Laparoscopic Sentinel Node Navigation Surgery for Gastric Cancer

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Short-term surgical results of gastric cancer improve with use of a laparoscopic approach compared to those after conventional laparotomy, particularly in patients with early gastric cancer (EGC). However, due to gastric resection and lymph node dissection, poor long-term quality of life (QOL) after gastric cancer surgery is equivalent between the approaches. Thus, gastric resection and lymph node dissection should be minimized to avoid injury to innervating nerves and the sphincter, to maintain gastric function, preserve gastric volume, and improve long-term QOL. Such a procedure should not impair the oncological outcome by removing the primary tumor and metastasis to lymph nodes. After analysis of the many single center feasibility studies, sentinel node biopsy (SNB) is useful for this purpose but sensitivity varies and is unsatisfactory. A large multicenter Japanese feasibility study showed promising results after clinical application of SNB in patients with EGC. Based on those results, a multicenter prospective randomized phase III trial of laparoscopic SNB conducted by the Korean surgical study group, the SENORITA (SEntinel Node ORiented Tailored Approach), is now ongoing. Prior to this phase III trial, a quality control study of participating institutions was completed in an effort to standardize and overcome the SNB learning curve. Laparoscopic SNB with gastric volume and function-preserving surgery to improve the long-term QOL without impairing the oncological outcome may be a surgical option after this trial in the subgroup of patients with EGC.

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INTRODUCTION

The incidence and death rate from gastric cancer are second and third most common, respectively in Korea.^{1,2} The proportion of patients with early gastric cancer (EGC) is increasing annually due to the national screening program and frequent self-check endoscopy based on concerns about gastric cancer. The standard EGC treatment is gastric resection with radical lymph node dissection, depending on the preoperative evaluation, except the absolute indication for endoscopic resection (ER).³ The 5-year overall survival rate in patients with EGC is > 90% using this standard surgery, and patients are living as long-term survivors. However, this standard

surgery for patients with EGC produces various short-term surgical complications and long-term impaired of quality of life (QOL) in terms of suboptimal diet, altered bowel habits, and poor nutrition. Thus, new concepts and trials have been discussed for long-term surviving patients after EGC.

After an increase in the use of minimally invasive surgery, such as laparoscopy and robotics for gastric cancer surgery, short-term QOL improved with similar morbidity to that of the conventional laparotomy but long-term oncological outcomes await prospective trials.^{4,5} However, long-term QOL after laparoscopic gastric cancer surgery is similar to that of conventional laparotomy due to the same gastric resection and lymph node dissection approach. Various surgical techniques,

such as proximal gastrectomy, pylorus preserving gastrectomy, and vagus nerve preserving surgery, have been used to improve long-term QOL but the results are not confirmative or encouraging.^{6,7} Injury to innervation and sphincters must be minimized to preserve gastric function and volume and improve long-term QOL. The type of minimal approach should not impair the oncologic outcomes in patients with EGC by removing the entire tumor burden from the primary tumor and metastatic lymph nodes. ER is a minimally invasive and organ-preserving procedure used only for absolute indicated patients with a very low possibility of lymph node metastasis. Many studies have been performed to expand the indications for ER, but the risk of recurrence due to lymph node metastasis has limited expansion.^{8,9} The sentinel node biopsy (SNB) concept was developed to minimize lymph node dissection if no metastasis are present in the SN. This approach minimizes damage to nerves and sphincters and preserves gastric volume by resecting small EGC lesions. This concept was postulated to preserve the gastric function and improve the troublesome long-term QOL in patients with EGC.

FEASIBILITY STUDIES AND META ANALYSIS OF SENTINEL NODE BIOPSY IN PATIENTS WITH GASTRIC CANCER

Many SNB gastric cancer feasibility studies have been published in the last decade mainly from Korea and Japan (Table 1). However, most were performed by a single institution with small numbers of patients. The SNB indication and techniques, such as biopsy method, tracers, injection site, and pathological evaluations, were not standardized so procedural details differ. Several review articles and meta-analyses have been reported about this topic in gastric cancer.¹⁰⁻¹² The pooled detection rate estimate was > 90% but sensitivity was 80%, with heterogeneity between studies. Several points have been suggested to improve SNB results, such as harvesting five or more SNs, preference for EGC rather than advanced gastric cancer, double tracers rather than a single tracer, submucosal rather than subserosal injection, and more precise pathological evaluations. The conclusion from all of these meta-analyses is that SNB is unsatisfactory for clinical application and should be used cautiously. Additional methods have been investigating recently to improve SNB results in patients with gastric cancer, particularly in terms of sensitivity.

PUBLISHED SENTINEL NODE BIOPSY CLINICAL TRIALS IN PATIENTS WITH GASTRIC CANCER

Two large-scale multicenter SNB feasibility studies

in patients with gastric cancer have been performed in Japan. The first is the Japan Clinical Oncology Group trial (JCOG0302) and the other is the Japanese Society for Sentinel Node Navigation Surgery (SNNS) trial. Several of the protocols differed between the studies and the final published results were totally different.¹³ Miyashiro et al. reported that the JCOG0302 study was stopped before all patients were recruited due to the high false-negative rate.¹⁴ The cause of the high false-negative rate was the simple pathological evaluation and insufficient experience of the participating institutions. Kitagawa et al. reported promising results for clinical applicability from the SNNS trial.¹⁵ They reported 97.5% detection rate with a mean of 5.6 SNs and 93% sensitivity. Among the four false-negative cases, two were T2 lesions, and the location of missed metastatic nodes was at the same sentinel basin in three cases. These results suggested that the optimal indication is T1 lesions, and that sentinel basin dissection rather than a pick-up biopsy is an adequate biopsy method.

A small phase II trial was reported from a single institution of Japan.¹⁶ Ichikura et al. reported that limited gastrectomy with SNB was satisfactory for short-term outcomes and recurrence during the observation period. Another single-center phase II trial from Korea is closing patient recruitment and we are waiting for the final results.¹⁷

ONGOING PHASE III TRIAL OF LAPAROSCOPIC SENTINEL NODE BIOPSY IN PATIENTS WITH GASTRIC CANCER

The controversial issue of SNB in gastric cancer has been investigated by many academic societies and institutional researchers. Several points were suggested to improve the SNB results. Moreover, most patients with EGC who will be long-term survivors want to save their stomach for improved QOL, and clinicians have the responsibility to solve this problem. A study group called SENORITA (SEntinel Node ORiented Tailored Approach) was launched by a Korean academic society that includes surgeons, gastroenterologists, pathologists, and nuclear medicine specialists to solve this problem in a phase III trial.¹⁸ The protocol for the SENORITA multicenter phase III trial has been developed and patient recruitment is ongoing.¹⁹ Briefly, the study is a non-inferior design of laparoscopic SNB with stomach preserving surgery compared to conventional standard laparoscopic gastrectomy (Fig. 1). The primary endpoint is 3-year disease free survival and the secondary endpoints are postoperative complications, QOL, 5-year disease free survival, and overall survival. The calculated sample size was 290 patients for each arm and the indication was cT1N0 < 3 cm, regardless of the histological

Table 1. Details of published feasibility studies on sentinel node biopsy¹⁰

Author	Year	No. of Pts	Age	Sex	Indication	Approach	Method of biopsy	Tracer	Injection site	No. of SNs	LND	Histol. Eval.	No of positive LNs	Detection rate	Sensitivity	NPV	PPV
Hiratuska	2001	74	-	-	EGC,AGC	Open	Pick up	Dye	ss	2.6	Radical	HE	10	98.6%	90.0%	98.4%	66.7%
Aikou	2001	18	-	-	EGC	Open	Basin	Dye,RI	sm	3.0	Radical	RT-PCR	6	94.4%	83.3%	91.7%	0%
Ichikura	2002	62	-	-	EGC	Open	Postgast	Dye	sm	7.3	Radical	HE	15	100%	86.7%	95.9%	0%
Kitagawa	2002	145	57	107:38	EGC,AGC	Open	Postgast	RI	sm	3.6	Radical	HE	24	95.2%	91.7%	98.3%	0%
Hundley	2002	14	66	8:6	-	Open	Pick up	Dye	ss	2.8	Radical	IHC	10	100%	70.0%	57.1%	85.7%
Miwa	2003	211	62	136:67	EGC	Open	Basin	Dye	sm	6.0	Radical, limited	HE	35	96.2%	88.6%	97.7%	45.2%
Yasuda	2003	21	-	-	-	Open	Postgast	RI	sm	3.9	Radical	HE	6	100%	100%	100%	0%
Carlini	2002	40	-	-	-	Open	Basin	Dye	-	-	Radical	RT-PCR	24	100%	91.7%	88.9%	68.2%
Ajisaka	2003	35	-	-	EGC	Open	Basin	Dye	sm	6.1	-	RT-PCR	6	100%	100%	100%	50.0%
Uenosono	2003	36	66	27:9	EGC	Open	Postgast	RI	sm	2.7	Limited	IHC	6	88.9%	100%	100%	50.0%
Ryu	2003	71	54	40:31	EGC,AGC	Open	Pick up	Dye	ss	2.5	Radical	HE	18	91.5%	61.1%	87.0%	72.7%
Song	2004	27	50	19:8	-	Open	Pick up	Dye	sm	2.7	Radical	HE	8	96.3%	100%	100%	100%
Kim	2004	46	53	-	EGC,AGC	Open	Pick up	RI	sm	2.0	Radical	IHC	13	93.5%	84.6%	93.8%	45.5%
Nimura	2004	84	-	-	EGC,AGC	Open,lapa	Pick up	Dye	sm	10.5	Radical	IHC	11	98.8%	100%	100%	27.3%
Karube	2004	41	59	31:10	EGC,AGC	Open	Pick up	Dye,RI	sm	5.0	Radical	IHC	13	100%	92.3%	96.6%	33.3%
Isozaki	2004	99	-	-	EGC,AGC	Open	Pick up	Dye	sm	3.3	Radical	HE	23	100%	65.2%	90.5%	0%
Tonouchi	2005	37	64	26:11	EGC,AGC	Open,lapa	Basin	Dye,RI	sm	4.0	Radical	IHC	4	94.6%	75%	96.7%	0%
Gretschel	2005	34	-	19:15	EGC,AGC	Open	Postgast	Dye,RI	sm	3.0	Radical	IHC	23	97.1%	95.7%	90.9%	100%
Uenosono	2005	104	64	81:23	EGC,AGC	Open	Pick up	RI	sm	4.0	Limited	IHC	33	95.2%	81.8%	91.7%	29.6%
Park	2006	100	56	69:31	EGC,AGC	Open	Pick up	Dye	ss	4.4	Radical	IHC	14	94.0%	78.6%	96.4%	54.6%
Zulfikaroglu	2005	32	58	26:6	EGC,AGC	Open	Pick up	RI	sm	2.4	Limited	IHC	9	96.9%	100%	100%	88.9%
Ishizaki	2006	101	62	57:44	EGC,AGC	Open	Pick up	Dye	sm	6.5	Radical	IHC	21	100%	85.7%	96.4%	0%
Rabin	2006	43	69	26:17	-	Open	Pick up	Dye	ss	2.9	-	IHC	31	79.1%	90.3%	78.8%	71.4%
Arigami	2006	61	65	44:17	EGC,AGC	Open	Postgast	RI	sm	4.6	Limited	RT-PCR	22	100%	95.5%	97.5%	0%

Pts = patients; SN = sentinel nodes; LND = lymph node dissection; Histol.Eval. = histological evaluation; LNs = lymph nodes; NPV = negative predictive value; PPV = positive predictive value; EGC = early gastric cancer; AGC = advanced gastric cancer; ss = subserosal; sm = submucosal; HE = Hematoxylin eosin; IHC = immunohistochemistry; RT-PCR = reverse transcriptase polymerase chain reaction.

Table 1. Continued

Author	Year	No. of Pts	Age	Sex	Indication	Approach	Method of biopsy	Tracer	Injection site	No. of SNs	LND	Histol. Eval.	No of positive LN's	Detection rate	Sensitivity	NPV	PPV
Mura	2006	10	70	6:4	EGC	Open	Pick up	Dye, RI	sm	3.1	Radical	IHC	2	100%	50.0%	88.9%	100%
Mochiki	2006	59	60	41:18	EGC, AGC	Open	Pick up	RI	sm	3.8	Radical	HE	24	96.6%	83.3%	89.2%	0%
Ichikura	2006	80	62	56:24	EGC	Open	Basin	Dye, RI	ss, sm	4.9	Radical, limited	HE	14	100%	92.9%	98.3%	38.5%
Arima	2006	24	63	15:9	-	Open	Postgast	RI	sm	-	-	HE	24	100%	87.5%	0%	-
Lee	2006	64	60	52:12	EGC	Open	Pick up	Dye, RI	sm	4.1	Radical	IHC	17	96.9%	70.6%	90.0%	41.7%
Rino	2006	38	62	29:9	EGC	Lapa	Postgast	Dye	sm	2.5	Radical	HE	4	92.1%	100%	100%	50.0%
Saikawa	2006	35	62	25:10	EGC	Lapa	Basin	Dye, RI	sm	3.9	Radical	RT-PCR	2	94.3%	50.0%	96.9%	0%
Ishikawa	2007	16	57	6:6	EGC	Lapa	Pick up	Dye	sm	2.9	Limited	HE	2	100%	50.0%	93.3%	0%
Gretschel	2007	35	60	19:16	EGC, AGC	Open	Pick up	Dye, RI	sm	3.0	Radical	IHC	24	97.1%	91.7%	83.3%	0%
Orsenigo	2008	34	62	19:15	EGC, AGC	Lapa	Pick up	Dye	sm	1.5	Limited	IHC	14	79.4%	35.7%	59.1%	0%
Ohdaira	2007	52	60	37:15	EGC, AGC	Open, lapa	Basin	Dye	sm	-	Radical	IHC	2	100%	100%	100%	0%
Yanagita	2008	133	-	-	EGC, AGC	Open	Postgast	RI	sm	4.3	Limited	IHC	19	98.5%	100%	100%	0%
Morita	2007	53	62	38:15	-	Open	Basin	Dye, RI	sm	4.6	Radical	IHC	11	100%	81.8%	95.5%	33.3%
Rino	2007	43	63	26:17	EGC, AGC	Open	Pick up	Dye	sm	3.5	Radical	HE	11	93.0%	81.8%	93.5%	77.8%
Yanagita	2008	160	-	119:41	EGC, AGC	Open	Pick up	RI	sm	4.4	Limited	IHC	30	98.8%	96.7%	99.2%	31.0%
Wang	2008	23	51	14:9	EGC	Lapa	Basin	Dye	sm	2.9	Radical	IHC	4	100%	100%	100%	50%
Kusano	2008	22	68	9:19	-	Open, lapa	Basin	Dye	ss	3.6	Limited	HE	10	90.1%	40.0%	62.5%	100%
Lee	2008	42	58	26:16	EGC, AGC	Lapa	Pick up	Dye, RI	sm	2.1	Radical	IHC	6	54.8%	66.7%	89.5%	100%
Lee	2008	50	60	32:18	EGC, AGC	Lapa	Basin	Dye, RI	sm	3.4	Radical	IHC	14	96.0%	85.7%	94.4%	100%
Ishii	2008	35	62	23:12	EGC, AGC	Open	Basin	Dye	sm	7.2	Limited	IHC	4	100%	100%	100%	25.0%
Lee	2008	21	52	13:8	EGC	Lapa	Basin	Dye, RI	sm	7.0	Radical	IHC	2	95.2%	100%	100%	50%
Yaquchi	2008	43	63	28:15	EGC, AGC	Open	Basin	Dye, RI	sm	8	Limited	HE	7	100%	85.7%	97.3%	0%
Yaquchi	2008	20	61	15:5	EGC, AGC	Open	Basin	Dye, RI	ss	8	Limited	HE	7	100%	100%	100%	0%
Tajima	2009	56	68	30:26	-	Open, lapa	Basin	Dye	Ss, sm	7.2	Radical	HE	17	96.4%	64.7%	86.0%	0%

Pts = patients; SN = sentinel nodes; LND = lymph node dissection; Histol.Eval. = histological evaluation; LN's = lymph nodes; NPV = negative predictive value; PPV = positive predictive value; EGC = early gastric cancer; AGC = advanced gastric cancer; ss = subserosal; sm = submucosal; HE = Hematoxylin eosin; IHC = immunohistochemistry; RT-PCR = reverse transcriptase polymerase chain reaction.

Fig. 1. Study protocol for the SENORITA trial.

Fig. 2. Laparoscopic sentinel basin dissection (SBD) with primary tumor resection. ESD = endoscopic submucosal dissection; R = resection.

result. Laparoscopic SNB will be done using basin dissection, and all harvested sentinel basin nodes will be examined by intraoperative frozen section with 2 mm slices. Primary tumor resection was proposed based on our previous publication but will be modified based on intraoperative findings (Fig. 2).

The most essential point for a SNB phase III surgical trial is to standardize and overcome the learning curve. The preceding quality control study of the participating institutions prior to the phase III trial is finished.^{21,22} This study was based on completing a checklist consisting of seven essential SNB steps associated with the endoscopic, surgical, and pathological procedures. If SNB was performed perfectly in 10 patients by completing these seven steps, that institution can participate in the phase III trial. The results showed 92.6% detection rate and 100% sensitivity.

CONCLUSION

Laparoscopic SNB with gastric organ and function-preserving surgery in patients with EGC may be a good

surgical option to improve short- and long-term QOL without impairing the surgical or oncologic outcomes in selected patients with EGC after validation by the SENORITA phase III trial

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