

# Lymph node mapping in gastric cancer: a pilot study in Western patients

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## SUMMARY

In East Asia, the role of lymph node (LN) mapping in assisting surgical lymphadenectomy, which is integral to the management of gastric cancer, has been explored. We sought to evaluate its safety and utility in Western patients. Thirteen patients with nonmetastatic gastric adenocarcinoma received endoscopic, peritumoural, submucosal indocyanine green fluorescence (ICG) injections before surgery, and ICG was assessed intraoperatively using a laparoscopic detection system. All patients underwent a laparoscopic subtotal gastrectomy, and 10 of them received D2 lymphadenectomies. ICG-mapped LNs fell outside the D1 distribution in all cases, outside the D1+ distribution in 54%, and within the D2 distribution in all cases. There were no ICG-related allergies, procedural complications, or perioperative deaths. We conclude that ICG LN mapping is safe and feasible in assisting LN dissections and localizing the primary tumour in Western patients. D2 dissections should be performed in patients with advanced gastric cancer, as LNs drained outside the D1/D1+ distributions in most cases.

**A**dequate lymphadenectomies for tumour staging and negative margins are critical to minimize disease recurrence<sup>1</sup> in patients with gastric cancer, as they frequently present with locally advanced disease. In East Asian countries, the standard treatment for locally advanced disease includes a D2 lymphadenectomy, as it is associated with longer overall survival (OS);<sup>1</sup> however, D2 dissections are not commonly performed in Western countries owing to concerns with associated morbidity and mortality.<sup>2</sup> Lymph node (LN) mapping with indocyanine green fluorescence (ICG) has been explored in East Asian countries as a useful technique to support D2 dissections and outline resection margins.<sup>3</sup> It has also been shown to identify skip metastases where positive LNs fall outside a typical dissection range,<sup>4</sup> emphasizing the need to perform extended lymphadenectomies. We aimed to assess the safety and utility of ICG-specific LN mapping in defining draining nodal stations and resection margins to help guide the extent of lymphadenectomy in laparoscopic gastric cancer resections among Western patients.

## TECHNIQUE

All patients received endoscopic submucosal peritumoural ICG injections immediately before laparoscopic surgical resection to facilitate LN mapping. Approximately 1 mL of 0.25 mg/mL ICG was injected into each of the 4 quadrants of the peritumoural submucosal layer. About 1 mg of total ICG was used for each case.

The ICG-fluorescent LNs, primary tumour, LN basins, and tracts were visualized using a PINPOINT endoscopic fluorescence imaging camera (Stryker) with 3 modes (Pinpoint mode, SPY mode, colourized mode) (Figure 1). The LN dissection and subtotal gastrectomy were performed according to recommended gastric cancer treatment guidelines.<sup>1</sup> A D1 dissection involves removal of LN basins 1, 3, 4, 5, 6 and 7. A D1+ dissection refers to a D1 dissection and removal of LN basins 8a and 9. The D2 dissection involves a D1+ dissection and removal of LN basins 11p and 12a.<sup>1</sup>

### SAFETY AND FEASIBILITY

Thirteen patients with histologically proven nonmetastatic gastric adenocarcinoma underwent LN mapping and laparoscopic subtotal gastrectomy (Table 1). We observed no ICG-related allergic reactions or procedural complications. Only 1 patient had a grade III Clavien–Dindo complication in the form of an upper gastrointestinal (GI) bleed owing to home use of a blood thinner. There was no 60-day perioperative mortality.

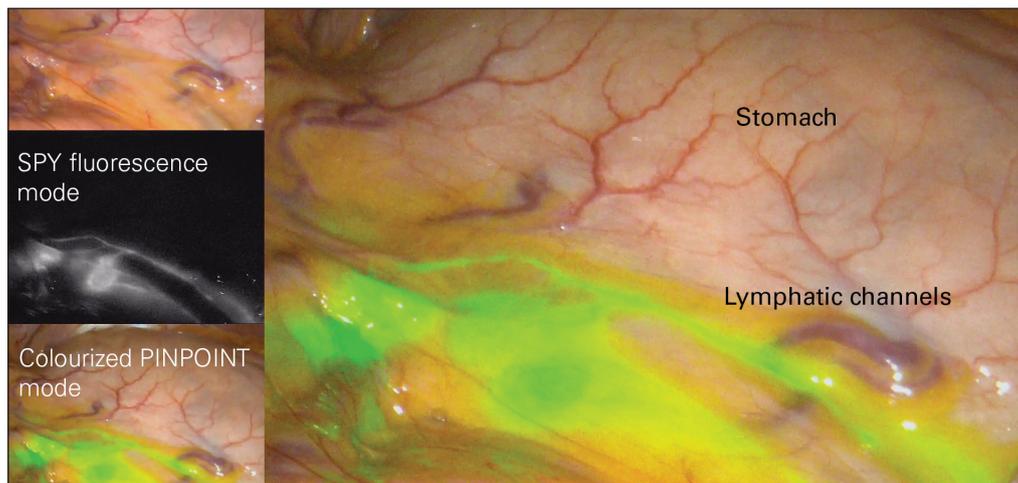
### LYMPH NODE DISTRIBUTION

All patients had more than 16 LNs harvested, with a median of 26 LNs (interquartile range [IQR] 24–34). Four patients had disease-positive LNs (Table 2). ICG-mapped LNs fell outside the D1 distribution in all cases and outside the D1+ distribution in 54% of cases but were all within the D2 distribution (Figure 2). In total, 66%, 62%, 50% and 14% of resected 8, 9, 11p and 12-a LN basins in the D2 distribution were ICG-lit, respectively. One patient had pathologic 12a LN that was not ICG-lit (Table 3).

**Table 1. Baseline patient characteristics**

Covariates	No. (%) of patients* n = 13
Age, median [IQR]	75 [62–84]
Male sex	7 (54)
Procedure	
Subtotal gastrectomy	13 (100)
Lymphadenectomy	
D1+	3 (23)
D2	10 (77)
Tumour Location	
Proximal third	1 (8)
Middle third	2 (15)
Distal third	10 (77)
pT stage	
pT1	2 (15)
pT2	7 (54)
pT3	3 (23)
pT4	1 (8)
pN stage	
pN0	9 (69)
pN1	1 (8)
pN2	1 (8)
pN3	2 (15)
Classification	
Intestinal	9 (69)
Diffuse	3 (23)
Mixed	1 (8)
Grade	
1	0 (0)
2	8 (62)
3	5 (38)
ICG Distribution	
Outside D1	13 (100)
Outside D1+	7 (54)
Outside D2	0 (0)
No. of LNs, median [IQR]	26 [24–34]
> 16 LNs harvested	13 (100)

ICG = Indocyanine green fluorescence; IQR = interquartile range; LN = lymph nodes.  
\*Unless indicated otherwise.



**Fig. 1.** Detecting indocyanine green fluorescence with laparoscopic fluorescence imaging camera.

Table 2. Perioperative clinical management and outcomes

Patient	cT stage	Neoadjuvant	Margins	pTN stage	Postoperative chemo	Complications
1	2	FLOT	neg	ypT2N3a	FLOT	No
2	1	No	neg	pT2N0	CAPOX	No
3	3	FLOT	neg	ypT2N0	FLOT	PF
4	1	No	neg	pT2N0	No	PF
5	1	No	neg	pT2N0	No	No
6	3	No	neg	pT4aN3a	No	No
7	3	FOLFOX	neg	ypT3N1	FOLFOX	No
8	2	No	neg	pT2N2	No	No
9	1	No	pos	pT3N0	CAPOX	GIB
10	3	No	neg	pT2N0	No	NSTEMI
11	2	No	neg	pT1bN0	No	No
12	3	FLOT	neg	ypT3N0	FLOT	No
13	3	FLOT	neg	ypT1bN0	FLOT	No

CAPOX = capecitabine, oxaliplatin; FLOT = 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin; GIB = gastrointestinal bleed; NSTEMI = non-ST-elevation myocardial infarction; PF = pancreatic fistula.

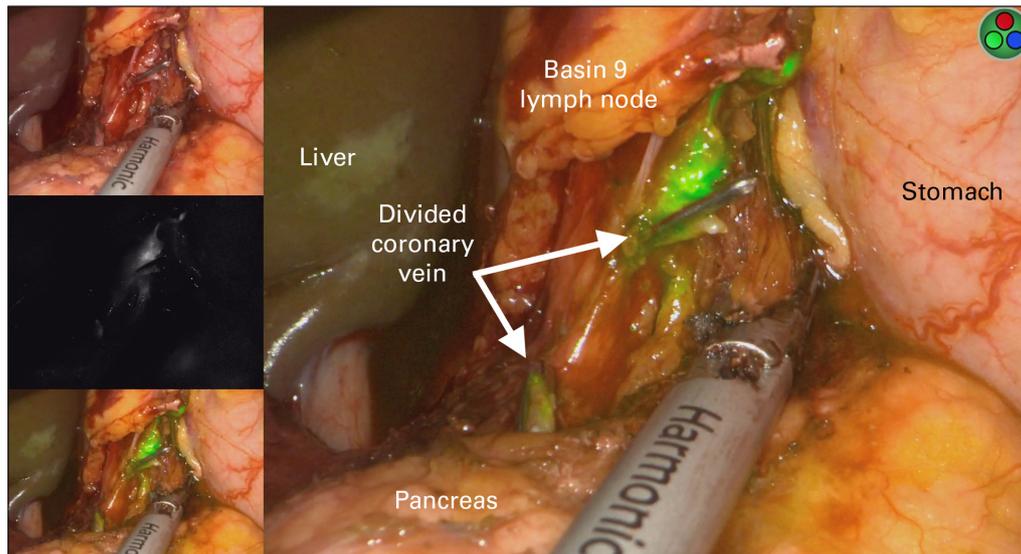


Fig. 2. Detection of a basin 9 lymph node.

Table 3: Patient-specific nodal mapping

Patient	No. of LNs	ICG D1* basins	ICG D1+/D2‡ basins	Positive D1 LN	Positive D1+/D2 LN
1	26	1, 3, 4, 5, 6	8, 12a	Yes	No
2	35	1, 3, 4, 5	9, 12a	No	No
3	18	1, 3, 5, 6, 7	9, 11p, 12a	No	No
4	33	1, 3, 4, 5, 7	9, 11p	No	No
5	24	3, 7	9, 11p	No	No
6	25	3, 4, 6, 7	9, 11p	Yes	No
7	30	3, 4, 5, 6	8	Yes	No
8	23	3, 4, 5, 6, 7	8, 9	Yes	Yes (12-a 1/1)
9	21	5, 6	8	No	No
10	31	3, 4, 6	8, 9	No	No
11	43	3, 5, 7	8	No	No
12	24	1, 3, 4, 5, 6, 7	8, 9, 11p	No	No
13	38	1, 3, 5, 6	8	No	No

ICG = indocyanine green fluorescence; LN = lymph node.

\*D1 = basins 1-7.

†D1+ = basins 8 and 9.

‡D2 = basins 11p and 12a.

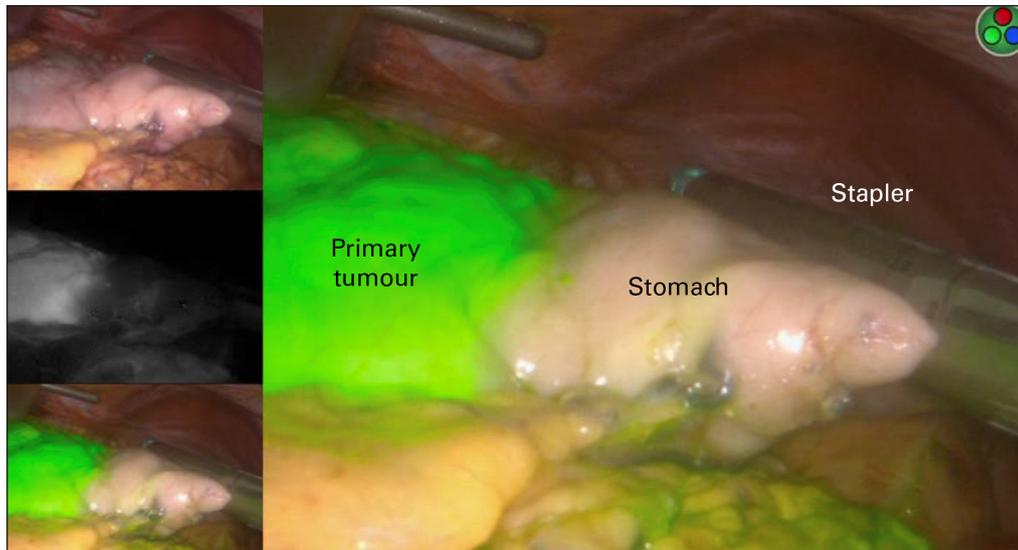


Fig. 3. Mapping of the proximal margin of the primary tumour.

### PRIMARY TUMOUR MAPPING

We used ICG mapping to determine the distance of resection from the primary tumour (Figure 3). Only 1 patient had a focal microscopic positive distal margin with discontinuous isolated tumour cells.

### DISCUSSION

We evaluated the application of LN mapping using ICG fluorescence in laparoscopic gastrectomies in a Western gastric cancer population. We found no associated adverse events and few postoperative complications (31%), which highlights the potential of ICG LN mapping to be adopted safely and effectively for this purpose. The absence of allergic reactions to ICG in our patient cohort is comparable to the results of other studies;<sup>3</sup> thus, we deem ICG mapping safe to incorporate.

We assessed the utility of ICG LN mapping in assisting extended LN dissections in Western patients with locally advanced gastric cancers. All patients had LNs outside the D1 distribution, and more than half had LNs outside the D1+ distribution (54%). East Asian<sup>5</sup> and Western<sup>4</sup> studies have reported the detection of ICG-lit LNs in the D2 distribution, complementing our findings. More specifically, Tummers and colleagues<sup>4</sup> found that 95% of LNs were outside D1 and 33% were outside the D1+ distribution; rates were slightly lower but similar in our study. Among our 4 patients with node-positive disease, only 1 had disease in the D2 distribution (basin 12a). Although this node was not ICG-lit, we emphasize how D2 lymphadenectomies can be useful in accounting for skip metastases, which frequently occur in areas outside the D1 dissection range.<sup>4</sup> Although we did not find ICG-lit

LN outside the D2 dissection plane, the identification of such LNs (i.e., basin 14v) has also been documented in the past.<sup>4</sup> Additionally, harvesting more than 16 LNs is crucial to accurate staging, treatment, and OS.<sup>1</sup> We were able to harvest an adequate number of LNs (> 16) using LN mapping, which compliments the findings of an East Asian trial that showed the ability to harvest more LNs using ICG.<sup>5</sup> Overall, ICG LN mapping is a feasible and effective method to encourage laparoscopic D2 lymphadenectomies, in adherence to the Japanese guidelines,<sup>1</sup> as the majority also have locally advanced disease (69%).

ICG mapping is also effective in isolating the primary tumour to achieve negative margins. One patient had a focal positive distal margin in our study, but these were isolated tumour cells discontinuous from the primary tumour. ICG mapping has been reported to have 100% accuracy for achieving negative tumour margins<sup>3</sup> and can be similarly used to reliably obtain negative margins in Western patients with locally advanced disease.

Our assessment was limited by our small sample; we evaluated only patients undergoing a laparoscopic resection. The declining incidence of gastric cancers in the Western population also limits the ability to draw statistically significant conclusions on safety and efficacy of the ICG LN mapping procedure. Future prospective studies are required to assess the impact of ICG LN mapping on long-term patient outcomes to better establish its role in laparoscopic gastrectomies.

### CONCLUSION

ICG mapping was safe and effective in identifying LNs outside the D1 distribution, assisting D2 lymphadenectomy and localizing the primary tumour in the

laparoscopic setting for locally advanced gastric cancers. It can be a useful tool in laparoscopic gastrectomies in Western patients with gastric cancer.

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