表　Lymphatic basin dissectionに基づいた機能温存根治手術(縮小手術)

| 占居部位 | 流域(basin) 数 | 流域(basin) 部位 | 術式 |
|---|---|---|---|
| M, L | 1 | 右胃大網動脈 | 胃局所切除術 |
| U, M | 2 | 左胃動脈<br>後胃動脈 | 噴門側胃切除術 |
| M, L | 2 | 左胃動脈<br>右胃大網動脈 | 胃横断切除術 |
| L | 2 | 右胃動脈<br>右胃大網動脈 | 小範囲幽門側胃切除術 |

合，腫瘍の位置と染色されるリンパ流域の数と場所に応じて，各種の機能温存根治手術を行うが，転移が陽性であった場合には，定型手術(D2)を行う。なお，リンパ流域が3つのときや，大彎・小彎の同側に2つあるような場合(左右の胃動脈流域，左右の胃大網動脈流域など)も，定型手術を施行するようにしている。

具体的な腫瘍の占居部位，リンパ流域と術式に関しては表にまとめて示したが，以下に簡単に説明する[12]。

### 1．胃局所切除術

リンパ流域が一つであれば，胃局所切除術が行える。最も典型的な例は，M，L(M寄りの)領域の大彎の早期胃癌で，流域が右胃大網動脈流域の場合である。

### 2．噴門側胃切除術，胃横断切除術，小範囲幽門側胃切除術

これらの3つの術式は，その腫瘍のリンパ流域が小彎と大彎の両側にそれぞれ1つずつある場合と考えられ，腫瘍が上部であれば噴門側胃切除術，中部であれば胃横断切除術，下部であれば小範囲幽門側胃切除術になる。

## 文　献


1. Miwa K, Kinami S, Taniguchi K et al: Mapping sentinel nodes in patients with early stage gastric carcinoma. Br J Surgery **90**: 178-182, 2003
2. 藤村　隆，木南伸一，伏田幸夫ほか: Sentinel node navigationを応用した早期胃癌に対する機能温存根治手術. 放射線生物研究**41**: 221-230, 2006
3. 芳野純治，若林貴夫，加藤芳理:超音波内視鏡所見．飯田三雄(編):新しい診断と治療のABC 14，胃癌，91-100，最新医学社，大阪，2003
4. 藤村　隆，米村　豊，谷口桂三ほか:術前CTによる胃癌のリンパ節転移診断．北陸外科学会誌**16**: 23-26，1997
5. Coller FA, Kay EB, MacIntyre RS: Regional lymphatic metastases of the stomach. Arch Surg **43**: 748-761, 1941
6. Kinami S, Fujimura T, Ojima E et al: PTD classification: proposal for a new classification of gastric cancer location based on physiological lymphatic flow. Int Clin Oncol **13**: 320-329, 2008
7. 高木　融，星野澄人，片柳　創ほか:センチネルリンパ節の同定　(1)RI法．臨牀消化器内科**22**: 1049-1054，2007
8. 藤村　隆，木南伸一，伏田幸夫ほか:センチネルリンパ節の同定　(2)色素法．臨牀消化器内科**22**: 1055-1063，2007
9. Nimura H, Narimiya N, Mitsumori N et al: Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. Br J Surg **91**: 575-579, 2004
10. Kusano M, Tajima Y, Yamazaki K et al: Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastrointestinal cancer. Dig Surg **25**: 103-108, 2008
11. Chao C, Wong SL, Ackermann D et al: Utility of intraoperative frozen section analysis of sentinel lymph nodes in breast cancer. Am J Surg **182**: 609-615, 2002
12. 藤村　隆，木南伸一，伏田幸夫ほか:縮小手術(機能温存根治手術)．消化器外科**31**: 708-715，2008


## Multimodal Diagnostic Approaches to Applying and Performing Function-preserving Curative Gastrectomy


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An improvement in the prognosis of early gastric cancer induces more patients who undergo gastrectomy to suffer from post-gastrectomy syndrome throughout their lives. Function-preserving curative gastrectomies are emerging to resolve the problems after gastrectomy, but such operations need rationales for reduction of dissected lymphatic stations and resected gastric extent as well as preservation of curability. We intraoperatively confirm lymph node metastasis using sentinel node mapping and lymphatic basin dissection, and perform function-preserving curative gastrectomies only if the patients do not have nodal metastasis. There are four types of this gastrec-

tomy depending on the tumor location and number of lymphatic basins: local resection, transactional gastrectomy, cardiac resection, and limited distal gastrectomy. To complete function-preserving curative gastrectomies, it is essential preoperatively to determine tumor status including tumor depth, size, and location using multimodal endoscopic examinations such as dye endoscopy and endoscopic ultrasonography. Furthermore, endoscopic sentinel node mapping by dye and radioisotope, and intraoperative frozen section biopsy of lymph nodes are required.
**key words**: function-preserving curative gastrectomy, sentinel node, lymphatic basin

## Legends to Figures and a Table

Figure 1 What is an optimal choice between EMR/ESD and standard gastrectomy?
There is a great difference in the quality of life between the patients receiving EMR/ESD and standard gastrectomy. Japanese guidelines for gastric cancer treatment recommend D1+$\alpha/\beta$ operation for a substitute, but there is little difference in resected gastric extent between D1+$\alpha/\beta$ and D2 operation. We succeeded in reducing resected gastric extent by sentinel node mapping and selective lymphatic dissection. EMR/ESD+selective lymphatic dissection may be carried out in the future.

Figure 2 Gastric segment from the viewpoint of lymphatic flow.
a. Rouviere's classification. (Reference; Rouviere H: Anatomie des lymphatiques de l'homme. 294–334, Masson, Paris, 1932)
b. Coller's classification. (Reference No. 5)

Figure 3 PTD classification and lymphatic basins.
Border between zone-P and zone-T, level of bifurcation of upper and lower branches of left gastric artery on the lesser curvature, and level between left and right gastroepiploic arteries on the greater curvature; border between zone-T and zone-D, levels 8 cm apart from the pylorus on both the lesser and the greater curvatures.

Figure 4 Sentinel node mapping.
Tracers are endoscopically injected using an endoscopic injector into submucosa at four points around tumor where cancer is not proven preoperatively. Dye and radioisotope are injected by 0.1–0.2 m*l* and 0.5 m*l*, respectively, at each point.

Figure 5 NAVIGATOR GPS (United States Surgical, USA, supplied by Tyco Health Care Japan).

Figure 6 Blue node and lymphatic basin.
Blue node and blue lymphatics are defined as lymph node and lymphatics stained blue by patent blue, respectively. Lymphatic basin is defined as area including blue node and blue lymphatics, exisiting along a main gastric feeding artery.

Table Function-preserving curative gastrectomy combined with lymphatic basin dissection.

# Selective lymphadenectomy of para-aortic lymph nodes for advanced gastric cancer

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**Abstract.** The Japanese randomized trial comparing standard D2 with D2 plus additional para-aortic lymph node (PAN) dissection for advanced gastric cancer (JCOG study 9501) did not demonstrate any difference in survival between the two groups. It is unknown whether there is any prognostic benefit in dissection for subgroups of PAN. Non-inferiority in survival of the patients with PAN metastasis to the patients having n2 metastasis was examined according to the subgroup of PANs and the tumor location. The survival curve of n2 patients (n=131) were retrospectively compared with that of patients with PAN metastasis (n=55) and also compared with that of patients with metastasis to subgroup of PANs by the location of primary tumor (regions U, M and L). Expectedly, the prognosis of the n2 patients is significantly better than that of the patients with PAN metastasis, but there was no difference in the survival times between the n2 (+) group and the a2-lat (+) or the b1-int (+) group, suggesting that the a2-lat or the b1-int dissection matched the D2 dissection. Furthermore, the importance in dissection of the a2-lat and the b1-int was investigated according to the primary tumor location. The patients with metastasis to a2-lat in the region U, a2-lat and b1-int in the region M and b1-int in the region L demonstrated prognostic non-inferiority to the patients having n2 metastasis. Selective lymphadenectomy of subgroups of PANs in which metastases are highly suspected according to the tumor location is one of treatment strategies to advanced gastric cancer.

## Introduction

Though the incidence of gastric cancer has decreased in the world, it is still one of leading causes of cancer death in many countries of different areas, such as Eastern Asia, Eastern Europe and Latin America. Hematological and peritoneal metastases in gastric cancer are life-threatening diseases, which should be treated with chemotherapy. It is probable that surgical intervention is able to improve prognosis of the patients with lymph node metastasis. Various types of lymph node dissection including D1, D2 and D3 have been tried to control lymph node metastasis in gastric cancer. Extended lymphadenectomy disappointed the expectation of survival improvement by two European randomized control studies comparing the D1 procedure with the D2 procedure (1,2), whereas another randomized trial reported in 2006 showed a significant benefit in patient survival for a D2 or D3 procedure as compared with D1 dissection, without increased operative mortality (3). It was reported that 20-30% of patients with advanced gastric cancer had metastasis to para-aortic lymph nodes (PANs) (4) and the 5-year survival of such patients reached 13 to 40% (5-7). These data facilitated to launch a randomized study on the importance of dissection of PANs. The Japanese randomized trial comparing standard D2 with D2 plus additional para-aortic lymphadenectomy for advanced gastric cancer (JCOG study 9501) was carried out between July 1995 and April 2001. Unfortunately, the JCOG study 9501 did not demonstrate any difference in survival between the two groups (8).

It remains unknown whether there is any prognostic benefit in subsets into which patients are classified according to primary tumor location or subgroup of PAN. Non-inferiority in survival of the patients with PAN metastasis to the patients having metastasis in the second-tier lymph nodes (n2) was retrospectively examined according to the subgroup of PANs and the tumor location.

## Patients and methods

All patients enrolled in this study were histologically proven gastric adenocarcinoma. A total of 937 patients who were assessed equal to or higher than clinical stage II received D2 (n=715) or D3 (n=222) surgery with the grade of residual tumor, R0 and R1 (9), in Kanazawa University Hospital between April, 1973 and December, 2002. D3 operation was defined as D2 plus PAN lymphadenectomy in the present study. PAN was subgrouped into a1, a2-lat, a2-int, b1-lat, b1-int and b2 (Fig. 1). The clinical and pathological findings except for factors H and P were based on the guidelines of the

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*Key words:* para-aortic lymph node, extended lymphadenectomy, gastric cancer

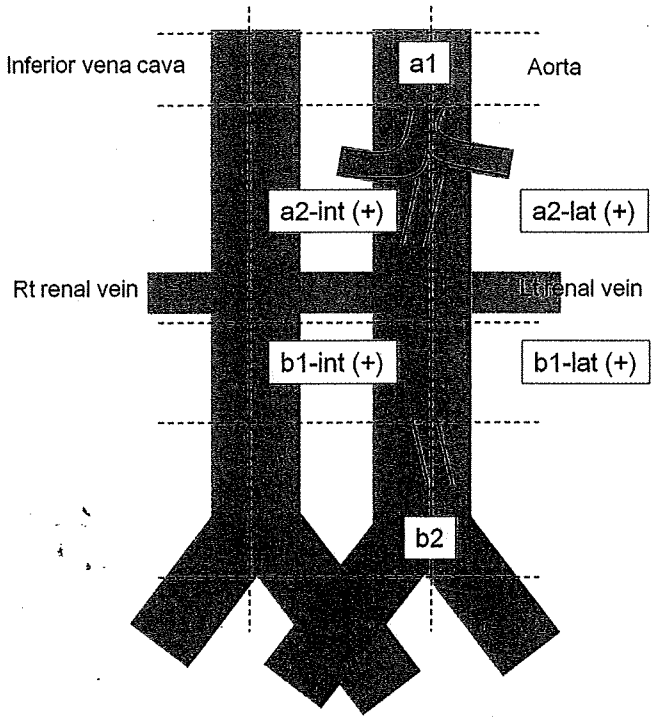


Figure 1. Subgroup of the para-aortic lymph nodes. The 'a1' lymph node is defined as node located between aortic foramen and upper margin of celiac axis in the craniocaudal direction. The 'a2' lymph node is defined as node located between upper margin of celiac axis and lower margin of left renal vein (LRV). The 'b1' lymph node is defined as node located between lower margin of LRV and upper margin of inferior mesenteric artery (IMA). The 'b2' lymph node is defined as node located between upper margin of IMA and bifurcation of abdominal aorta. The '-int' and '-lat' lymph nodes in the lateral direction are defined as nodes located between center of aorta and center of inferior vena cava and nodes located on the left side to center of aorta, respectively.

second edition of General Rules of Gastric Cancer, edited by the Japanese Research Society for Gastric Cancer (10). The factors H and P were described according to the guidelines of the first edition (11).

To examine metastatic rates in subgroups of the PANs, 222 patients receiving D3 operation were analyzed. Survival curve of patients with PAN metastasis [PAN (+) patients] was compared with that of patients with metastasis to n2 [n2 (+) patients]. A total of 131 n2 (+) patients consisted of 71 and 60 patients undergoing D2 and D3 operations, respectively, while all 55 PAN (+) patients received D3 operation. Furthermore, survival curves of n2 (+) patients and patients with metastasis to subgroup of PANs were compared by the location of primary tumor (regions U, M and L).

The significant difference in proportions between groups was determined with the Chi-square test. Patient survival was calculated with the Kaplan-Meier method and survival curves were compared with the log-rank method. Statistical significance was defined as a p-value <0.05.

## Results

Patient demographics of n2 (+) patients and PAN (+) patients is summarized in Table I. The patients in the n3 group had tumor with deep invasion, peritoneal dissemination, extended level of lymph node metastasis intraoperatively estimated (sN)

Table I. Patient characteristics.

| | n2 (+) (n=131) | PAN[a] (+) (n=55) | P-value |
|---|---|---|---|
| Gender | | | |
| Man/Woman | 79/52 | 34 /21 | 0.98 |
| Average age (range) | 59 (19-70) | 59 (18-71) | 0.42 |
| Gross type | | | |
| 0 | 11 | 3 | 0.091 |
| 1 | 5 | 1 | |
| 2 | 48 | 12 | |
| 3 | 42 | 28 | |
| 4 | 14 | 9 | |
| 5 | 11 | 2 | |
| Tumor location | | | |
| U/M/L | 37/44/50 | 19/16/20 | 0.67 |
| Tumor depth | | | |
| 1/2/3/4 | 33/19/58/21 | 4/6/30/15 | 0.018 |
| H | | | |
| 0/1 | 130/1 | 53/2 | 0.43 |
| P | | | |
| 0/1 | 123/8 | 45/10 | 0.023 |
| sN | | | |
| 0/1/2/PAN[a] | 14/37/68/12 | 0/13/15/27 | <0.001 |
| Histology | | | |
| D/Ud/Sq[b] | 65/65/1 | 16/39/0 | 0.026 |
| Surgery | | | |
| Total gastrectomy | 61 | 41 | <0.001 |
| Distal gastrectomy | 60 | 8 | |
| Proximal gastrectomy | 6 | 1 | |
| Pancreatoduodenectomy | 3 | 3 | |
| Others | 1 | 2 | |

PAN[a], Para-aortic lymph node; D/Ud/Sq[b], differentiated/undifferentiated/squamous.

and undifferentiated-type cancer, comparing with those in the n2 group. Distal gastrectomy in the n2 (+) group was more frequently performed than in the PAN (+) group.

Metastatic rates in subgroups of the PANs were as follows; 9.4% (20/212) in a2-lat, 6.5% (13/199) in a2-int, 7.4% (14/188) in b1-lat, 6.5% (13/200) in b1-int, 7.7% (1/13) in a1 and 57% (4/7) in b2. In the D2 group, 472 patients showed n0; 114, n1; 107, n2 and 20, n3, while 51 patients showed n0; 56, n1; 60, n2 and 55, n3, in the D3 group. The metastasis to PANs in the D2 group was diagnosed by sampling of PANs.

The survival was compared between the PAN (+) patients and the n2 (+) patients (Fig. 2). The 1- and 5-year survival rates of the n2 (+) patients were 78 and 43%, while the 1- and 5-year survival rates of the PAN (+) patients were 63 and 22%. The prognosis of the n2 (+) patients is significantly better than that of the PAN (+) patients. Then, the survival curve of the n2 (+) patients was compared with that of the patients with metastasis to each subgroup of PANs (Fig. 3). The 1- and 5-year survival rates of the patients with metastasis

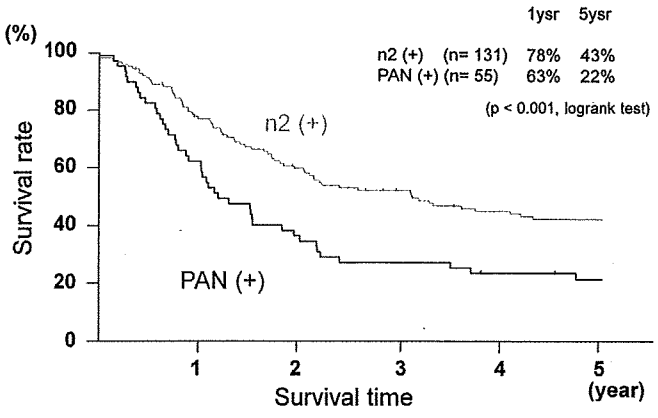


Figure 2. Survival curves of the n2 (+) group and the PAN (+) group.

in a2-lat or b1-int were 60 and 35% or 92 and 54%, respectively. There was no difference in the median survival times between the n2 (+) group and the a2-lat (+) or the b1-int (+) group, suggesting that the a2-lat or the b1-int dissection matched the D2 dissection in the prognosis. On the other hand, the 1- and 5-year survival rates of the patients with metastasis in a2-int or b1-lat were 62 and 15% or 50 and 14%, respectively, thus significantly lower than those of the patients with the n2 (+) group. These data indicated that the a2-lat and the b1-int were candidates for selective lymphadenectomy in PAN dissection.

Furthermore the importance in dissection of the a2-lat and the b1-int was investigated according to the primary tumor location. The 1- and 5-year survival rates of the n2 (+) patients were 77 and 36%, respectively, while these rates of the patients with metastasis in a2-lat were 86 and 57%, respectively, in region U (Fig. 4). There was no difference in the median survival times between the n2 (+) group and the a2-lat (+) group, suggesting that the a2-lat dissection matched the D2 dissection in the prognosis in region U. Though the survival time of the b1-int (+) group was marginally shorter than that of the n2 (+) group, no conclusion could be made because of very few patients with the b1-int (+) group. Similar analyses were carried out for the cancers of regions M and L (Figs. 5 and 6). These analyses indicated that the a2-lat and b1-int dissection in the region M and the b1-int dissection in region L matched the D2 dissection in the prognosis.

## Discussion

The Japanese randomized trial for D2 plus para-aortic lymphadenectomy in advanced gastric cancer (JCOG study 9501) failed in showing prognostic benefit. However, only 8.5% of patients had pathological metastasis in PANs and the 5-year survival rate reached 18.2% (8). The positive rate of PAN-metastasis in the JCOG study was much lower than expected, while the survival rate of their study is consistent with ones of previous studies. The 5-year survival rate of patients with liver metastases or peritoneal dissemination is as low as <5%, much worse than that of patients with PAN metastasis. These results supported that dissection of PANs is likely to improve the survival of the patients with PAN metastasis other than liver metastases or peritoneal dissemination. Taken together, the JCOG study 9501 could not prove superiority in the prognosis of patients with PAN-metastasis receiving PAN dissection to D2 dissection, but only

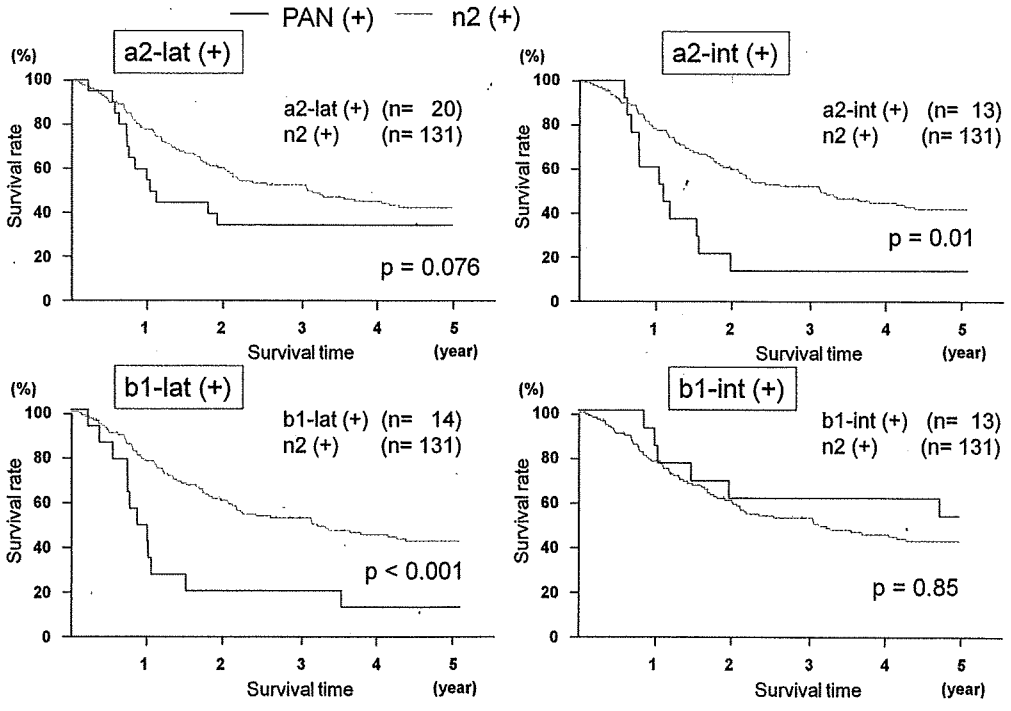


Figure 3. Survival curves of the n2 (+) group and the PAN (+) group according to the subgroup of PANs. There was no difference in the median survival times between the n2 (+) group and the a2-lat (+) or the b1-int (+) group, while the survival time of the n2 (+) group was significantly longer than that of the a2-int (+) or b1-lat (+) group.

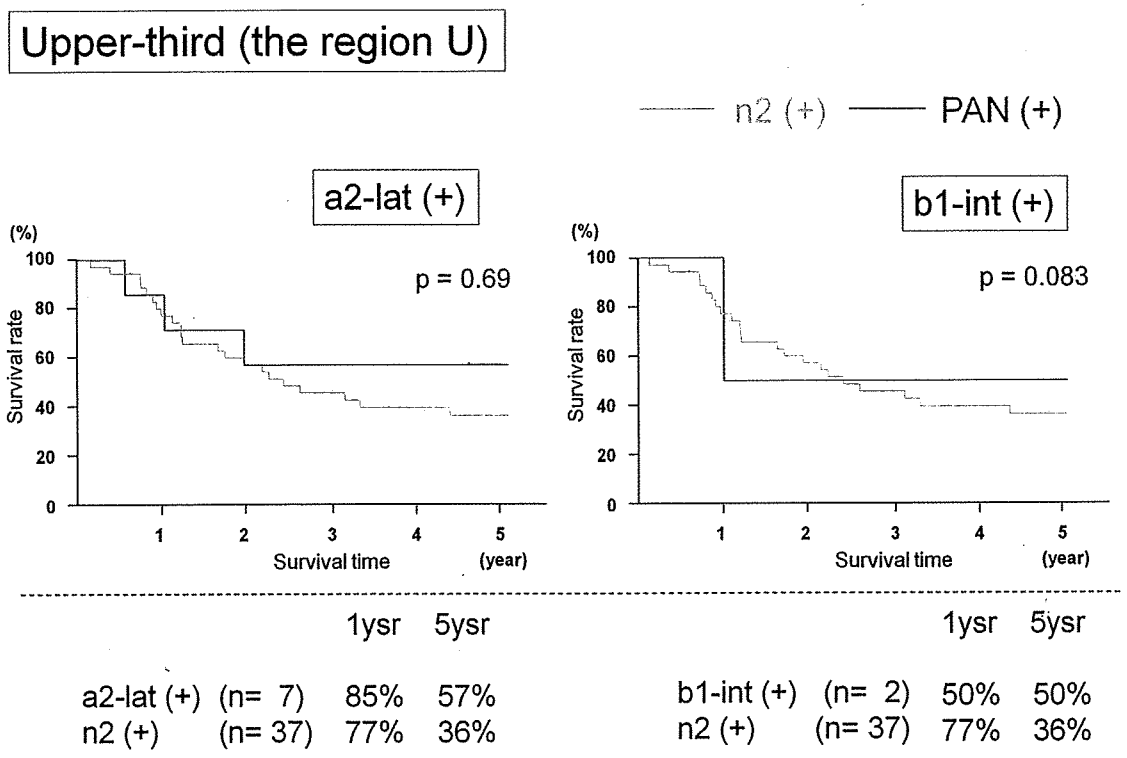


Figure 4. Survival curves of the n2 (+) group and the a2-lat (+) or the b1-int (+) group of the upper-third gastric cancer. There was no difference in the median survival times between the n2 (+) group and the a2-lat (+) group. The survival time of the b1-int (+) group was marginally shorter than that of the n2 (+) group.

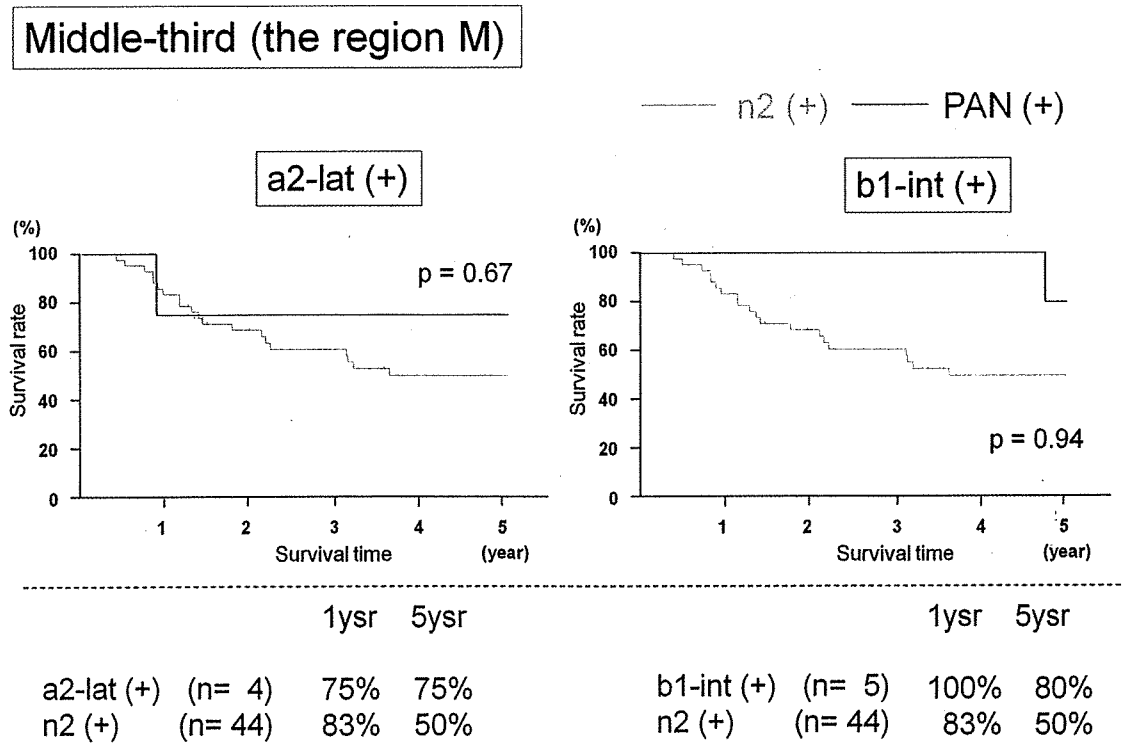


Figure 5. Survival curves of the n2 (+) group and the a2-lat (+) or the b1-int (+) group of the middle-third gastric cancer. There was no difference in the median survival times between the n2 (+) group and the a2-lat (+) or the b1-int (+) group in the middle-third stomach.

disclose difficulty in selection of real candidates for PAN dissection, that is, patients with PAN metastasis.

There are many studies describing risk factors pre-operatively predicting PAN metastases. Macroscopic N stage (N2 to N4) and tumor size (≥5 cm in diameter) were associated with PAN metastasis in the JCOG study 9501 (12). But only 20% of patients were N2 to N4 and 13% having tumor with >5 cm had actual PAN metastasis in this study. Thus, these

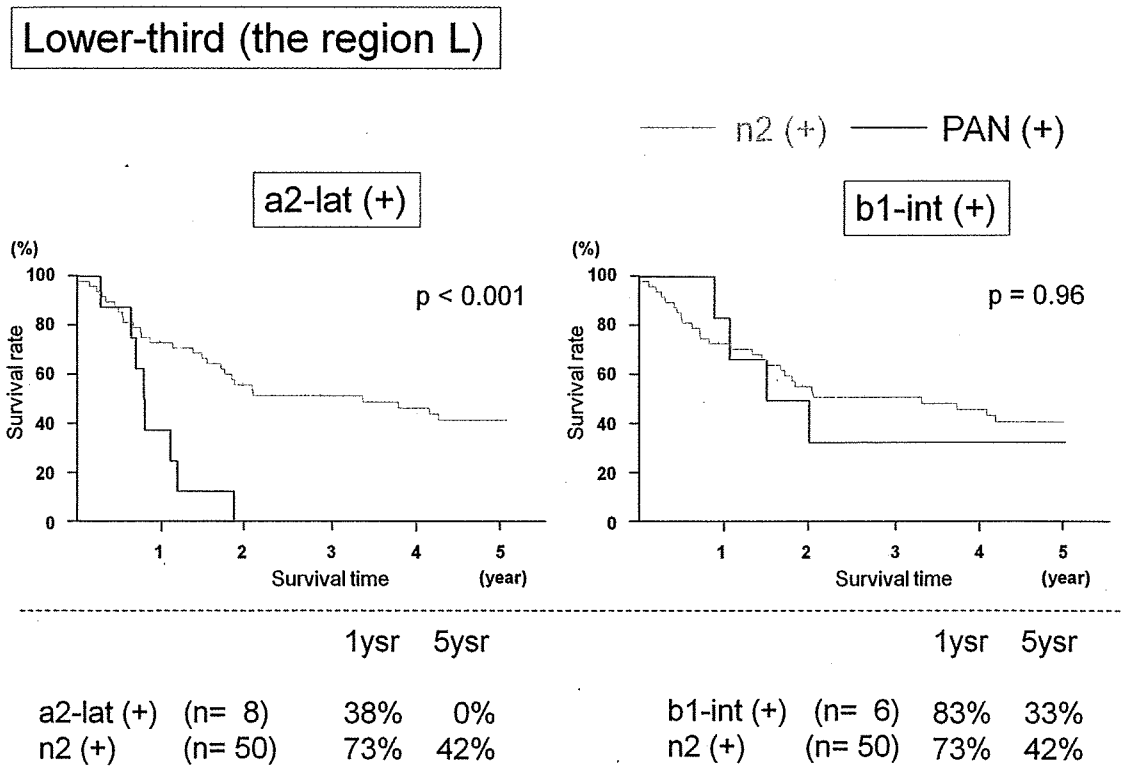


Figure 6. Survival curves of the n2 (+) group and the a2-lat (+) or the b1-int (+) group of the lower-third gastric cancer. There was no difference in the median survival times between the n2 (+) group and the b1-int (+) group, but the survival time of the n2 (+) group was significantly longer than that of the a2-lat (+) group.

predictive factors may be necessary conditions, but not sufficient ones. Other risk factors included depth of tumor invasion (13), total number of metastatic lymph nodes (14) and lymphatic metastases to the stations #7 and #8 (15). It is difficult, however, intraoperatively to prove whether patients fit these risk factors. On the other hand, several factors indicating good prognosis of the patients with PAN metastasis, including number of metastatic PANs (<3 or 4) (6,16) and total number of metastatic lymph nodes (<11) (16). But, again, it is hard to obtain such information before or during operation. These facts explain the difficulty in the patient selection for PAN dissection. We have performed PAN dissection to patients of gastric cancer without severe serosal invasion, but with lymph node metastasis to No. 3, 7, or 9 and showing H0, P0, M0 and Cy0 (17).

Lymphatic flow from the stomach drains into the perigastric nodes, next the node around the celiac axis or its main branches and finally into the PANs before joining the cisterna chyli as a systemic circulation. The main lymphatic route from the stomach to the PAN differs between the primary tumor locations. Research on lymphatic routes from perigastric nodes to PANs have been carried out using various tracers such as dyes, charcoals and radioisotopes. Yonemura (5) classified these lymphatic flows into 4 routes: i) Left subdiaphragmatic pedicle; ii) Celiac pedicle; iii) Superior mesenteric pedicle; and iv) Retropancreatic pedicle. The left subdiaphragmatic pedicle is characteristic of upper-third gastric cancer, especially, cardia cancer. This lymphatic flow reaches PANs next to the left side of aorta, that is, a2-lat. The lymphatic flow of the upper-third of the stomach drains into a2-lat not only along this left subphrenic artery, but also along the left gastric artery and the celiac axis. In this sense, a2-lat is likely to be important nodes for the upper-third gastric cancer. On the other hand, both the superior mesenteric and retropancreatic pedicles are characteristic of the lower-third gastric cancer. These lymphatic channels finally connect to the PANs next to the right side of aorta including a2-int and b1-int. The celiac pedicle is supposed to be a route common to whole area of the stomach. Metastasis to the PANs is strongly related with these lymphatic routes to the PANs. It is reported that PAN metastasis in the upper-third gastric cancer frequently occurs on the left side of aorta, while PAN metastasis in the lower-third gastric cancer tends to occur on the right side of aorta (14,18).

Nishi reported that the prognosis of a2-lat metastasis in the upper-third gastric cancer is very close to the one of n2 metastasis (18). Sasako *et al* (19) summarized a nationwide questionnaire asking location tendency in subgroups of PANs in the patients who received para-aortic lymphadenectomy and survived longer than 5 years after surgery. This study indicated that the most and the second most of the survivors in the 61 patients had metastases in a2-lat (n=31) and b1-int (n=11), respectively. Most of the survivors according to the sub-groups by the tumor location were registered at the a2-lat in the upper third and the middle third cancer (n=16 and n=7, respectively) and b1-int in the lower third cancer (n=7). These data strongly support our conception of selective lymph-adenectomy of subgroups of PANs according to the tumor location.

Sano *et al* (4) reported that there was no significant difference in postoperative morbidity or mortality between D2 and D3, but in the D3 group volume of blood loss was high

and the hospitalization was longer compared to the D2 group in the JCOG study 9501. Another randomized study conducted by Yonemura *et al* (20) demonstrated that both morbidity and mortality in the D3 group were significantly higher than those in the D2 group. If an advantage in elongation of survival would be achieved by the D3 operation, a little higher post-operative morbidity may be allowable, but two major randomized studies have failed in demonstrating survival benefits by PAN dissection (8,21). In this situation, whole lymphadenectomy of the PANs should be avoided for all the patients with advanced gastric cancer. It is important to balance survival advantage with postoperative morbidities in the treatment of these patients.

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## References

1. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H and Dutch Gastric Cancer Group: Extended lymph-node dissection for gastric cancer. N Engl J Med 340: 908-914, 1999.
2. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M and Fayers P: Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Br J Cancer 79: 1522-1530, 1999.
3. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY and Whang-Peng J: Nodal dissection for patients with gastric cancer: a randomized controlled trial. Lancet Oncol 7: 309-315, 2006.
4. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y and Okajima K: Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy-Japan Clinical Oncology Group study 9501. J Clin Oncol 22: 2767-2773, 2004.
5. Yonemura Y: Lymphatic systems of the stomach and the patterns of lymph node metastasis. In: Contemporary Approaches Toward Cure of Gastric Cancer. Yonemura Y (ed). Maeda Shoten, Kanazawa, pp3-18, 1996.
6. Isozaki H, Okajima K, Fujii K, Nomura E, Izumi N, Mabuchi H, Nakamura M and Hara H: Effectiveness of paraaortic lymph node dissection for advanced gastric cancer. Hepatogastroenterology 46: 549-554, 1999.
7. Kunisaki C, Shimada H, Yamaoka H, Wakasugi J, Takahashi M, Akiyama H, Nomura M and Moriwaki Y: Significance of para-aortic lymph node dissection in advanced gastric cancer. Hepatogastroenterology 46: 2635-2642, 1999.
8. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K and Japan Clinical Oncology Group: D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 359: 453-462, 2008.
9. Sobin LH and Wittekind C: TNM Classification of Malignant Tumours. 6th edition. Wiley-Liss, New York, 2002.
10. Japanese Research Society for Gastric Cancer: Japanese Classification of Gastric Carcinoma. 2nd English edition. Kanehara, Tokyo, 1998.
11. Japanese Research Society for Gastric Cancer: Japanese Classification of Gastric Carcinoma. 1st English edition. Kanehara, Tokyo, 1995.
12. Nomura E, Sasako M, Yamamoto S, Sano T, Tsujinaka T, Kinoshita T, Furukawa H, Shimizu T, Hiratsuka M, Kobayashi O, Kurokawa Y, Tanigawa N and Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group: Risk factors for para-aortic lymph node metastasis of gastric cancer from a randomized controlled trial of JCOG9501. Jpn J Clin Oncol 37: 429-433, 2007.
13. Kosaka T, Usami K, Ueshige N, Hasegawa T, Yoshitani S, Sugaya J, Nakano Y and Takashima S: Paraaortic lymph node dissection for gastric cancer in 244 consecutive cases. Hepatogastroenterology 53: 629-633, 2006.
14. Baba M, Hokita S, Natsugoe S, Miyazono T, Shimada M, Nakano S, Takao S and Aikou T: Paraaortic lymphadenectomy in patients with advanced carcinoma of the upper-third of the stomach. Hepatogastroenterology 47: 893-896, 2000.
15. Yonemura Y, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, Kamata S, Yamamoto H, Kim BS, Matsuki N, Sawa T, Noh SH and East Asia Surgical Oncology Group: Metastasis in para-aortic lymph nodes in patients with advanced gastric cancer, treated with extended lymphadenectomy. Hepatogastroenterology 54: 634-638, 2007.
16. Kunisaki C, Shimada H, Yamaoka H, Takahashi M, Ookubo K, Akiyama H, Nomura M and Moriwaki Y: Indications for paraaortic lymph node dissection in gastric cancer patients with paraaortic lymph node involvement. Hepatogastroenterology 47: 586-589, 2000.
17. Miwa K and Fujimura T: Indications of paraaortic lymph node dissection in gastric cancer from the viewpoint of long survivors. Geka Chiryo (in Japanese) 84: 562-567, 2001.
18. Nishi M: Para-aortic lymph node metastases in gastric cancer. In: Gastric Cancer Surgery Based on Clinicopathological Features. Nakayama Institute of Cancer Research, Tokyo, pp39-44, 1995.
19. Sasako M, Sano T, Katai H and Maruyama K: Problems of the lymph node grouping in the Japanese classification of gastric carcinoma. Shujutsu (in Japanese) 52: 737-743, 1998.
20. Yonemura Y, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, Kamata S, Yamamoto H, Kim BS, Matsuki N, Sawa T, Noh SH and East Asia Surgical Oncology Group: Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons. Hepatogastroenterology 53: 389-394, 2006.
21. Yonemura Y, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, Kamata S, Kim BS, Matsuki N, Sawa T, Noh SH and East Asia Surgical Oncology Group: Randomized clinical trail of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer. Int J Clin Oncol 13: 132-137, 2008.

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特集 センチネルリンパ節理論の消化器癌への応用

# 6 センチネルリンパ節生検の日常臨床への導入：多施設共同研究

## (1) 日本臨床腫瘍研究グループ(JCOG)

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*Key words*：センチネルリンパ節，胃癌，多施設共同研究，低侵襲

要 旨

センチネルリンパ節生検を日常臨床へ導入するためには，まずその妥当性が示されなければならない．早期胃癌のリンパ節転移は少なく，センチネルリンパ節生検の妥当性を検証するには多数例での検討が必要であり，方法論を統一した多数例での多施設共同研究が必須となる．現在，日本臨床腫瘍研究グループ(Japan Clinical Oncology Group；JCOG)と Sentinel Node Navigation Surgery(SNNS)研究会による二つの多施設共同研究が行われているが，両研究には留意すべき相違点がある．結果が公表された際には，両者の相違点をふまえて解釈する必要がある．

## はじめに

胃癌におけるセンチネルリンパ節(sentinel node；SN)の概念(SN concept)が注目されるようになり5年以上が経過しているが[1)~5)]，未だ悪性黒色腫や乳癌の領域[6)~8)]のように日常診療に用いられる現状にはない．SN concept の消化器癌への応用として，SN 生検を日常臨床へ導入するためには，まずその妥当性が示されなければならない[9)]．早期胃癌のリンパ節転移は少なく，SN 生検の妥当性を検証するには多数例での検討が必要であり，方法論を統一した多数例での多施設共同研究が必須となる．

現在，日本臨床腫瘍研究グループ(Japan Clinical Oncology Group；JCOG)と Sentinel Node Navigation Surgery(SNNS)研究会による二つの多施設共同研究が行われている．JCOG による多施設共同研究について SNNS 研究会との相違点を示しながら概説する．

## Ⅰ．胃癌治療におけるセンチネルリンパ節の意義

この項のポイント
- SN とは腫瘍からのリンパ流を直接受けるリンパ節のことである．
- SN 生検によりリンパ節転移陰性を精度高く診断可能であれば，個々の症例ごとにリンパ節転移の有無を知るためのより確実・合理的な適応決定法となる．

SN とは腫瘍からのリンパ流を直接受けるリンパ節のことである[10)]．SN を同定することが

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可能であり，かつそこにリンパ節転移が認められなければ，SN以外のリンパ節には転移がないとして治療を行ってもよいのではないかと考えられている．

理論的には，リンパ節転移の可能性が非常に低い，もしくはなければ，予防的に胃切除術やリンパ節郭清を行う意味はないと考えられる．SN生検によりリンパ節転移陰性を精度高く診断可能であれば，個々の症例ごとにリンパ節転移の有無を知るためのより確実・合理的な適応決定法となる．根治性を損なうことなくリンパ節郭清を省略できれば，機能温存術式や腹腔鏡下手術などの外科手術治療のみならず，内視鏡的切除適応拡大などへの展開が可能となる．

術前・術中にリンパ節転移を精確に診断することは困難であり，術前診断から得られた所見を過去のデータと照合することによりリンパ節転移がないであろう症例を割り出すという現在の適応決定法では，根治性を保つために適応を厳しくせざるをえない．胃癌に対する定型手術，すなわち広範囲胃切除と系統的リンパ節郭清が，胃癌治療成績向上に果たしてきた役割は大きいが，リンパ節郭清を行わずに治癒できる可能性がある多くの早期胃癌患者にも，結果的には不必要と考えられるリンパ節郭清を伴う広範囲胃切除が行われている[11]．リンパ節転移陰性を精度高く診断する指標を確立することがこの問題のブレークスルーとなり，ここにSN conceptの重要性がある[12]．

## II．日本臨床腫瘍研究グループ(JCOG)による多施設共同研究

この項のポイント

- SN生検の妥当性を検証するためには，方法論を統一した多数例での多施設共同研究が必須となる．
- JCOG 0302の目的は，早期胃癌患者に対して，色素法で同定されたリンパ節の術中迅速病理診断陰性の場合にリンパ節郭清を行わないことの妥当性を評価することである．

胃癌に関するSN conceptに関しては，2000年以降，北川らのRI法による36例の報告[2]，筆者らの色素法による77例の報告[1]に続いて種々の報告がなされているが，症例数が限られ，方法も多種多様である．早期胃癌のリンパ節転移は2割以下で，SN生検の妥当性を示す偽陰性割合を検証するためには多数例での検討が必要であり，方法論を統一した多数例での多施設共同研究が必須となる．現在，JCOGとSNNS研究会による二つの多施設共同研究が

**用語解説**

◆センチネルリンパ節の同定：トレーサーは色素かradioisotope(RI)か？

一般診療で広く用いるのにはさまざまな問題があるRIに対し，色素は取り扱いが容易であるが経時変化に弱い．なお，欧米の報告で散見されるpatent blueやisosulfan blue(Lymphazurin)ではショックを引き起こす可能性が低いとはいえないが[14]，用途は異なるものの広く臨床現場で使用されているICGは，取り扱いが容易かつ安価であり，リンパ系着色剤としての有用性[15]が知られている．

◆センチネルリンパ節の摘出：pick up法かbasin法（lymphatic basin dissection)か？

支配動脈に伴走して5流域に分類される胃のリンパ流のうち，早期胃癌におけるlymphatic basinの89％を占める1～2流域をリンパ節郭清するbasin法[16]は，数個のリンパ節の生検のみでリンパ節転移診断を行うpick up法[17]と比べて，リンパ節転移が郭清流域内に含まれる可能性が高くなると予想されるが，リンパ節郭清省略を目的とするSN conceptとの整合性が問われる．

表　JCOG と SNNS 研究会による二つの多施設共同研究の比較

| | JCOG | SNNS 研究会 |
|---|---|---|
| primary endpoint | 偽陰性割合(術中迅速病理診断) | 転移検出感度 |
| 対象 | sT1N0 | cT1-2N0 |
| トレーサー | ICG | $^{99m}$Tc スズコロイド<br>1% isosulfan blue |
| 同定方法 | 術中 pick up(時間規定あり) | 術野サンプリングしたものに加えて切除標本での検索 |
| 転移検索方法 | 術中迅速病理診断 | 術中迅速診断を原則とするが最終的転移診断は永久標本判定 |
| 登録方法 | 術中登録 | 術前日までの前登録 |
| 参加施設 | 30 施設(手技慣れ各施設 5 例) | 30 例以上の経験をもつ 12 施設 |
| 予定登録数 | 1,550 例 | 500 例 |

行われている(表).

JCOG 胃がん外科グループによる多施設共同研究「早期胃癌におけるセンチネルリンパ節生検の妥当性に関する研究(JCOG 0302)」(UMIN-CTR 試験 ID：C 000000059)は，早期胃癌患者に対して，indocyanine green (ICG)を用いて同定された green node(GN)を SN とみなし，GN の術中迅速病理診断でリンパ節転移が陰性の場合にリンパ節郭清を行わないことが妥当であるかどうかを評価することを目的とする．primary endpoint は偽陰性割合(GN 迅速病理診断転移陰性例/組織学的リンパ節転移陽性例)である．

本試験は，胃癌における SN 生検の妥当性を評価する試験であり，同意の得られた内視鏡的切除の対象とならない早期胃癌患者の術中に登録を行う．腫瘍部位の漿膜側から色素(ICG)を注入し GN を同定する．これを摘出して迅速病理診断に提出し，通常のリンパ節郭清を伴う胃切除を『胃癌治療ガイドライン』[13]に沿って施行する．後日，リンパ節の固定標本の病理結果と GN の結果を比較検討する(図).

本試験の結果により SN 生検によってリンパ節転移の有無を診断することが妥当であると判断された場合，SN 転移陰性の早期胃癌患者に対しては第Ⅲ相試験が行われることなく，胃局所切除術などのリンパ節郭清を省略した術式が標準治療となると予想される．現時点での臨床応用が妥当であるかどうかを評価する臨床試験であり，SN 転移診断は術中診断に限定されている．たとえば，術中の迅速病理診断で転移な

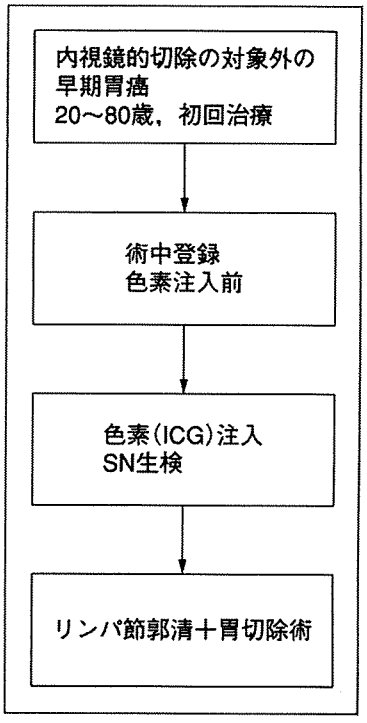


図　JCOG 0302 の概要

しとされたGNの術後検索で転移を認めた場合，SN conceptとしては問題ないのだが，本試験では偽陰性と扱われる．なお，本試験のベースとなった筆者らのpilot studyでは多切片での転移検索を行っていたが[1]，多施設共同研究であるために最大割面1切片のHE染色のみでの検索という制約が加わっている．また，SN生検の手技慣れ期間が施設当り5例と設定されているが，後述のSNNS研究会によるアンケート結果からすれば，ラーニングカーブが少なく見積もられている．

## Ⅲ．JCOGとSNNS研究会による多施設共同研究の相違点

この項のポイント

- JCOGとSNNS研究会による多施設共同研究には留意すべき相違点があり，結果が公表された際には，両者の相違点をふまえて解釈する必要がある．

JCOG 0302は現時点での臨床応用が妥当であるかどうかを評価する臨床研究であるため，SN conceptの妥当性のみならず，術中迅速病理診断および手技慣れ期間(ラーニングカーブ)の問題が包含されている点に留意すべきである．すなわち，肯定的な結果が得られた場合は，その時点で臨床応用の根拠となるが，否定的な結果であった場合，SN concept自体の問題なのか，最大1割面の術中迅速病理診断による転移検索法の問題なのか，ラーニングカーブの問題なのかという疑問が残ることになる．

SNNS研究会標準手技プロトコール作成委員会による多施設共同研究「胃癌におけるセンチネルリンパ節を指標としたリンパ節転移診断に関する臨床試験」は，早期胃癌に加えて一部の進行胃癌(cT 2)を対象とし，$^{99m}$Tcスズコロイドと1% isosulfan blueを内視鏡を用いて病巣周囲粘膜下層に原則4カ所注入するもので，primary endpointは転移検出感度(リンパ節郭清の結果で所属リンパ節に少なくとも1個以上のリンパ節に転移が認められた症例のうちSNに転移を有した症例の割合)である．

JCOG 0302との相違点として，トレーサー併用であること，術野サンプリングしたものに加えて切除標本での検索を許容すること，術中迅速病理診断を原則とするが最終的リンパ節転移診断は永久標本での判定であること，30例以上の経験をもつ12施設に限定したものであること，などがあげられる(表)．SNNS研究会が行ったアンケート調査から，ラーニングカーブとして30例を要するとみられたことをふまえ，手技慣れを前提にSN conceptが胃癌においても成立するかをみることを主眼としており，術中迅速病理診断およびラーニングカーブの影響を受けにくいように設定されている．しかしながら，SN同定およびこれを指標としたリンパ節転移診断が胃切除前に限定されていないため，肯定的な結果が得られても，その結果をもって術中診断による臨床応用が可能とはいえず，臨床応用のためには別ステップを要することになる．

## おわりに

胃癌におけるSN conceptは，多施設共同研究によりその妥当性が検証されている段階であり，日常診療として安易に臨床応用すべき状況にはない．JCOGとSNNS研究会による二つの多施設共同研究は，SN conceptの胃癌への応用が可能かどうかを見極める重要な試験である．その結果が待たれるが，両研究には留意すべき相違点があり，結果が公表された際には，両者の相違点をふまえて解釈する必要がある．

## 文　献

1) Hiratsuka, M., Miyashiro, I., Ishikawa, O., et al.：Application of sentinel node biopsy to gastric cancer surgery. Surgery 129；335-340, 2001
2) Kitagawa, Y., Fujii, H., Mukai, M., et al.：The role of the sentinel lymph node in gastrointestinal cancer. Surg. Clin. North Am. 80；1799-1809, 2000
3) Kitagawa, Y., Fujii, H., Mukai, M., et al.：Radio-guided sentinel node detection for gastric cancer. Br. J. Surg. 89；604-608, 2002
4) Ichikura, T., Morita, D., Uchida, T., et al.：Sentiel node concept in gastric carcinoma. World J. Surg. 26；318-322, 2002
5) 市倉　隆，小野　聡，望月英隆：Sentinel node navigation surgery—消化器癌への応用の可能性．医学のあゆみ 205；586-590, 2003
6) Morton, D. L., Wen, D. R., Wong, J. H., et al.：Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch. Surg. 127；392-399, 1992
7) Krag, D. N., Weaver, D. L., Alex, J. C., et al.：Surgical resection and radio-localization of the sentinel node in breast cancer using a gamma probe. Surg. Oncol. 2；335-340, 1993
8) Giuliano, A. E., Kirgan, D. M., Guenther, J. M., et al.：Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann. Surg. 220；391-401, 1994
9) 宮代　勲，平塚正弘，石川　治，他：胃癌における sentinel node concept の現状．外科 68；1688-1693, 2006
10) Nieweg, O. E., Tanis, P. J. and Kroon, B. B. R.：The definition of a sentinel node. Ann. Surg. Oncol. 8；538-541, 2001
11) 平塚正弘，宮代　勲：センチネルリンパ節からみた胃癌対策．Front. Gastroenterol. 10；242-247, 2005
12) 宮代　勲，平塚正弘，今岡真義：センチネルリンパ節の概念は消化器癌の外科治療を変えるか？変えるとする立場から．Front. Gastroenterol. 6；116-120, 2001
13) 日本胃癌学会編：胃癌治療ガイドライン(医師用)2004年4月改訂(第2版)．金原出版，東京，2004
14) Cimmino, V. M., Brown, A. C., Szocik, J. F., et al.：Allergic reactions to isosulfan blue during sentinel node biopsy—a common event. Surgery 130；439-442, 2001
15) 高山　敏，古賀和久，大浦　憲，他：Indocyanine green のリンパ系着色剤としての有用性．応用薬理 19；603-614, 1980
16) 三輪晃一，木南伸一，鯵坂秀行，他：リンパ区域郭清を伴う早期胃がんの機能温存縮小手術．日外会誌 106；280-285, 2005
17) 平塚正弘，宮代　勲，石川　治：胃癌—色素法による成績．北島政樹，久保敦司編：Sentinel Node Navigation—癌治療への新しい展開．171-176，金原出版，東京，2002



## *Summary*

### Outline of the Japan Clinical Oncology Group Trial—Evaluation of Feasibility and Accuracy of Diagnosis Using Sentinel Node Biopsy in Early Gastric Cancer (JCOG 0302)

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Multi-institutional prospective clinical trials to evaluate feasibility and accuracy of diagnosis using sentinel node biopsy in early gastric cancer are essential for clinical application of this technique. Two clinical trials, the Japan Clinical Oncology Group trial (JCOG 0302) and the Japanese Society for Sentinel Node Navigation Surgery trial, are ongoing in Japan. Several noteworthy differences between these two trials are noted.



***Key words*** : sentinel node, gastric cancer, multi-institutional prospective clinical trial, less-invasive



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# Detection of Sentinel Node in Gastric Cancer Surgery by Indocyanine Green Fluorescence Imaging: Comparison with Infrared Imaging

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**Background:** Secure methods for clinical detection of the sentinel node (SN) are in great demand to avoid unnecessary resection. This was a clinical exploration/feasibility study of a novel detection system for SN biopsy using indocyanine green (ICG) fluorescence imaging in gastric cancer surgery.

**Methods:** SN biopsy using ICG dye was performed in three patients who had gastric cancer. ICG fluorescence images were obtained using a detection system comprising a charge-coupled device (CCD) camera with a cut filter as the detector and light emitting diodes (LED) as the light source. The nodes were also examined simultaneously by an infrared (IR) imaging videoscope.

**Results:** Immediately after intraoperative ICG injection, the fluorescence imaging system allowed easy visualization of the lymphatic vessels draining from the primary gastric tumor toward the lymph nodes and tracing of the moving injected dye. Some lymph vessels and nodes were hardly recognized by ICG green color or IR imaging. The ICG fluorescence system also allowed visualization of the lymph node when ICG was injected the day before surgery, similar to the radio-guided method.

**Conclusions:** Detection of SNs in gastric cancer surgery using the ICG fluorescence imaging system is a promising novel technique and may perhaps prove useful for laparoscopic surgery.

**Key Words:** Sentinel node—Gastric cancer—Indocyanine green fluorescence imaging—Light emitting diode (LED)—Infrared (IR) imaging.

The sentinel node (SN) technique has been used in the management of a variety of cancers to avoid unnecessary lymphadenectomy.[1–3] We were the first group to use SN biopsy with indocyanine green (ICG) in open gastric cancer surgery with a high success rate, and reported that the SN status can predict the lymph node status with a high degree of accuracy.[4] Legal considerations and costs limit the use of radioactive substances in general hospitals; thus, the dye-guided method is safe, convenient, and cost-effective compared with the radioactive probe-guided method.[5,6] However, the technique has certain limitations, such as loss of visibility in dense fat and rapid transit of the dye; thus, adequate training is required.[7–9] These limitations are more critical in laparoscopic surgery.

Convenient but reliable detection methods are, therefore, in great demand for clinical application of this technique. Recently, Kitai et al.[10] reported a

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preliminarily study in which SN biopsy guided by ICG fluorescence imaging is a promising technique in breast cancer surgery. Our study was a clinical exploration/feasibility study of a novel detection technique for SN biopsy using ICG fluorescence imaging in gastric cancer surgery. We compared the fluorescence images with those of infrared (IR) imaging videoscope reported by some surgeons [11,12] to produce successful results and enhancement of the visibility of ICG.

## MATERIALS AND METHODS

Fluorescence images were obtained using the ICG fluorescence imaging system, the photodynamic eye (PDE) system (Hamamatsu Photonics, Hamamatsu, Japan). For the first two patients, a prototype system was used.[10] The light source was a light-emitting diode (LED) that emitted light at a wavelength of 760 nm, and the detector was a charge-coupled device (CCD) camera equipped to filter out light with a wavelength below 820 nm. The LEDs were aligned on a board, and the CCD camera was set at the center. The fluorescence signals were sent to a digital video processor.

SN biopsy was conducted as described previously.[4] For this study, ICG (Diagnogreen; Dai-Ichi Pharm. Co., Tokyo, Japan) in a volume of 2–4 ml was injected just around the primary tumor using an intraoperative endoscopic puncture needle in the first two patients and 1 day before surgery in the other patient. All lymph nodes that stained green or bright with fluorescence by the ICG were excised before gastrectomy and were sliced into 2-mm sections for intraoperative histological examination with hematoxylin and eosin staining. The nodes were also examined simultaneously using an IR imaging videoscope to compare images obtained by the two methods.

The first two patients (a 66-year-old man and 60-year-old woman) were enrolled and treated at the Osaka Medical Center for Cancer and Cardiovascular Diseases in March 2005. The other, a 73-year-old man, was treated in March 2007. All three patients had T1 gastric cancer and received distal gastrectomy with lymphadenectomy according to the Japanese classification of gastric carcinoma.[13] The preoperative diagnosis was based on gastric endoscopy, abdominal ultrasonography, and computed tomography. Informed consent was obtained from every patient preoperatively, and the study was approved by the Human Ethics Review Committee of Osaka Medical Center for Cancer and Cardiovascular Diseases.

## RESULTS

Immediately after intraoperative ICG injection in the first two patients, the ICG fluorescence imaging system clearly visualized the lymphatic vessels draining the primary tumor toward the lymph nodes with gradually moving injected dye seen as bright fluorescent image (Fig. 1a, d). Fine faint-green-colored lymphatic channels were easy to recognize by means of ICG fluorescent imaging (Fig. 1a, b). Similarly, faint-green-colored lymph nodes were also easy to find through the fat tissue (Fig. 1d, e). Green fluorescently labeled nodes were dissected out as SNs and sliced for intraoperative histological examination. Surgeons could confirm the removed lymph nodes stained ICG green by fluorescent imaging (Fig. 2). The lymphatic vessels and nodes were also recognized by their dark color on absorption images using IR imaging videoscope, in contrast to the bright color by fluorescence imaging (Fig. 1c, f). However, individual nodes could be visualized more clearly even through adipose tissue by fluorescence imaging (Fig. 1d, f). Although ICG was injected using an endoscopic puncture needle 1 day before operation in the third patient, the ICG fluorescence imaging system could visualize the fluorescent lymph nodes—that were otherwise hardly recognized by the green color only—through dense fat (data not shown).

The green-colored nodes were successfully detected as SNs in all three patients (four, one, and four nodes, respectively), either with or without the ICG fluorescence imaging system. In the present study, none of the three patients had lymph node metastases in both SNs and non-SNs, and none developed any adverse event after ICG injection.

## DISCUSSION

False-negative SN biopsy may lead to local control failure. The significance of the technical learning curve for SN biopsy has already been discussed.[7–9] Substantial experience is required to develop the technical skill necessary to achieve a high success rate, meaning that the accuracy of SN biopsy depends on the individual surgeon.

ICG is a popular diagnostic reagent approved clinically for examination of hepatic and circulatory function.[14] As a tracer for SN biopsy, the injected ICG binds rapidly to albumin and is carried more specifically through the lymphatic vessels than indigo carmine or Evans blue.[15] The ICG-related allergic reactions are fewer than those of blue dyes such as

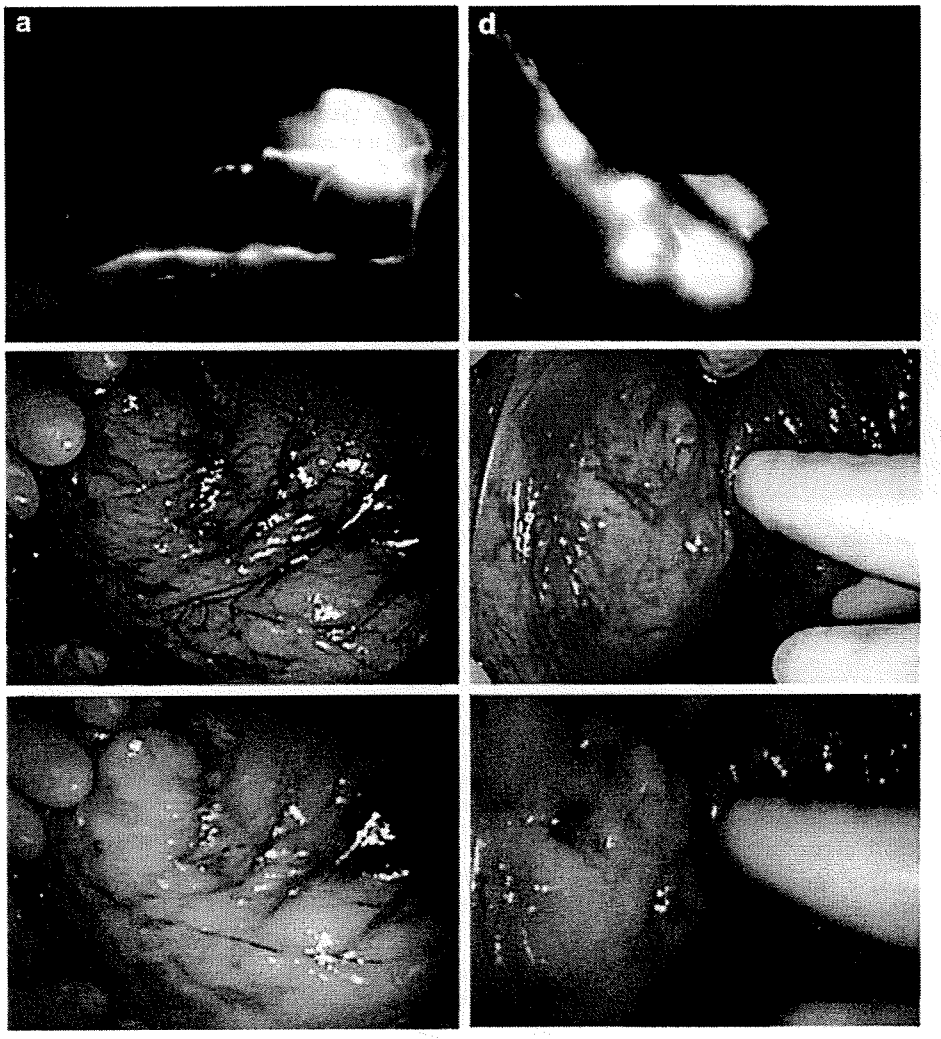


**FIG. 1.** The indocyanine green (ICG) fluorescence imaging system clearly visualized lymphatic vessels from the primary gastric tumor toward the lymph nodes. Fine lymph vessels colored faint green (b) were easier to recognize by ICG fluorescent imaging (a) or IR imaging (c). Lymph nodes hardly recognized by the green color only (e) were also easier to identify through fat by fluorescent imaging (d) or IR imaging (f). The fluorescence imaging system could clearly visualize four nodes at station number six (d), although the IR imaging videoscope could not (f).

isosulfan blue.[16] ICG has an absorption peak of 800 nm *in vivo* and is detected green in color. Detection by absorption spectroscopy is more sensitive than color perception, and some surgeons reported that infrared ray electronic endoscopy (IREE) with ICG injection is useful for SNs detection.[11,12] However, Ishikawa et al.[11] reported an obese patient with a false-negative SN by laparoscopic SN navigation using the IREE system although infrared rays can penetrate fatty tissues up to a depth of 3 mm.

Kitai et al. [10] noted, in their preliminary report of ICG fluorescence imaging in breast cancer surgery, that the sensitivity of fluorescence spectroscopy is much greater than that of absorption spectroscopy. They also reported that fluorescence was observed from an ICG solution embedded 1-cm deep in the material with optical properties compatible to human tissue in a preliminary study using a phantom. Based on our experience, the ICG fluorescence imaging system was sensitive in one patient injected with the dye 1 day before surgery, similar to the radio-guided method. One advantage of preoperative tracer injection is that it eliminates the time-consuming intraoperative endoscopy, but has the disadvantage of loss of real-time tracing. However, if there is no risk that the nodes stained 1 day after injection are different from those that receive lymphatic drainage first from the tumor site, preoperative injection might be a safer procedure than intraoperative injection. This would avoid lymphatic vessel injury, since ICG leakage from injured lymphatic vessels makes further fluorescence observation difficult, leading to detection failure.

The clinical significance of SN concept in gastric cancer surgery is to eliminate unnecessary lymph node resection. Thus, its combination with laparoscopic surgery, a minimal-access procedure, could make gastric surgery less invasive. But, to date, laparoscopic SN biopsy has not been widely

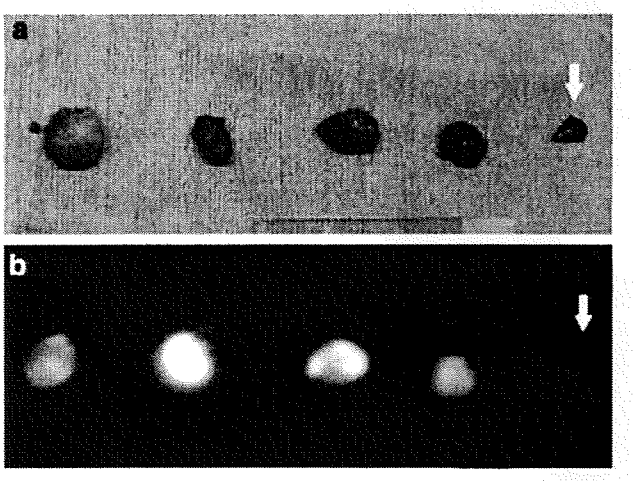


FIG. 2. Using fluorescent imaging, surgeons could confirm that the excised lymph nodes stained indocyanine green (ICG). *Arrows* indicate a negative control lymph node from station number 4sb which was recognized as a non-SN in the surgical field by the green color, IR imaging videoscope, and the ICG fluorescence imaging system.

accepted.[17] Laparoscopic gamma probing remains under development, and the shine-through effect from the injection site seriously restricts the use of this method. Tonouchi et al.[18] reported a false-negative case resulting from a detection error attributable to the shine-through effect of a radio-guided method. As for the dye-guided SN biopsy, several limitations—such as loss of visibility in dense fat and rapid transit of the dye—are more critical in laparoscopic surgery. A laparoscopic-ICG fluorescence imaging system would overcome such limitations of the dye-guided SN biopsy, although it is not available at present.

Although further studies of larger population sample are necessary, the dye-guided method using an ICG fluorescent imaging system is a potentially safer, more convenient, and more cost-effective replacement of the radio-guided one. It is a promising technique that makes dye-guided SN biopsy in both open and laparoscopic gastric cancer surgery easier, and possibly shortens the learning curve.

## ACKNOWLEDGMENT

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## REFERENCES

1. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping, sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; 220:391–8.
2. Krag DN, Weaver DL, Alex JC, et al. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 1993; 2:335–9.
3. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; 127:392–9.
4. Hiratsuka M, Miyashiro I, Ishikawa O, et al. Application of sentinel node biopsy to gastric cancer surgery. *Surgery* 2001; 129:335–40.
5. Bostick P, Essner R, Glass E, et al. Comparison of blue dye and probe-assisted intraoperative lymphatic mapping in melanoma to identify sentinel nodes in 100 lymphatic basins. *Arch Surg* 1999; 134:43–9.
6. Giuliano AE, Jones RC, Brennan M, et al. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997; 15:2345–50.
7. Morrow M, Rademaker AW, Bethke KP, et al. Learning sentinel node biopsy: results of a prospective randomized trial of two techniques. *Surgery* 1999; 126:714–20.
8. Sanidas EE, de Bree E, Tsiftsis DD. How many cases are enough for accreditation in sentinel lymph node biopsy in breast cancer? *Am J Surg* 2003; 185:202–10.
9. Cox CE, Salud CJ, Cantor A, et al. Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. *J Am Coll Surg* 2001; 193:593–600.
10. Kitai T, Inomoto T, Miwa M, et al. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer* 2005; 12:211–5.
11. Ishikawa K, Yasuda K, Shiromizu A, et al. Laparoscopic sentinel node navigation achieved by infrared ray electronic endoscopy system in patients with gastric cancer. *Surg Endosc* 2007; 21:1131–4.
12. Nimura H, Narimiya N, Mitsumori N, et al. Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. *Br J Surg* 2004; 91:575–9.
13. Japanese Gastric Cancer A. Japanese classification of gastric carcinoma—2nd english edition *Gastric Cancer* 1998; 1:10–24.
14. Caesar J, Shaldon S, Chiandussi L, et al. The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin Sci* 1961; 21:43–57.
15. Takayama S, Furuhama K, Ohura K, et al. Experimental studies on the usefulness of indocyanine green (ICG) as a lymphatic vital dye (in Japanese). *Oyo Yakuri / Pharmacometrics* 1980; 19:603–14.
16. Cimmino VM, Brown AC, Szocik JF, et al. Allergic reactions to isosulfan blue during sentinel node biopsy–a common event. *Surgery* 2001; 130:439–42.
17. Kitagawa Y, Fujii H, Mukai M, et al. Current status and future prospects of sentinel node navigational surgery for gastrointestinal cancers. *Ann Surg Oncol* 2004; 11:242S–4S.
18. Tonouchi H, Mohri Y, Tanaka K, et al. Laparoscopic lymphatic mapping and sentinel node biopsies for early-stage gastric cancer: the cause of false negativity. *World J Surg* 2005; 29:418–21.

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Operation

# 胃癌におけるセンチネルリンパ節同定法

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## はじめに

理論的には，リンパ節転移の可能性が非常に低い，もしくはなければ，予防的に胃切除術やリンパ節郭清を行う意味はないと考えられる。術前診断から得られた所見を過去のデータと照合することによりリンパ節転移がないであろう症例を割り出すという現在の適応決定法では，根治性を保つために適応を厳しくせざるをえない。胃癌に対する定型手術が治療成績向上に果たしてきた役割は大きいと思われるが，リンパ節郭清を行わずに治癒できる可能性がある多くの早期胃癌患者にも，結果的には不必要と考えられるリンパ節郭清を伴う広範囲胃切除が行われている。

リンパ節転移陰性を精度高く診断する指標の確立が，この問題のbreakthroughとなる[1]。センチネルリンパ節（sentinel node，以下SN）の概念（以下SN concept）の重要性はそこにある。

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key words：センチネルリンパ節，胃癌，リンパ節郭清

## I. 胃癌におけるセンチネルリンパ節の概念とその検証

SNとは腫瘍からのリンパ流を直接受けるリンパ節のことである[2]。SNを同定することが可能であり，かつそこにリンパ節転移が認められなければ，SN以外のリンパ節には転移がないとして治療を行えるのではないかと期待されている。

SN conceptを日常臨床へ導入するには，SNをどのように同定するのか，同定したSNに転移が認められなければSN以外のリンパ節に転移がないといっていいのかを検証する必要があり，①SN同定のためのトレーサーの種類と注入法，②SNの同定と摘出法，③SN転移検索法，についての検討を要する。

### 1. トレーサーの種類と注入法

トレーサーとしてradioisotope（RI）を用いた方法では，放射線による被曝，診断に測定機器を手術室に持ち込む必要がある，試薬の取り扱いが煩雑，薬価が高いなど，一般診療に広く用いるという観点からみればいくつかの問題がある。これに対し，色素をトレーサーとする方法は，特殊な機器が不要であり，薬剤の取り扱いも容易であるが，経時的変化に弱く，RI法同様，手技慣れが求められる。なお，色素のうち，欧米の報告で散見されるpatent blueや

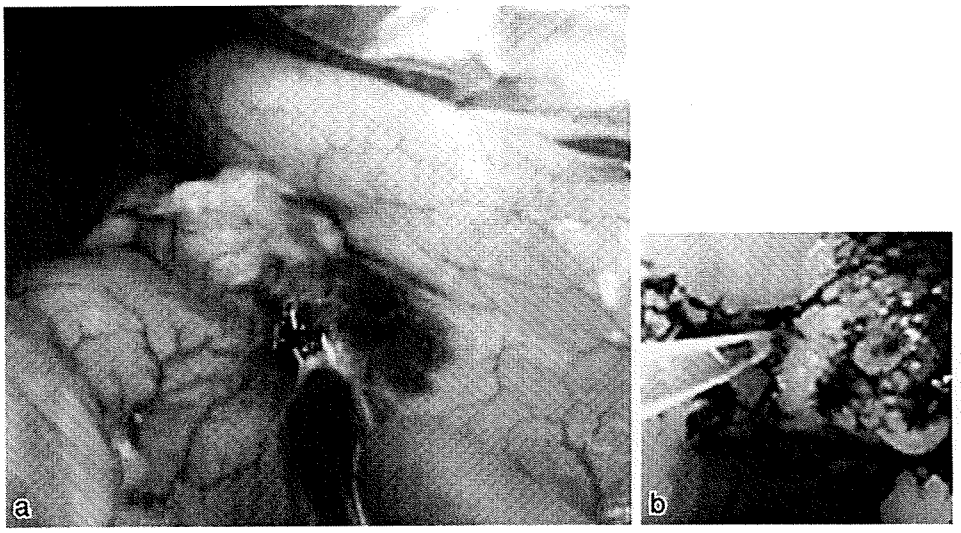

**図 1　センチネルリンパ節同定のためのトレーサー注入**
a）開腹下に胃癌原発巣の位置を確認し，漿膜側から 26 ゲージ針を用いて，ICG を分注する。
b）内視鏡を用いて，ICG を病変周囲粘膜下層へ分注する。両者ともトレーサーとして色素の ICG を用いているが，ほかの色素や RI でも同様である。漿膜側および粘膜側からの注入のいずれにおいても，原発巣に近接して周囲を取り囲むように注入することが重要と考えられており，高度の線維化を伴う病変へのトレーサー注入にはより留意が必要である。

isosulfan blue（Lymphazurin）はショックを引き起こす可能性が低いとはいえないが[3]，indocyanine green（ICG）は異なる用途ではあるものの広く臨床現場で使用されており，安価で，リンパ系着色剤としての有用性も知られている[4]。

SN 同定には適切なトレーサーの注入が不可欠である。リンパ節転移の可能性がほとんどない対象に対しては内視鏡的切除を考慮すべきであり，SN concept を生かすべき対象は，リンパ節転移が低頻度ながらも無視できない程度にある対象，すなわち，主に，M 癌で潰瘍（UL）を伴うものや SM 癌といえる。組織学的 M 癌の 57％と SM 癌の 62％が UL（＋）であることから[5]，SN 生検対象の多くが UL（＋）症例といえる。漿膜側および粘膜側からの注入のいずれの方法においても，原発巣に近接して周囲を取り囲むように注入することが重要と考えられており，高度の線維化を伴う病変へのトレーサー注入にはより留意が必要である（**図 1**）。なお，注入すべき病巣部位の確認は触診でわかることも多いが，術前の内視鏡で病巣に接してクリップでマーキングしておくとわかりやすい。

### 2. センチネルリンパ節の同定・摘出法

SN の同定・摘出法には，ピックアップ法[6,7]や basin 法（lymphatic basin dissection）[8]がある（**図 2**）。また，basin ではなく station での同定・摘出の提唱もある[9]。流域を郭清する basin 法では，支配動脈に伴走して 5 流域に分類される胃のリンパ流のうち，早期胃癌における lymphatic basin の 89％を占める 1-2 流域をリンパ節郭清するものであり，数個のリンパ節の生検のみでリンパ節転移診断を行うピックアップ法に比べると，リンパ節転移が郭清流域内に含まれる可能性が高くなると予想されるが，リンパ節郭清省略を目的とする SN concept との整合性が問われる。

### 3. センチネルリンパ節の転移検索法

術中の SN 生検を臨床応用するには，胃切除前にリンパ節転移陰性を診断する必要があり，