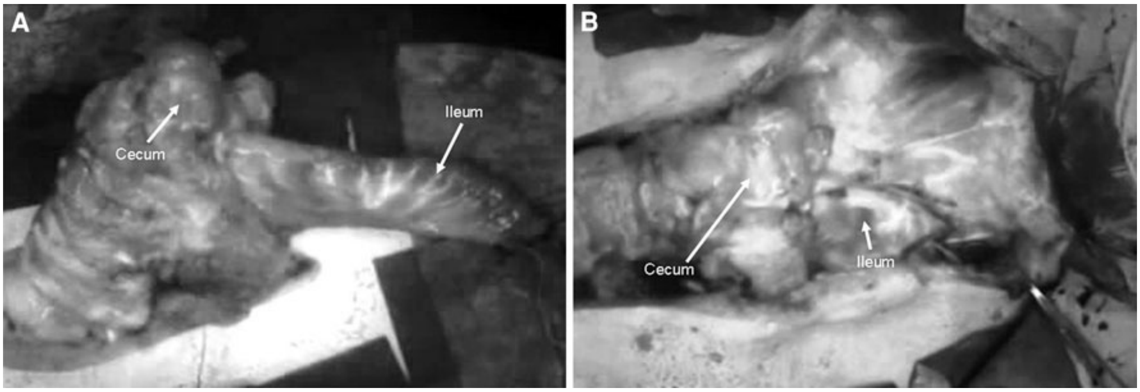

Fig. 3 **a** The blood flow in the reconstructive colon detected by the HEMS was poor before arterial microvascular anastomosis. **b** After micro-arterial anastomosis, the arterial blood flow via the iliocolic artery dramatically increased

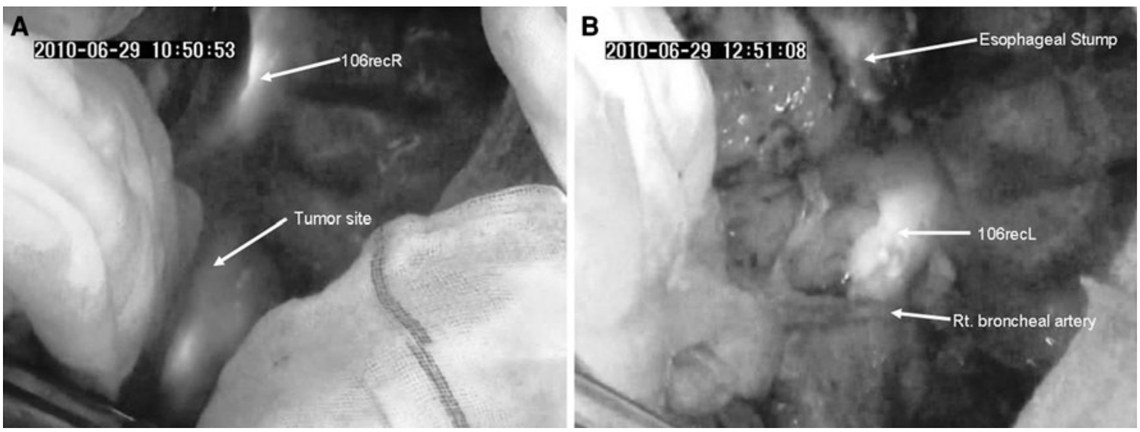

Fig. 4 Concerning SNNS, many lymph nodes suspected of being metastatic and the lymphatic vessels were fluorescent in the paraesophageal and lower mediastinal region, especially in the area along the left recurrent nerve. At thoracotomy (**a**) and after esophageal mobilization (**b**)

The postoperative courses of all of the cases were uneventful, with no mortalities or anastomotic leakage observed. Recurrent nerve palsy and anastomotic stenosis were observed in two and one cases, respectively.

Discussion

The HEMS is a new device consisting of an ultra-high sensitive color CCD camera, which captures the ICG fluorescence illuminated with a LED. In principle, ICG will generate 800–850 nm near-infrared fluorescence after its administration if near-infrared rays of 760–780 nm are used for irradiation. Near-infrared rays, which are essentially invisible, can be visualized by projection on a monitor and recording of the fluorescence by a special CCD camera. The HEMS has a 760-nm light source (LED) as the excitation light, and an 840-nm near-infrared cut-on filter. As the image shown on the monitor is in color, operators can view the positional relationship between the target tissue and the surrounding tissue, and high efficiency as an image support device during surgery can be expected for the HEMS. Moreover, the image sensor built in the camera is a single CCD, and since this system simultaneously records visible light and near-infrared rays, it shows a natural image. The work distance from the photographic subject to the front of the camera is 50–70 cm, so the camera is sufficiently far away so as not to get in the way of the operation.

This new device is now being applied for CABG surgery and SNNS in head and neck cancer and breast cancer [1–3]. We previously tested the HEMS in swine and found it to be suitable for deep-layer, prolonged and back table observations [4]. After the animal studies, we applied this new device in the field of gastroenterology for (1) SNNS for gastric [5] and colonic cancer, (2) the detection of liver tumors and identification of the demarcation line in hepatic surgery, and (3) confirmation of the blood flow of the bowel in emergency surgeries, such as strangulation ileus or non-occlusive mesenteric ischemia.

Although the stomach is said to have sufficient intraluminal blood flow for use as a reconstruction vehicle [11, 12], the direct blood supply via the marginal arteries was shown to be the main source for the stomach in this study. In addition, blood was observed to be supplied more from the right gastric artery than from the right gastroepiploic artery. The arterial blood supply and venous perfusion were confirmed to be poor in the colon as a substitute, not only macroscopically, but also by the HEMS. Many reports have advocated the necessity of microvascular anastomosis for supercharged blood flow, and it is reported to be essential, especially when reconstruction is performed using the ileum or colon [13–16] and for esophageal reconstruction after salvage esophagectomy [17]. At our institute, the procedure has been performed on a case-by-case basis according to the macroscopic findings for the reconstructive substitute. The use of the HEMS can play an essential role in deciding on the use of an additional or improved procedure. That is, additional microvascular anastomosis should be kept in mind not only for the colon and jejunum but also for the stomach, or preservation of the route from the right gastric artery to the left gastric artery in the lesser curvature should be considered to maintain the blood flow of the stomach via this route.

Concerning SNNS, we concluded that the appropriate density of ICG dye was 0.05 mg/ml for SNNS, and that it should be injected near the tumor site using an endoscope the day before gastric cancer surgery [5]. Although in this study, our experience with SNNS included only one patient, we found that the same condition used in gastric cancer surgery was not suitable for SNNS in esophageal cancer surgery, because the fluorescence was too intense. The reason is unclear, but it may be because there is less fat and connective tissue in the mediastinum than in the abdomen, or because the esophagus has only adventitia without peritoneum, so that the ICG dye can expand over a wider area. Additionally, the mediastinum was relatively deep and narrow, making it difficult to view the area; thus, whole-field observation was difficult. Other conditions appropriate for SNNS should be examined for esophageal cancer surgery.

In the future, the luminescence of the HEMS should be quantified, and the necessity of microvascular anastomosis should be decided objectively depending on that value. This value may predict not only anastomotic leakage, but also anastomotic stenosis, because anastomotic stenosis may in some part result from ischemia and micronecrosis. In addition, the results of this method should be assessed in comparison with other modalities, such as transit-time flowmetry or angiography [18, 19]. To improve the conditions for SNNS, the ICG density should be decreased to decrease the intensity of the fluorescence, making the HEMS applicable for esophageal cancer surgery.

In conclusion, the present preliminary study showed that HEMS-guided esophageal surgery was feasible under room light. Intravenous injection of ICG dye at 0.5 g/kg body weight was adequate for observing the blood flow in the esophageal substitute during surgery for esophageal cancer.

Conflict of interest None of the authors (K. Kubota, M. Yoshida, J. Kuroda, A. Okada, K. Ohta, and M. Kitajima) has any conflict of interest.

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