Annals of Medicine and Surgery 20 (2017) 61–65

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

New method of indocyanine green fluorescence sentinel node mapping for early gastric cancer

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HIGHLIGHTS

- ICG fluorescence SN mapping for early gastric cancer using PINPOINT® is described.
- ICG positive nodes were able to be observed in all the patients.
- The mean of ICG positive lymph nodes was 8.6.
- One patient had a metastatic lymph node in SN.
- PINPOINT® make identification of SNs easy and simple for gastric cancer surgey.

ARTICLE INFO

Article history:
Received 18 February 2017
Received in revised form
11 June 2017
Accepted 11 June 2017

Keywords:
Gastric cancer
Sentinel node
Gastrectomy
PINPOINT®

ABSTRACT

Background: The present study describes the retrospective feasibility study of ICG fluorescence SN mapping in back-table for early gastric cancer using PINPOINT®.

Method: SN mapping were performed as following; the day before surgery, 0.5 ml ICG was injected endoscopically in four quadrants of the submucosa surrounding the gastric cancer using an endoscopic puncture. Intraoperatively, the gastrocolic ligament was divided to visualize all possible directions of lymphatic flow from the stomach. PINPOINT® (NOVADAQ, Canada) was used to illuminate regional lymph nodes from the serosal side. Positive staining was confirmed by at least 3 surgeons and an endoscopist during surgery (Figure 1). Lymph node dissection and gastrectomy were performed according to the criteria of gastric cancer treatment guidelines of JGCA.

Result: All 6 patients had gastrectomy with laparoscopic approach. ICG positive lymphatic flow and lymph nodes were able to be observed in all the patients. Final pathological diagnosis was all StageI and curative resection.

All the patients had ICG positive lymphatic area in left gastric artery (LGA) area.

Two patients with tumor located in L area had ICG positive flow to right gastroepipoloic artery (RGEA) area. The mean of ICG positive lymph nodes was 8.6. One patient had a metastatic lymph node in station No.4, which was positive for ICG.

Conclusion: Our method made identification of ICG positive lymph nodes easy in SN mapping in back-table under room light. Although further accumulation and analysis are necessary, we may be able to apply this method for intraoperative SN mapping of laparoscopic gastric cancer surgey.

1. Introduction

Gastrectomy with D2 dissection has been a standard surgical procedure for resectable gastric cancer in the treatment guidelines of the Japanese Gastric Cancer Association (JGCA) [1,2]. These recommendations are based on the large amounts of data obtained from patients who had undergone gastrectomy in Japan.

However, some studies from western countries reported that patients with gastric cancer treated by D2 dissection had a significantly higher rate of complications, a higher postoperative

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http://dx.doi.org/10.1016/j.amsu.2017.06.019

mortality rate and a longer hospital stay than those who had D1 dissection [3]. More attention should be payed to the improvement of postoperative quality of life without impairing long term outcome. Gastrectomy with D2 seems to be an overly invasive surgery for patients with pN0 gastric cancer.

According to this background, sentinel node concept has been introduced for early gastric cancer surgery. In fact, Several successful single-institution studies for sentinel node (SN) mapping in gastric cancer have been reported [4–8].

However, the indications and the procedures applied for SN mapping in these previous reports varied. Kitagawa et al. conducted prospective multicenter trial for sentinel node mapping using the dual tracer method with technetium 99 m–labeled tin colloid and 1% isosulfan blue dye [9]. In several institutions, indocyanine green fluorescence SN mapping has been performed [8,14].

Recently, PINPOINT® (NOVADAQ, Canada) has developed for ICG fluorescence guided surgery [10–12]. Evaluations of the blood supply for reconstructed organ and anastomosis in gastrointestinal surgery has been reported. In our institute, PINPOINT has been applied for gastric cancer surgery to identify lymphatic flows and SNs.

The present study describes the retrospective feasibility study of ICG fluorescence SN mapping in back-table for early gastric cancer using PINPOINT.

2. Patients and methods

The protocol was approved by the Ethics Committee for Biomedical Research of the International University of Health and Welfare Hospital, and all patients provided informed consent.

Nine patients diagnosed as early gastric cancer with no obvious metastasis were admitted to our hospital between September and December in 2015. In this study, six patients with cT1N0 or cT2N0 gastric cancer were enrolled and evaluated retrospectively.

Injection of the tracer was performed according to Kitagawa's dual tracer method [4,9]. The day before surgery, ICG (ICG: Diagnogreen®; Dai-Ichi Sankyo Pharm, Tokyo, Japan) was injected in four quadrants of the submucosal layer of the primary lesion by using an endoscopic puncture needle (Fig. 1). As a preliminary trial, for five case each 50.0 μg/ml of the ICG was injected. During the course of this trial, quality of camera scope for ICG fluorescence imaging was fixed and improved, and the number of ICG positive lymph node increased too much. Therefore, we decrease the concentration of ICG to 33.3 μg/ml for last case.

Intraoperatively, surgical field was made to visualize all possible directions of lymphatic flow. For ICG fluorescence imaging, PINPOINT® was used and illuminated regional lymph nodes from the serosal side with three modes (Pinpoint mode, spy mode, colorized mode) (Fig. 2). Positive staining was confirmed by at least 3 surgeons during surgery.

Lymph node dissection and gastrectomy were performed according to the criteria of gastric cancer treatment guidelines of JGCA regardless of intraoperative SN result. Range for the node dissection and gastrectomy depended on the preoperative diagnosis of the depth and location. This is because SN biopsy has established false negative rates and has not been incorporated into standard work-up as per oncological surgery guidelines (such as NCCN).

Postoperatively, back-table observation of staining nodes and pathological examination with haematoxylin and eosin staining was performed (Fig. 3). Findings of macroscopy and pathology were described according to the Japanese classification of gastric carcinoma (3rd English edition) [3].

Injection of the ICG and laparoscopic gastrectomy were performed by two surgeons (Hironori Ohdaira and Masashi Yoshida). Pathological examination were done by one pathologist (Shinya Okada).

3. Results

No allergic reaction were observed after ICG injection.

All the six patients' characteristics are listed in Table 1. All the patients had gastrectomy with laparoscopic approach. Case⑤ patient was suspected that the depth of tumor was muscularis propria. We judged that this clinical T2 patient had no lymph

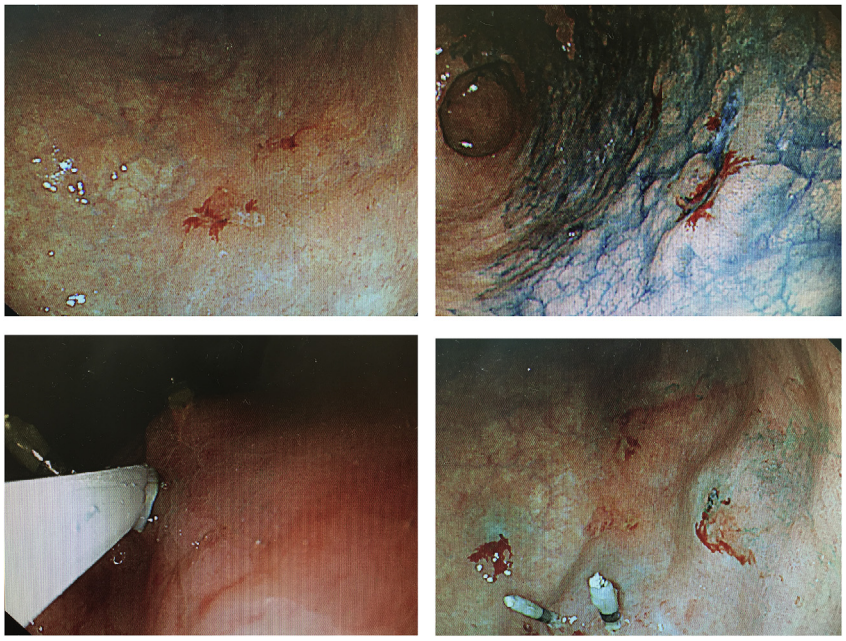

Fig. 1. Injection of the tracer. The day before surgery, ICG was injected in four quadrants of the submucosal layer of the primary lesion by using an endoscopic puncture needle.

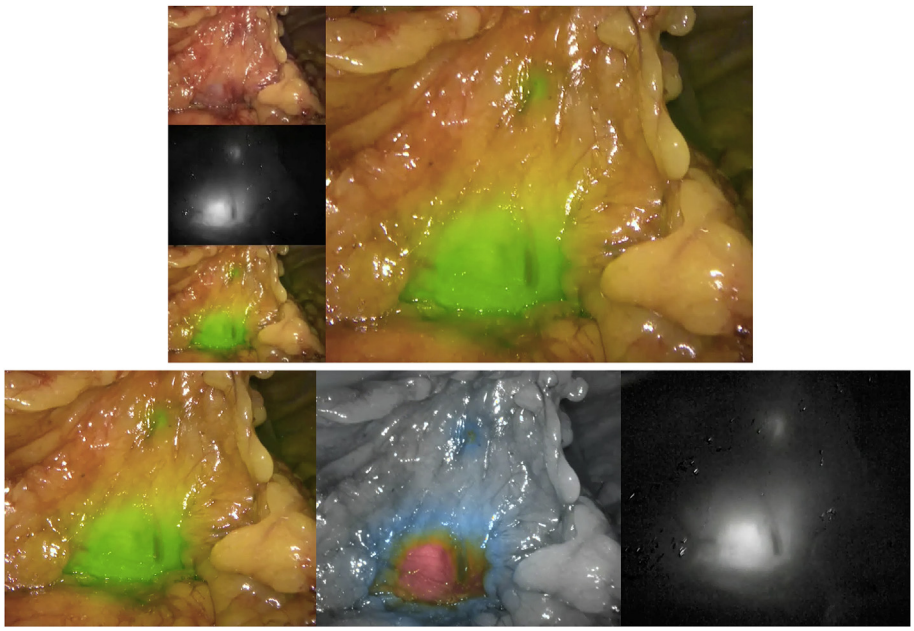

Fig. 2. Intra-operative ICG fluorescence imaging with PINPOINT® (Pinpoint mode, colorized mode, spy mode). This image was obtained from Case② patient.

node metastasis in preoperative CT, and we were able to gain curative resection without neo-adjuvant chemotherapy. Therefore, distal gastrectomy with D2 dissection was performed. Total gastrectomy was selected for two patients with tumor located in U/Less area.

The results of pathology and SN mapping are shown in Tables 2 and 3. We were able to observe the ICG positive lymphatic flow and lymph nodes in all 6 patients. Final pathological diagnosis showed all Stage I.

All the patients had ICG positive lymphatic area in left gastric artery (LGA) area.

Two patients with tumor located in L area had ICG positive flow to right gastroepipoloic artery (RGEA) area.

The mean of ICG positive lymph nodes was 7.0 ± 4.7. Case② patient had a metastatic lymph node in station No.4. This node was positive for ICG.

All patients had curative resection. The median of postoperative follow up was 13 months (range 11–14). Although observation after surgey is short, there are no recurrence and metastasis.

4. Discussion

Several successful studies for SN mapping in gastric cancer have been reported.

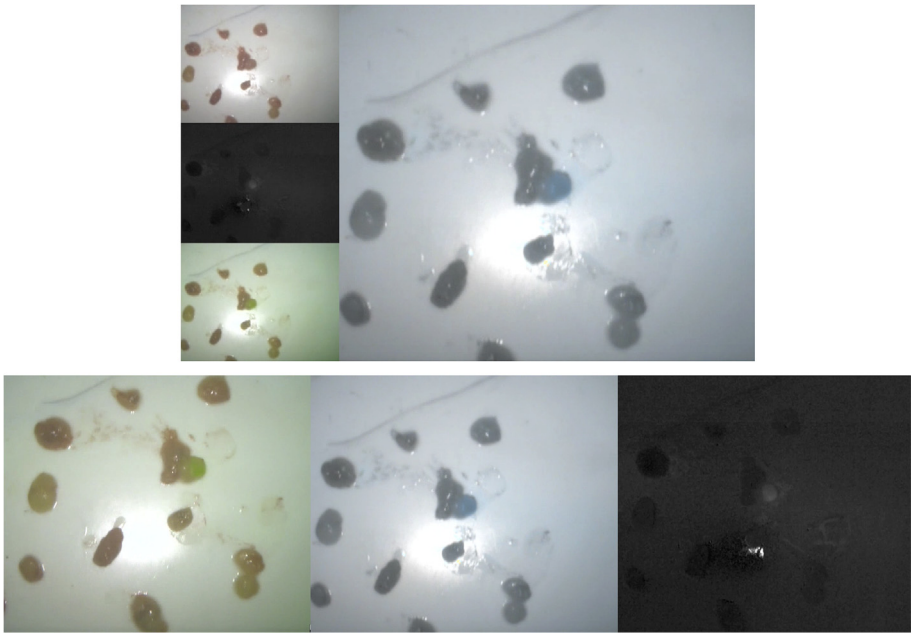

Fig. 3. Postoperative back-table observation of staining nodes obtained from Case② patient.

Table 1
Patients characteristic 1.

Case no.	Age/sex	Tumor location/ macroscopic findings	procedure	LN dissection
①	65/F	L/Less IIc 12 mm	DG	D1+
②	69/M	M/Gre IIc 20 mm	DG	D1+
③	76/M	U/Less IIa 20 mm	TG	D1+
④	70/M	U/Less IIa 22 mm	TG	D1+
⑤	75/F	L/Ant type3 12 mm	DG	D2
⑥	75/M	U/Less IIc 15 mm	TG	D1+

U: upper third.
M: middle third.
L: lower third.
Less: lesser lesser curvature.
Gre: greater curvatures.
DG: distal gastrectomy.
TG: total gastrectomy.

Table 3
Results of SN biopsy and diagnostic Accuracy.

Variable	No.	%
SN identification		
Detected	6	100
Undetected	0	0
No. of identified SNs		
Mean ± SD	7.0 ± 4.7	
pN factor	6	
pN positive	1	17
pN negative	5	83
SN metastasis	1	
pSN positive	1	100
pSN negative (false negative)	0	0

Miwa et al. reported SN mapping in gastric cancer using patent blue [5]. Isozaki et al. evaluated SN identification with isosulfan blue. SN mapping using dye is easy and simple methods [13].

Some surgeons use ICG fluorescence-guided method for SN mapping. Nimura et al. reported the method combined with infrared ray electronic endoscopy (IREE) (Olympus Optical, Tokyo, Japan) [8]. Kinami et al. applied the Photodynamic Eye (PDE) (Hamamatsu Photonics Co., Ltd., Hamamatsu, Shizuoka, Japan) to detect ICG fluorescence [14].

ICG fluorescence-guided methods had a critical problem. The original detection systems for ICG fluorescence have gray scale imaging and require a dark room. The operation can be interrupted during the observation of the fluorescence.

In cooperation with Sato's (Kochi Medical School) development of hypereye charge-coupled device camera system: HyperEye Medical System (HEMS; Mizuho Corporation, Tokyo, Japan), Yoshida et al. applied it to sentinel node mapping in the early gastric cancer patients. HEMS can simultaneously detect color and near-infrared rays and can be used under bright light [15,16]. The operation can be continued, simultaneously under the guidance of ICG fluorescence.

However, method with the HEMS have demerits. Recent laparoscopic surgery for gastric cancer have tendency that mini-laparotomy for removing the specimen is placed at the umbilicus and incision size become smaller. We considered that camera heads of HEMS may not be suitable for SN mapping and navigation with laparoscopy in the future.

To overcome demerits of these methods, we applied PINPOINT® for gastric cancer surgery to identify lymphatic flows and SNs. Jafari et al. performed intraoperative assessment of anastomotic perfusion in laparoscopic left-Sided/anterior resection for colorectal disease with PINPOINT [11]. Sherwinter et al. showed a video of a laparoscopic cholecystectomy performed under NIR cholangiographic guidance and highlights its ability to identify anomalous anatomy [17].

The system includes a surgical laparoscope and camera head optimized for visible and near infrared illumination and imaging, and is designed to be connected to a medical grade-high definition color video monitor and all components may be mounted on a stand-alone endoscopy tower [18].

The PINPOINT system allows simultaneous display of multiple images, including standard high definition white light image, SPY image and Colorized image. As figures, clear view and image were obtained [17]. Main lesion and SNs were identified in all cases. Case1 and 6 had preoperative endoscopic submucosal dissection (ESD).

The results of our methods was similar to what previous paper reported [9,19,20]. The detection rate of ICG fluorescence imaging was 100.0%. ICG positive lymphatic area existed in left gastric artery (LGA) area in all the patients. Two patients with tumor

Table 2
Patients characteristic 2.

Case no.	Pathology	Lymphatic area positve for ICG	Nunber of LN positve for ICG	SN(metastaticLN/ICG positive LN)
①	por sm n0(0/33) ly1 v0	LGA, RGA,RGEA	8	No.3(0/3), No.4d(0/1), No.6(0/2) No.7(0/1), No.8a(0/1)
②	por m n1(1/21) ly0 v0	LGA, RGA	3	No.4d(1/1), No.6(0/1), No.8a(0/1)
③	tub2 sm n0(0/32) ly1 v0	LGA	8	No.2(0/2), No.3(0/3), No.7(0/3)
④	muc sm n0(0/42) ly2 v2	LGA, LGEA	16	No.1(0/2), No.2(0/2), No.3(0/11) No.4sb(0/1)
⑤	tub1 sm n0(0/45) ly0 v0	LGA, RGA, RGEA	8	No.1(0/1), No.3(0/5), No.6(0/1) No.8a(0/1)
⑥	tub1 m n0(0/45) ly0 v0	LGA	1	No.1(0/1)

por: poorly differentiated adenocarcinoma.
muc: mucinous adenocarcinoma.
tub1: well differentiated adenocarcinoma.
tub2: moderately differentiated adenocarcinoma.
m: mucosa.
sm: submucosa.
LGA: left gastric artery.
LGEA: left gastroepiploic artery.
RGA: right gastric artery.
RGEA: right gastroepiploic artery.

located in L area had ICG positive flow to right gastroepipoloic artery (RGEA) area.

It is the key findings that metastatic lymph node in Case 2 was positive for ICG. The number of ICG positive node and existence of metastatic LN within the direction of ICG flow is important for SN related surgery. Our findings in Table 2 reflects this concept. Decreasing false negative (metastatic LN with non–ICG positive) is the key for the SN navigation. Kitagawa et al. reported 1% of false negative [9]. We believe that our method with clear images has the possibility for improvement of detection including sentinel and metastatic LN.

Limitation of this method is optimal concentration of ICG and timing for tracer injection. There is no reports describing the ICG concentration with PINPOINT® because of new device. We should think differently from all other SN methods with ICG. We performing the injection the day before surgery according to Kitagawa's dual tracer method and Kinami's ICG method [4,14]. Only just 6 cases, SNs were all identified and mean SNs was 8.6. Accumulating further cases, now we are examining whether 33.3 μg/ml of ICG is adequate concentration for injection and optimal count of SNs or not.

In conclusion, our method with ICG and PINPOINT® made identification of ICG positive lymph nodes easy in SN mapping in back-table under room light. Although further accumulation and analysis are necessary, we may be able to apply this method for avoiding unnecessary D2 dissection, intraoperative SN mapping and modified resection of laparoscopic gastric cancer surgey [21–24].

Ethical approval

The protocol was approved by the Ethics Committee for Biomedical Research of the International University of Health and Welfare Hospital, and all patients provided informed consent.

Sources of funding

None to declare.

Author contribution

All authors contributed equally to the manuscript.

Conflicts of interest

None to declare.

Guarantor

Hironori Ohdaira, First Author.
Masashi Yoshida, Senior Author.

Acknowledgements

The authors declare no conflict of interest. No funding was received for the present study.

References

[1] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines (ver. 3), Gastric Cancer 2011 (2010) 113–123.
[2] Japanese Gastric Cancer Association, Japanese classification of gastric carcinoma: 3rd English edition, Gastric Cancer 14 (2011) 101–112.
[3] J.J. Bonenkamp, J. Hermans, M. Sasako, et al., Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer, N. Engl. J. Med. 340 (1999) 908–914.
[4] Y. Kitagawa, H. Fujii, M. Mukai, et al., Intraoperative lymphatic mapping and sentinel lymph node sampling in esophageal and gastric cancer, Surg. Oncol. Clin. N. Am. 11 (2002) 293–304.
[5] K. Miwa, S. Kinami, K. Taniguchi, et al., A. Mapping sentinel nodes in patients with early-stage gastric carcinoma, Br. J. Surg. 90 (2003) 178–182.
[6] M.C. Kim, G.J. Jung, J.H. Lee, et al., Sentinel lymph node biopsy with 99mTC tin-colloid in patients with gastric carcinoma, Hepatogastroenterology 50 (Suppl 2) (2003) (ccxiv-ccxv).
[7] T. Aikou, Y. Kitagawa, M. Kitajima, et al., Sentinel lymph node mapping with GI cancer, Cancer Metastasis Rev. 25 (2006) 269–277.
[8] H. Nimura, N. Narimiya, N. Mitsumori, Y. Yamazaki, K. Yanaga, M. Urashima, Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer, Br. J. Surg. 91 (2004) 575–579.
[9] Y. Kitagawa, H. Takeuchi, Y. Takagi, et al., Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan, J. Clin. Oncol. 31 (2013) 3704–3710.
[10] F. Ris, R. Hompes, C. Cunningham, et al., Near-infrared (NIR) perfusion angiography in minimally invasive colorectal surgery, Surg. Endosc. 28 (2014) 2221–2226.
[11] M.D. Jafari, S.D. Wexner, J.E. Martz, et al., Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study, J. Am. Coll. Surg. 220 (2015) 82–92.
[12] A. Matsui, E. Tanaka, H.S. Choi, et al., Real-time intra-operative near-infrared fluorescence identification of the extrahepatic bile ducts using clinically available contrast agents, Surgery 148 (2010) 87–95.
[13] H. Isozaki, T. Kimura, N. Tanaka, et al., An assessment of the feasibility of sentinel lymph node-guided surgery for gastric cancer, Gastric Cancer 7 (2004) 149–153.
[14] S. Kinami, T. Oonishi, J. Fujita, et al., Optimal settings and accuracy of indocyanine green fluorescence imaging for sentinel node biopsy in early gastric cancer, Oncol. Lett. 11 (2016) 4055–4062.
[15] T. Handa, R.G. Katare, S. Sasaguri, T. Sato, Preliminary experience for the evaluation of the intraoperative graft patency with real color charge-coupled device camera system: an advanced device for simultaneous capturing of color and clear-infrared images during coronary artery bypass graft, Interact. Cardiovasc. Thorac. Surg. 9 (2009) 150–154.
[16] M. Yoshida, K. Kubota, J. Kuroda, et al., Indocyanine green injection for detecting sentinel nodes using color fluorescence camera in the laparoscopy-assisted gastrectomy, J. Gastroenterol. Hepatol. 27 (2012) 29–33.
[17] D.A. Sherwinter, Identification of anomolous biliary anatomy using near-infrared cholangiography, J. Gastrointest. Surg. 16 (2012) 1814–1815.
[18] J. Fengler, Near-infrared fluorescence laparoscopy-technical description of PINPOINT® a novel and commercially available system, Colorectal Dis. 17 (Suppl 3) (2015) 3–6.
[19] H. Ohdaira, H. Nimura, N. Takahashi, et al., The possibility of performing a limited resection and a lymphadenectomy for proximal gastric carcinoma based on sentinel node navigation, Surg. Today 39 (2009) 1026–1031.
[20] Y. Tajima, K. Yamazaki, Y. Masuda, et al., Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer, Ann. Surg. 249 (2009) 58–62.
[21] H. Takeuchi, Y. Kitagawa, Minimally invasive function-preserving surgery based on sentinel node concept in early gastric cancer, Transl. Gastroenterol. Hepatol. 1 (2016) 23.
[22] N. Takahashi, H. Nimura, T. Fujita, et al., Laparoscopic sentinel node navigation surgery for early gastric cancer: a prospective multicenter trial, Langenbecks Arch. Surg. 402 (2017) 27–32.
[23] N. Takahashi, H. Nimura, T. Fujita, et al., Quantitative assessment of visual estimation of the infrared indocyanine green imaging of lymph nodes retrieved at sentinel node navigation surgery for gastric cancer, BMC Surg. 16 (2016) 35.
[24] N. Mitsumori, H. Nimura, N. Takahashi, et al., Sentinel lymph node navigation surgery for early stage gastric cancer, World J. Gastroenterol. 20 (2014) 5685–5693.