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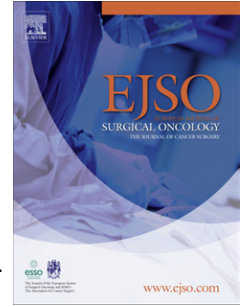


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SENTINEL LYMPH NODE BIOPSY TO DIRECT TREATMENT IN GASTRIC
CANCER. A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract

Gastric cancer is one of the main causes of cancer-related deaths around the world. The prevalence of early gastric cancer (EGC) among all gastric cancers of 45%–51% in Japan, but only 7%–28% in Western countries. The prevalence of EGC is growing partly because of better diagnostics and screening programmes. Possible treatment options for EGC treatment are expanded by the introduction of endoscopic mucosal resection and endoscopic submucosal dissection. Therefore, detailed knowledge about nodal metastatic risk is warranted. We performed a systematic review of the literature concerning studies investigating the role of sentinel lymph node biopsy in EGC and whether there is enough evidence to introduce SLN as a part of treatment for EGC in the Netherlands. Several detection substances (dye or radiocolloid) and injection methods (submucosal or subserosal) are investigated. An overall sensitivity percentage of 85.4% was found. In comparison, high and clinically sufficient percentages were observed for specificity (98.2%), negative predictive value (90.7%) and accuracy (94%). Subgroup analyses showed that the combination of dye and radiocolloid detection substances is the best method for sentinel lymph node detection in early gastric cancer. However, the precise method of sentinel lymph node biopsy in EGC has to be determined further. Large, randomized series should be initiated in Europe to address this issue.

Introduction

Early gastric cancer (EGC) is defined as tumor invasion confined to the mucosa or submucosa, irrespective of nodal metastases, i.e. T1N0-2 (see *Table 1*). This definition reflects an appreciation that EGC represents a subset of gastric cancers that has a favorable prognosis compared to invasive gastric cancers that extend beyond the submucosa (T2-4). Gastric cancer is one of the most common causes of cancer mortality worldwide. The incidence of gastric cancer and the percentage of gastric cancer-related deaths are unevenly distributed throughout the world. The disease is most common in the Eastern World with the prevalence of EGC among all gastric cancers 45%–51% in Japan, but only 7%–28% in western countries.(1) Differences in treatment strategies for EGC between Japan and western countries are maintained.(1) Most screening programmes for gastric cancer have been developed in Asian countries.(2) In the Netherlands the primary curative therapy of all stages of gastric cancer consists of the complete resection of the tumor and prophylactic lymph node dissection. The extent of lymph node dissection is still much debated.(3) However, the need for a prophylactic lymph node dissection in EGC is probably negligible with respect to locoregional recurrence and overall survival, because of the very low risk of finding positive lymph nodes (see *Table 1*). (4,5) It is estimated that 80 to 97% of the patients with EGC do not benefit from a lymphadenectomy, but are harmed by the coinciding morbidity. Non-invasive and endoscopic techniques as computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) are limited by their low sensitivity rates in predicting lymph node metastases in gastric cancer. For this problem sentinel lymph node biopsy could be helpful.(6) Investigators from the East and West are stimulated to conduct multiple studies investigating the role of sentinel lymph node (SLN) biopsy in EGC in the past decade. The surgical treatment of early gastric cancer relates to the extend of lymphadenectomy. Therefore detailed knowledge about the nodal metastatic risk is warranted. In this systematic review we investigate whether there is enough prove to introduce SLN as a treatment for EGC in the Netherlands.

Methods

Systematic search

Relevant studies were identified through a search of the electronic database PubMed. The following search terms were used: “gastric cancer”, “gastric carcinoma”, “early gastric cancer”, “sentinel lymph node”, “sentinel node”. Inclusion criteria were: study objective to investigate the role of SLN biopsy in gastric cancer, article in the English language and inclusion of at least 10 patients in the study. Twenty-one studies fulfilled the inclusion criteria. Subsequently, reference lists of the selected studies were crosschecked. The selection and analysis of studies has been performed independently by three investigators (DJL, HWS, RLAL, AED). Studies available for analysis (ref (7-26)) were subjected to a quality control using the QUADAS tool.(27) Quality was considered to be good for two studies, moderate for 12 studies and poor for four studies. The selection and analysis of the studies has been performed independently by three investigators (DJL, HWS, AED).

Statistics

The following definitions were used:

SLN detection rate = number of patients with detected SLNs / total number of patients investigated.

SLN positivity rate (SLN+) = number of patients with positive SLN / total number of patients with detected SLNs.

Sensitivity = number of patients with true positive SLN / (number of patients with true positive SLN + number of patients with false negative SLN).

Specificity = number of patients with true false SLN / (number of patients with true false SLN + number of patients with false positive SLN).

Positive predictive value (PPV) = number of patients with true positive SLN / (number of patients with true positive SLN + number of patients with false positive SLN).

Negative predictive value (NPV) = number of patients with true negative SLN / (number of patients with true negative SLN + number of patients with false negative SLN).

Accuracy (ACC) = (number of patients with true positive SLN + number of patients with true negative SLN) / total number of patients with detected SLNs.

The accuracy of the various procedures for detecting sentinel lymph nodes and subgroup analysis were tested with Meta-Disc software using negative likelihood ratios, and subgroup analyses were performed according to detection method.(28) $P < 0.05$ was determined significant.

Results

An overview of the results from the studies included in the analysis is presented in *Table 2*. A total of 1314 patients were included in the 21 reviewed studies, with a mean number of 63 patients per study (range 13 – 211; median 53). Tumor depth varied between T1 and T3 between the studies. All studies excluded patients with metastatic disease. Largely, the SLN detection methods used in these studies can be separated on the basis of detection substance employed into two groups, i.e. radiocolloid or dye. Four of the 21 studies investigated multiple modalities for SLN biopsy.(11,20,22,25,26) In 16 of the 21 studies a detection dye (indocyanine green, isosulfan blue or patent blue) was used(7,9-15,18-20,22-24,26), while a radiocolloid (^{99m}Tc tin colloid, ^{99m}Tc sulphur colloid or ^{99m}Tc colloidal rhenium sulphide) was used in nine.(8,11,15-17,21,22,25,26) Of these 21 studies one compared, but did not combine both methods.(22) In 3 other studies the combination of a dye and radiocolloid was used to maximize SLN detection.(11,15,26) The method of application (pre-/peroperative and submucosal/-serosal) is depending on the substance employed. All studies using a radiocolloid injected the detection substance peritumorally in the submucosal layer of the stomach via endoscopic route one day preoperatively. In nine out of 17 an endoscope was used in to inject the dye in the submucosal layer (10-12,15,18,20,22,23,26), while 8/17 injected the detection substance peritumorally in the subserosal layer during laparotomy.(7,9,13,14,19,23,24) In one study the detection effect of indocyanine green was enhanced by using infrared ray electronic endoscopy (IREE).(18) Another study using dye detection investigated the difference between the submucosal and subserosal techniques(23), three others used the submucosal dye application in combination with a radiocolloid.(11,15,26)

The SLN detection rates varied from 66.7% to 100% (mean 94.7%; median 96.6) between the studies. The low SLN detection rate of 66.7% was observed in the study investigating the role of the size of radiocolloid-particles related to detection success. A detection rate of 66.7% was found with a particle size of 500 nm, while with the other investigated particle sizes of 100 and 50 nm detection rates of 100% were observed. The three dye and radiocolloid combination studies showed detection rates of respectively 100%, 100% and 97%. With all detection methods combined, a mean of 3.5 SLNs per patient was observed (range 1.6 – 10.5; median 3). The highest number of SLNs per patient was found with the combination of indocyanine green and IREE; here, the detection rate was 98.8%. SLN positivity (SLN+) varied significantly between studies with a range of 5.2% to 73.4% (mean 28.1%; median 21.4%). No association could be observed between tumour depth and SLN+ as result of the given data.

Table 3 shows the overall results of all studies combined. The mean and median percentages for the sensitivity were 85.4% and 88.9% respectively with a wide range from 45.5% to 100%. Low sensitivity percentages of less than 90% were observed in 13/21 studies. (10-12,14,17,20-26) In two of

the 13 studies better sensitivity percentage of 90-100% was obtained by using the combination method(9,24), while one showed a similar result with IREE.(18) In general, a low sensitivity percentage was found for all detection substances (i.e. dye or radiocolloid) and application methods (i.e. submucosal via endoscopic route or subserosal via laparotomy). A high sensitivity was found in studies using a subserosal dye technique or combination method. The mean and median negative predictive value (NPV) for all studies combined were 90.7 and 95.7%. The mean overall specificity (Spec) and positive predictive value (PPV) were 98.2 and 99% respectively. Positive SLNs proved to be false-positive very rarely.(9) Good results are seen for the accuracy (Acc) percentages (mean 94%; median 96.4%).

Subgroup analyses according to detection method (see Table 4) showed better discriminative power for the radiocolloid detection method than dye methods, irrespective of the application method of the dye. However, a tendency towards the best discriminative power was seen for the combination of dye and radiocolloid.

Discussion

In this systematic review of the current literature not enough prove was found to introduce SLNB in the treatment protocol for EGC in the Netherlands. The overall sensitivity of <90% is just too low to justify immediate introduction of the SLN biopsy procedure in EGC in analogy of the requested sensitivity percentage of > 95% for SLN biopsy as in other solid organ malignancies. For a proper implementation of the SLN biopsy procedure in early gastric cancer several problems need to be solved. First, the amount of false-negative SLN biopsy results should be limited to increase the sensitivity of the procedure. A sensitivity of at least 90-95% should be guaranteed for safe introduction of the procedure in patient care. The lack of expertise is part of the explanation for the current low sensitivity. Several investigators report a significant increase in the sensitivity of SLN biopsy with growing experience with the procedure,(20,24) but it is not known exactly how many patients are needed to complete the learning curve.(24) Although some investigators claim that they were able to optimize their technique with a learning curve of less than ten cases,(20) it seems reasonable to assume that the plateau-phase in the learning curve is reached when detection and accuracy rates are around 95%. Secondly the literature about EGC and SLN procedures is mainly coming from the Asian countries. Because the incidence of gastric cancer is higher in these countries and because the tumour types seem to differ, it may be hazardous to extrapolate the results from these studies to patients in Western countries.(29,30) One of the differences is the frequency of the locations of the gastric tumors related to the differences in risk factors. The most important risk factor for gastric cancer is an infection by *Helicobacter pylori* bacteria. This infection is primarily related to distal gastric cancer,(29) which is where most of the tumours of patients from the Eastern world are primarily located. This in contrast to the countries in the Western world where most of the gastric cancers are located in the cardia. This difference, among others, can be of importance for the ability of the SNL procedure to detect positive lymph nodes. In the papers included in our review no clear distinction is made between early gastric cancer(T1) and locally advanced gastric cancer (T2-4). Therefore, not all results are comparable. However, we can postulate that the SLN biopsy procedure could be relevant for clinical practice in EGC to limit the extent of surgery. Lymph node metastases are present in 84% of all patients with gastric cancer (ref 30, table 1). Based on current knowledge prophylactic lymphadenectomy could be omitted in patients with a T1 tumor and SLN biopsy negative for metastasis. In these patients, the finding of a positive SLN biopsy should be followed by a lymphadenectomy as part of standard therapy. Lymphadenectomy should also be applied as a standard procedure for patients with T2 ,T3 and T4 tumours, because for patients with these stages of gastric cancer the risk of lymph node metastasis is well above 50%(table 1) and using SLN biopsy will not be of any benefit for them. Considering all the above, the combination of dye and radiocolloid for lymph node detection is the best

on most counts. The precise role of sentinel lymph node biopsy in EGC remains to be determined. Large, randomized series should be initiated in Europe to address this issue. Advances in laparoscopic and endoscopic surgical procedures and a growing older patient population with co-morbidities require such initiatives as less-extended procedures are performed. It is recommended to perform a minimum of ten procedures using the combination of dye and radiocolloid substances before clinically initiating SLN biopsy in EGC.

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Reference List:

1. Norihiro Yuasa, Yuji Nimura. Survival after surgical treatment of early gastric cancer, surgical techniques, and long-term survival. *Langenbecks Arch Surg* (2005) 390: 286–293
2. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, Sobue T. The Japanese Guidelines for Gastric Cancer Screening. *Jpn J Clin Oncol* 2008; 38(4): 259-67.
3. The Japanese Gastric Cancer Association (JGCA). Introduction to JGCA gastric cancer treatment guidelines. 2001. Ref Type: Report
4. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of Lymph Node Metastasis From Early Gastric Cancer: Estimation With a Large Number of Cases at Two Large Centers. *Gastric Cancer* 2000; 3(4): 219-25.
5. Hohenberger O, Gretschel S. Gastric Cancer. *Lancet* 2003; 362(9380): 305-15.
6. Dassen AE, Lips DJ, Hoekstra CJ, Pruijt JF, Bosscha K. FDG-PET Has No Definite Role in Preoperative Imaging in Gastric Cancer. *Eur J Surg Oncol* 2009; 35(5): 449-55
7. Hiratsuka M, Miyashiro I, Ishikawa O, Furukawa H, Motomura K, Ohigashi H, Kameyama M, Sasaki Y, Kabuto T, Ishiguro S, Imaoka S, Koyama H. Application of Sentinel Node Biopsy to Gastric Cancer Surgery. *Surgery* 2001; 129(3): 335-40.
8. Kitagawa Y, Fuji H, Mukai M, Kubota T, Otani Y, Kitajima M. Radio-Guided Sentinel Node Detection for Gastric Cancer. *Br J Surg* 2002; 89(5): 604-8.
9. Hundley JC, Shen P, Shiver SA, Geisinger KR, Levine EA. Lymphatic Mapping for Gastric Adenocarcinoma. *Am Surg* 2002; 68(11): 931-5.
10. Ichikura T, Morita D, Uchida T, Okura E, Majima T, Ogawa T, Mochizuki H. Sentinel Node Concept in Gastric Carcinoma. *World J Surg* 2002; 26(3): 318-22.
11. Hayashi H, Ochiai T, Mori M, Karube T, Suzuki T, Gunji Y, Hori S, Akutsu N, Matsubara H, Shimada H. Sentinel Lymph Node Mapping for Gastric Cancer Using a Dual Procedure With Dye- and Gamma Probe-Guided Techniques. *J Am Coll Surg* 2003; 196(1): 68-74.
12. Miwa K, Kinami S, Taniguchi K, Fushida S, Fujimura T, Nonomura A. Mapping Sentinel Nodes in Patients With Early-Stage Gastric Carcinoma. *Br J Surg* 2003; 90(2): 178-82.
13. Simsa J, Hoch J, Leffler J, Schwarz J, Pospisil R, Vajtrova R. Sentinel Node Biopsy in Gastric Cancer: Preliminary Results. *Acta Chir Belg* 2003; 103(3): 270-3.
14. Ryu KW, Lee JH, Kim HS, Kim YW, Choi IJ, Bae JM. Prediction of Lymph Nodes Metastasis by Sentinel Node Biopsy in Gastric Cancer. *Eur J Surg Oncol* 2003; 29(10): 895-9.
15. Tonouchi H, Mohri Y, Tanaka K, Konishi N, Ohmori Y, Kobayashi M, Watanabe Y, Matsumura K, Takeda K, Kusunoki M. Lymphatic Mapping and Sentinel Node Biopsy During Laparoscopic Gastrectomy for Early Cancer. *Dig Surg* 2003; 20(5): 421-7.
16. Uenosono U, Natsugoe S, Higashi H, Ehi K, Miyazono F, Ishigami S, Hokita S, Aikout T. Evaluation of Colloid Size for Sentinel Nodes Detection Using Radioisotope in Early Gastric Cancer. *Cancer Lett* 2003; 200(1): 19-24.
17. Kim MC, Kim HH, Jung GJ, Lee JH, Choi SR, Kang DY, Roh MS, Jeong JS. Lymphatic Mapping and Sentinel Node Biopsy Using 99mTc Tin Colloid in Gastric Cancer. *Ann Surg* 2004; 239(3): 383-7.
18. Isozaki H, Kimura T, Tanaka N, Satoh K, Matsumoto S, Ninomiya M, Ohsaki T, Mori M. An Assessment of the Feasibility of Sentinel Lymph Node-Guided Surgery for Gastric Cancer. *Gastric Cancer* 2004; 7(3): 135-7.
19. Song X, Wang L, Chen W, Pan T, Zhu H, Xu J, Jin M, Finley KR, Wu J. Lymphatic Mapping and Sentinel Node Biopsy in Gastric Cancer. *Am J Surg* 2004; 187(2): 270-3.
20. Nimura H, Narimiya N, Mitsumori N, Yamazaki Y, Yanaga K, Urashima M. Infrared Ray Electronic Endoscopy Combined With Indocyanine Green Injection for Detection of Sentinel Nodes of Patients With Gastric Cancer. *Br J Surg* 2004; 91(5): 575-9.

21. Zulfikaroglu B, Koc M, Ozmen MM, Kucuk NO, Ozalp N, Aras G. Intraoperative Lymphatic Mapping and Sentinel Lymph Node Biopsy Using Radioactive Tracer in Gastric Cancer. *Surgery* 2005; 138(5): 899-904.
22. Gretschel S, Bembenek A, Ulmer Ch, Hunerbein M, Markwardt J, Schneider U, Schlag PM. Prediction of Gastric Cancer Lymph Node Status by Sentinel Lymph Node Biopsy and the Maruyama Computer Model. *Eur J Surg Oncol* 2005; 31(4): 393-400.
23. Lee JH, Ryu KW, Kim CG, Kim SK, Choi IJ, Kim YW, Chang HJ, Bae JM, Hong EK. Comparative Study of the Subserosal Versus Submucosal Dye Injection Method for Sentinel Node Biopsy in Gastric Cancer. *Eur J Surg Oncol* 2005; 31(9): 965-8.
24. Park DJ, Lee HJ, Lee HS, Kim WH, Kim HH, Lee KU, Choe KJ, Yang HK. Sentinel Node Biopsy for CT1 and CT2a Gastric Cancer. *Eur J Surg Oncol* 2006; 32(1): 48-54.
25. Mochiki E, Kuwano H, Kamiyama Y, Aihara R, Nakabayashi T, Katoh H, Asao T, Oriuchi N, Endo K. Sentinel Lymph Node Mapping With Technetium-99m Colloidal Rhenium Sulfide in Patients With Gastric Carcinoma. *Am J Surg* 2006; 191(4): 465-9.
26. Gretschel S, Bembenek A, Hunerbein M, Dresel S, Schneider W, Schlag PM. Efficacy of Different Technical Procedures for Sentinel Lymph Node Biopsy in Gastric Cancer Staging. *Ann Surg Oncol* 2007; 14(7): 2028-3
27. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The Development of QUADAS: a Tool for the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews. *BMC Med Res Methodol* 2003; 3:25.
28. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a Software for Meta-Analysis of Test Accuracy Data. *BMC Med Res Methodol* 2006; 6: 31.
29. A.E. Dassen a, *, V.E.P.P. Lemmens b,c, L.V. van de Poll-Franse b,d, G.J. Creemers e, S.J. Breninkmeijer f, D.J. Lips a, A.A.M. vd Wurff g, K. Bosscha a, J.W.W. Coebergh b,c. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: A population-based study in the Netherlands. *European Journal of Cancer* 2010;46(6):1101-1110
30. Yan Yi, Jinming Yu, Baosheng Li *, Fujun Yang, Wei Huang, Hongfu Sun, Heyi Gong, Tao Zhou, Haiqun Lin. Pattern of lymph node metastases and its implication in radiotherapeutic clinical target volume delineation of regional lymph node in patients with gastric carcinoma. *Radiotherapy and Oncology* 96 (2010) 223–230

TABLE 1. T-status and Observed Metastatic Lymph Node Involvement According to Depth of Tumor Invasion

T-status	Depth of tumor invasion of gastric wall	Metastatic lymph node involvement	Reference
T_{is}	Intraepithelial tumor without invasion of lamina propria		Yan Yi et al, Radiotherapy and Oncology 2010.
T_{1a}	Tumor invasion of mucosa and/or muscularis mucosa	2 – 5%	
$1b$	Tumor invasion of submucosa	6 – 23%	
T_2	Tumor invasion of muscularis propria or subserosa	10 – 41%	
T_3	Tumor penetration of serosa	70%	
T_4	Tumor invasion of adjacent structures	84%	

Derived from International and Japanese Gastric Cancer Associations (*Gastric Cancer 1998;1:10-24*) and the International Union Against Cancer (UICC) TNM staging system (*6th edn, 2002*) T_{is} (carcinoma in situ). Early gastric cancer is defined as tumor invasion confined to the mucosa or submucosa, irrespective of nodal metastases, i.e. T_1N_0 . The incidence of lymph node metastasis is low in early gastric cancer patients, with more than a 90% 5-year survival rate. The overall prognosis for patients with gastric cancer remains poor, with a 5-year survival rate of 5 to 15%. (Akoh, 1992; Itoh, 1989)

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TABLE 2. Results Sentinel Lymph Node (SLN) Procedures in Gastric Cancer

Reference	Method	TNM [^]	N	Detection succes- rate	SLN/pt (range)	SLN+†	Sens	Spec	PPV	NPV	Acc SLN status	Acc frozen biopsy	Skip metastasis [‡] (detected)	SLN micrometastasis [‡]
Hiratsuka M, et al. <i>Surgery</i> 2001	Indocyanine green; subserosal; laparotomy	T ₁₋₂	74	98.6%	2.6 (1-9)	12.3%	90%	100%	100%	98.4%	98.6%	-	-	-
Kitagawa Y, et al. <i>Br J Surg</i> 2002	^{99m} Tc tin colloid; submucosal; endoscopically	T ₁₋₂	145	95%	3.6 (1-8)	7.8%	91.7%	100%	100%	98.4%	98.6%	-	0.8% (100%)	-
Hundley JC, et al. <i>Am Surg</i> 2002.	Isosulfan blue; subserosal, laparotomy	T ₁₋₃	14	100%	2.8 (1-5)	28.2%	70%	75%	90%	50%	70%	-	-	0%
Ichikura T, et al. <i>World J Surg</i> 2002	Indocyanine green; submucosal; endoscopically	T ₁₋₂	62	100%	4.5 [#] (1-12)	24%	86.7%	100%	100%	95.7%	93.5%	-	1.6% (0%)	-
Hayashi H, et al. <i>J Am Coll Surg</i> 2003	^{99m} Tc tin colloid + Patent blue; submucosal; endoscopically (cb)	T ₁₋₂	31	90%	3.7	10.7%	85.7%	100%	100%	95.5%	96.4%	-	-	0%
				90%	3.6	21.4%	71.4%	100%	100%	91.3%	92.9%	-	-	0%
				100%		22.8%	100%	100%	100%	100%	100%			
Miwa K, et al. <i>Br J Surg</i> 2003	Patent blue; submucosal; endoscopically	T ₁₋₃	211	96.2%	6 (1-16)	5.2%	88.6%	100%	100%	97.8%	98.1%	98.6%	1.4% (100%)	-
Simsa J, et al. <i>Acta Chir Belg</i> 2003	Patent blue; subserosal; laparotomy	T ₁₋₃	13	100%		61.5%	100%	100%	100%	100%	100%	84.6%	-	0%

Reference	Method	TNM [^]	N	Detection succes-rate	SLN/pt (range)	SLN+†	Sens	Spec	PPV	NPV	Acc SLN status	Acc frozen biopsy	Skip metastasis† (detected)	SLN micrometastasis†
Ryu KW, et al. EJSO 2003	Isosulfan blue; subserosal; laparotomy	T ₁₋₂	71	91.5%	2.5 (1-8)	28.2%	61.1%	100%	100%	87%	89.2%	-	10.8% (0%)	-
Tonouchi H, et al. Dig Surg 2003 [^]	^{99m} Tc tin colloid +	T ₁	17	82.4%	2.8 (1-9)									
	Patent blue; submucosal; endoscopically		17	88.2%	2.5 (1-6)									
	(cb)		17	100%	4.2 (2-9)	17.6%	100%	100%	100%	100%	100%	33.3% ^{^^}	11.8% (50%)	66%
Uenosono U, et al. Canc Lett 2003	^{99m} Tc tin colloid; 500 nm	T ₁₋₂	12	66.7%	1.8 (0-4)	37.5%	100%	100%	100%	100%	100%	100%	25%	-
	100 nm		13	100%	3.8 (1-6)	7.7%	100%	100%	100%	100%	100%	100%	0%	-
	50 nm submucosal; endoscopically		11	100%	3.0 (1-7)	18.2%	100%	100%	100%	100%	100%	100%	9.1%	-
	(overall)		36	88.9%	2.9 (0-7)	18.8%	100%	100%	100%	100%	100%	100%	9.4%	-
Kim M-C, et al. Ann Surg 2004	^{99m} Tc tin colloid; submucosal; endoscopically	T ₁₋₃	46	93.5%	2 (1-8)	25.6%	84.6%	100%	100%	93.8%	95.3%	97.7%	7% (100%)	0%
Isozaki H, et al. Gastric Cancer 2004	Isosulfan blue; submucosal; endoscopically	T ₁₋₃	144	97.2%	3.3 (1-9)	-	-	-	-	-	-	-	-	-
Song X, et al. Am J Surg 2004	Isosulfan blue; subserosal; laparotomy	T ₁₋₃	27	96.3%	2.7 (1-6)	20%	100%	100%	100%	100%	100%	-	0	-

Reference	Method	TNM ^a	N	Detection succes-rate	SLN/pt (range)	SLN+ [†]	Sens	Spec	PPV	NPV	Acc SLN status	Acc frozen biopsy	Skip metastasis [†] (detected)	SLN micrometastasis [†]
Nimura H, et al. Br J Surg 2004	Indocyanine green; submucosal; endoscopically + IREE	T ₁₋₂	84	98.8%	5.5	8.4%	63.6%	100%	100%	94.7%	95.2%	-	-	-
				98.8%	10.5	13.3%	100%	100%	100%	100%	-	-	-	
Zulfikaroglu B, et al. Surgery 2005	148 MBq ^{99m} Tc filtered sulfur colloid; submucosal; endoscopically	T ₁₋₃	32	97%	2.4 (1-8)	18%	100%	95.5%	90%	100%	96.7%	97%	10% (100%)	0%
Gretschel S, et al. EJSO 2005.	^{99m} Tc colloidal rhenium sulphide; + Patent blue; submucosal; endoscopically (cb)	T ₁₋₃	15	93.3%	3 (1-5)	57.1%	88.9%	100%	100%	83.3%	92.9%	-	11.1% (0%)	21.7%
			19	100%	3 (1-6)	73.4%	100%	100%	100%	100%	100%	-	7.1% (0%)	
			34											
Lee JH, et al. EJSO 2005	Isosulfan blue; subserosal (laparotomy) versus submucosal (endoscopically)	T ₁₋₂	71	91.5%	2.5	16.9%	61.1%	100%	100%	87%	89.2%	-	-	-
			50	94%	2.9	10.6%	45.5%	100%	100%	85.7%	87.2%	-	-	-
Park DJ, et al. EJSO 2006	Indocyanine green; subserosal; laparotomy	T ₁₋₂	100	94%	4.4	11.7%*	78.6%*	100%*	100%*	96.4%*	96.8%*	-	-	4.3%
			50			22.2%**	71.4%**	100%**	100%**	88.6%**	91.1%**	-	-	

Reference	Method	TNM [^]	N	Detection succes-rate	SLN/pt (range)	SLN+†	Sens	Spec	PPV	NPV	Acc SLN status	Acc frozen biopsy	Skip metastasis [‡] (detected)	SLN micrometastasis [§]
Mochiki E, et al. <i>Am J Surg</i> 2006	^{99m} Tc colloidal rhenium sulphide; submucosal; endoscopically	T ₁₋₃	59	96.6%	3.8 (1-10)	35.1%	83.3%	100%	100%	89.2%	93%	-	-	-
Gretschel S, et al. <i>Ann Surg Oncol</i> 2007	^{99m} Tc colloidal rhenium sulphide; + Patent blue; submucosal; endoscopically (cb)	T ₁₋₃	35	97%	3 (1-10)	64.7%	91.7%	100%	100%	83.3%	94.1%	-	-	-
			35	97%	3 (1-6)	47.1%	66.7%	100%	100%	55.6%	76.5%	-	-	-
			35	97%	3 (1-10)	64.7%	91.7%	100%	100%	83.3%	94.1%	-	-	-
Cozzaglio L et al. <i>EJSO</i> 2010	Patent blue dye technique	T ₁₋₂	29	96.5%	1.6 (1-3)	61%	75%	75%	88%	55%	75%	-	-	18%

Abbreviations: Acc accuracy; cb combination; IREE infrared ray electronic endoscopy; NPV negative predictive value; PPV positive predictive value; Sens sensitivity; Spec specificity; SLN sentinel lymph node.

[^]The actually observed T-status is mentioned; all studies excluded patients with metastatic disease.

[†]SLN positivity (+) for metastasis is calculated by the equation: patient with SLN positive for tumor/total patients with SLNs found.

[‡]Skip metastases are defined as lymph node metastases in D2 or D3 compartments, without involvement of the perigastric D1 compartment. Percentage calculated by the equation: patient with skip metastasis/total patients studied.

[§]SLN micrometastasis detection rate is defined by the equation: SLN micrometastasis positive/total SLN metastasis positive.

^{||}Based on the results of group patients injected with 4 ml 1.25% indocyanine green, excluding the group injected with 8ml 0.63% indocyanine green, as the former is the preferred method to identify SLNs according to the investigators.

[^]Study investigating laparoscopic gastrectomy with lymphatic mapping.

^{^^}In the SNs of 2 of 3 patients with positive lymph nodes micrometastasis were found in frozen-sections by immunohistochemistry staining, not in the frozen-section examination by hematoxylin & eosin staining (diagnostic accuracy frozen biopsy 1 out of 3, 33%).

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*and**Results of respectively hematoxylin&eosin and immunohistochemistry staining on final pathological non-frozen examination.

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TABLE 3. Summary of Results of Sentinel Lymph Node Biopsy Procedures

	Sens	Spec	PPV	NPV	Acc
<i>Mean</i>	85.5%	98.2%	99%	90.7%	94%
<i>Median</i>	88.9%	100%	100%	95.7%	96.4%
<i>Range</i>	45.5– 100%	75 – 100%	88 – 100%	50 – 100%	70 – 100%

Abbreviations: Acc accuracy; NPV negative predictive value; PPV positive predictive value; Sens sensitivity; Spec specificity. All number are presented in percentages.

TABLE 4. Negative Likelihood Ratio for Sentinel Lymph Node Biopsy Procedures

	N	Neg LHR	95% CI	
total	31	0,230	0,178	0,297
dye total	17	0,283	0,209	0,382
SM	9	0,264	0,162	0,430
SS	8	0,308	0,2207	0,430
Radiocolloid	11	0,163	0,108	0,247
dye and radiocolloid	3	0,101	0,037	0,342

Abbreviations: N number of studies; neg LHR negative likelihood ratio; CI confidence interval

The included number SLN biopsy procedures (N) is 31, because all individual arms of the studies are counted.