Annals of Surgical Oncology, **11**(3):236S–241S
DOI: 10.1245/ASO.2004.11.913

Minimal Residual Disease Assessment in Sentinel Nodes of Breast and Gastrointestinal Cancer: A Plea for Standardization

Fania S. Doekhie, MD, Koen C. M. J. Peeters, MD, Rob A. E. M. Tollenaar, MD, PhD, and Cornelis J. H. van de Velde, MD, PhD

Lymph node dissection plays an important role in staging and treatment of solid cancers. Sentinel node biopsy (SNB) has been introduced to minimize the extent of surgery and to enable assessment of minimal residual disease (MRD) without compromising accurate staging or survival. This review addresses the variation in technical aspects and outcome of SNB and MRD assessment in patients with breast and gastrointestinal cancer. Quality control leading to standardization of SNB and pathological examination will enable reliable comparison of studies, which is necessary for consensus of diagnostic and therapeutic strategies.

Key Words: Breast cancer—Colorectal cancer—Gastric cancer—Micrometastases—Minimal residual disease—Sentinel node.

The histological status of lymph nodes is one of the most important prognostic indicators in patients with cancer originating from solid tumors. Staging cancer to determine the need for adjuvant therapy presently occurs through lymphadenectomy. Lymphadenectomy is a staging tool that may also have therapeutic value, even in patients without nodal involvement by standard pathological methods.[1,2] In colorectal cancer patients without nodal involvement, overall survival improves with increasing number of lymph nodes recovered.[3] Also, in invasive bladder cancer, both node-negative and node-positive patients had prolonged overall survival with an increasing number of lymph nodes examined.[4] This benefit is possibly due to the presence of minimal residual disease (MRD) in hematoxylin and eosin (H&E)-negative lymph nodes.

Lymphadenectomy may be associated with considerable morbidity, especially in breast cancer and melanoma patients. To minimize the extent of lymphadenectomy without compromising accurate staging and survival, sentinel node biopsy (SNB) has been introduced. Sentinel nodes are the first possible sites of metastasis along the route of lymphatic drainage from a primary tumor. The histopathological state of the sentinel node is presumed to reflect that of all regional lymph nodes. SNB can be performed by injecting a vital dye, a radioactive colloid, or both around the primary tumor. Techniques vary substantially between institutions and researchers, however, which complicates reliable assessment of the role of SNB.

An advantage of SNB is the lower number of lymph nodes that have to be examined compared with regional lymph node dissection. Laborious and expensive focused examination techniques like immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR) can therefore be applied in a limited number of sentinel nodes to detect the presence of so-called minimal residual disease, comprising micrometastases and isolated tumor cells. Micrometastases are defined as a cohesive cluster of malignant cells, from 0.2 mm to 2.0 mm in diameter. Micrometastases and isolated tumor cells are usually not detected with conventional pathological examination techniques. The prognostic significance of micrometastases and the therapeutic consequences of upstaging by MRD assessment, however, are far from clear. Nevertheless, in some countries treatment

Received October 28, 2003; accepted November 17, 2003.

From the Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands.

Address correspondence and reprint requests to: Cornelis J. H. Van de Velde, MD, PhD, FRCS, FRCPS, Department of Surgery K6-R, Leiden University Medical Center, P. O. Box 9600, 2300 RC, Leiden, The Netherlands; Fax: 31-71-5266750; E-mail: c.j.h.van_de_velde@lumc.nl.

decisions are already based on MRD assessment, implying possible overtreatment. This review addresses the role of SNB and MRD in (sentinel) lymph nodes in breast, gastric, and colorectal carcinoma and pleads for standardized and randomized trials in this field.

BREAST CANCER

Axillary lymph node dissection (ALND) contributes to both treatment and staging. Overgaard et al.[5] reported large differences in local recurrence rates in a trial investigating the efficacy of radiotherapy following total mastectomy. There were clear variations in the extent and quality of surgery, because more than half of the local recurrences appeared on the chest wall. It was concluded that radiotherapy after surgery improved local control. However, if surgical procedures improve, the benefits of standard radiotherapy might be questionable. It is clear that the quality of surgery dictates the value of adjuvant treatment. This stresses the need for standardized and quality-controlled SNB, because staging and treatment decisions depend on removing and investigating only one or a few sentinel nodes. Currently, most centers use a combination of radioactive tracer and blue dye, which improves the identification of multiple sentinel lymph nodes in comparison with the use of one tracer alone.[6] Table 1 highlights studies published since 1998 on SNB in breast cancer patients; each study included more than 100 patients. Most centers use the combination of blue dye and radioactive colloid to detect sentinel nodes. Considerable variation in the volume of tracer used and the technique for examination of resected sentinel nodes might explain different success and false-negative rates. The site of injection is often inaccurately reported, and it remains unclear whether massage has been performed.

In focused-examination studies of H&E-negative lymph nodes, there is considerable variation in the technique, marker, or antibody used and in the data analysis. Dowlatshahi[7,8] showed upstaging by serial sectioning and immunohistochemistry of 9% to 33%. The clinical relevance of MRD assessment is debatable. Studies that showed a survival disadvantage due to the presence of micrometastases had larger populations (range, 147 to 921 patients) and longer follow-up (at least 6 years) than studies that did not show any survival difference. Moreover, most studies did not consider the size of the micrometastases, even though the size of nodal metastases linearly correlates with survival.[8] Also, the role of isolated tumor cells in lymph nodes has not been determined.[9] It might be difficult to distinguish isolated tumor cells from mesenchymal cells, mesothelial cells, and contamination by benign or malignant epithelium. These technical difficulties are probably common but are infrequently reported.

MRD assessment in sentinel nodes with immunohistochemistry and serial sectioning reveals a higher detection rate of micrometastases in sentinel nodes than in the regional lymph nodes.[10] This is in line with the sentinel node hypothesis. An overview study showed that in 38% to 67% of patients with breast cancer the sentinel node is the only involved lymph node.[11] When the sentinel node is the only involved lymph node it can be argued that ALND is not necessary. In the AMAROS (After Mapping of the Axilla Radiotherapy Or Surgery) Trial, coordinated by the European Organization for Research and Treatment of Cancer, patients with positive sentinel nodes are randomized to ALND or axillary radiotherapy. The presence of any tumor deposit, detected with either H&E staining or IHC, has consequences for the local treatment of the axilla (i.e., surgery or radiotherapy) but not for systemic treatment. Recently, concern has been

TABLE 1. *An overview of the sentinel node (SN) biopsy studies in breast cancer*

Reference	Type of tracer	Average no. of SNs	Success rate mapping (%)	Upstaging method	False-negative rate (%)
Nwariaku et al.[36]	Tc + blue dye	1.84	81	ss	4
Borgstein et al.[37]	Tc	1.2	100	IHC	2
Krag et al.[38]	Tc	2.6	91	—	11
Hill et al.[39]	Tc + blue dye	2.1	100	IHC	11
Veronesi et al.[40]	Tc + blue dye	1.4	99	ss	7
Winchester et al.[41]	Tc	3.1	90	ss	8
Bass et al.[42]	Tc + blue dye	2.0	93	IHC	2
Morrow et al.[43]	Tc + blue dye	1.8	79	—	13
Fraile et al.[44]	Tc	2.0	96	IHC	4
Kollias et al.[45]	Tc + blue dye	1.4	81	IHC	6
Tafra et al.[46]	Tc + blue dye	2.2	87	IHC	13
Nano et al.[47]	Tc + blue dye	—	87	IHC	7

Tc, 99m technetium; ss, serial sectioning; IHC, immunohistochemistry.

expressed that many pathology laboratories have adopted IHC techniques and many oncologists recommend adjuvant chemotherapy upon IHC-detected metastases only.[12] Giving patients a toxic and often expensive treatment with possibly limited benefits, on the basis of IHC findings alone, is not supported by the literature and should therefore not be encouraged.

It can be concluded that SNB for breast cancer is presently performed with acceptable success rates and low false-negative rates despite considerable variation in SNB techniques. Special techniques to detect micrometastases can lead to upstaging in a considerable number of patients, but it remains unclear whether these findings should affect the choice of adjuvant treatment.

GASTRIC CANCER

The widespread use of gastroscopy has increased identification of gastric cancer at an early stage. Nodal involvement occurs in only 2% to 18% of T1 tumors and in about 50% of T2 tumors.[13] This means that a larger-than-necessary lymphadenectomy is performed in a substantial number of patients. The debate on the benefits of D1 compared with D2 lymph node dissection is still ongoing. Furthermore, the value of adjuvant therapy in relation to the extent of surgery is intensely discussed.[14] An extended lymphadenectomy is associated with considerable postoperative morbidity and mortality, especially in Western countries.[15,16] However, reliable tools are lacking to predict nodal involvement. SNB might minimize the surgical procedure and predict the status of nonsentinel nodes.

The studies on feasibility of SNB in gastric cancer are rather limited. Table 2 shows that different types of tracers are being used and different numbers of SNs are retrieved. Moreover, IHC was applied in only one of these SNB studies.[17] Endoscopic submucosal injection is feasible for administration of a radioactive tracer or a dye. Identification of the sentinel node by means of a radiolabeled colloid and perioperative detection with a gamma probe has the drawback of detecting radiation not only from lymph nodes but also from the adjacent injection site. Therefore, most experience has been gained with the application of dyes. All the displayed studies, initiated in the Far East, showed acceptable feasibility in early-stage disease (i.e., T1 or T2). In Western countries, however, gastric cancer is often diagnosed at an advanced stage, potentially limiting the role of SNB in these patients.

In Table 3, three of five IHC studies using anticytokeratin antibodies showed an adverse effect of micrometastases on survival. There are remarkable differences in the antibodies used, the number of resected lymph nodes, and the proportion of patients upstaged. Noguchi et al.[18] reported that RT-PCR with keratin 19 was more sensitive than histological examination for the detection of gastric micrometastases in lymph nodes. However, the prognostic significance of micrometastases detected with this technique was not addressed.

The majority of the reports on gastric carcinoma originate from specialized centers that have gained experience with the technically demanding procedure in a patient population less prone to postoperative morbidity and mortality than in Europe and the United States.

In conclusion, the initial and limited experience indicates that SNB has potential value in staging and treating gastric cancer. However, only patients with early-stage disease, a patient category not very often encountered in Western populations, may benefit from SNB. Moreover, the existing variation in technical aspects of SNB and MRD assessment hampers the introduction of treatment decisions based on MRD assessment.

COLORECTAL CANCER

The treatment of node-negative colorectal cancer consists of surgical resection of the primary tumor without adjuvant therapy. However, up to 30% of these patients will develop metastases, possibly due to micrometastases in the regional lymph nodes. We showed that patients

TABLE 2. *An overview of the sentinel node (SN) biopsy studies in gastric cancer*

Reference	No. of patients	Type of tracer	Volume of tracer (mL)	Average no. of SNs (range)	Success rate, mapping (%)	False-negative rate (%)
Hiratsuka et al.[48]	72	Indocyanine green	5	2.6 (1–9)	99	10
Aikou et al.[17]	18	Tc + blue dye	2 (Tc)	3	94	17
Yasuda et al.[49]	26	Tc	2	4 (2–8)	100	18
Ichikura et al.[50]	62	Indocyanine green	4	4.5 (1–12)	100	13
			8	8.6 (1–25)		
Kitagawa et al.[51]	145	Tc	2.0	3.6 (1–8)	95	8
Miwa et al.[52]	211	Blue dye	0.8	6 (1–19)	96	11

Tc, 99m technetium.

TABLE 3. *Immunohistochemistry studies on H&E-negative lymph nodes in gastric cancer*

Reference	Antibody	No. of H&E-node-negative patients	No. of nodes per patient	Node sectioning	Upstaging (%)	Prognostic value
Maehara et al.[53]	CAM 5.2	34	12.4	Single	23.5	Adverse
Cai et al.[54]	CAM 5.2	69	24.6	Single	25	Adverse
Morgagni et al.[55]	MNF 116	139	10.7	Multiple	17	No difference
Fukagawa et al.[56]	AE1/AE3	107	41.9	Single	35.5	No difference
Lee et al.[57]	AE1/AE3	70	23.7	Single	40	Adverse

H&E, hematoxylin and eosin.

with carcinoembryonic antigen (CEA) RT-PCR–negative lymph nodes had a significantly better five-year disease-free survival than patients with positive lymph nodes (91% versus 50%; $P = .02$).[19] Three other RT-PCR studies[20–22] also showed an adverse effect on prognosis, whereas only three of 10 immunohistochemistry studies showed an adverse effect.[22,23] Again, the IHC studies show clear variation in the number of resected lymph nodes, the use of serial sectioning and antibodies, and the degree of upstaging, which ranges from 10% to 76%.[22,24–32]

Noura et al.[22] studied the same paraffin-embedded lymph nodes with CEA RT-PCR and cytokeratin immunohistochemistry and showed that CEA RT-PCR had prognostic value, whereas immunohistochemistry did not.

SNB in colorectal cancer patients is still under development. In contrast to breast cancer, SNB is not performed in colorectal cancer to avoid unnecessary lymphadenectomy but to enable focused examination of a few lymph nodes. An important consequence of intraoperative SNB in colorectal cancer patients is the identification of aberrant lymphatic drainage patterns in up to 14% of the patients, leading to an adjustment of the initial surgical resection plan.[33,34] Table 4 summarizes studies that examined SNB in more than 25 patients with colorectal cancer. Blue dye was used in most of the studies, with moderate variations in volume and site of injection. However, there is a wide range in the number of detected SNs. Success rates, false-negative rates, and upstaging techniques vary and are influenced by disease stage. In rectal cancer, the dye method is limited by restricted visibility of the dye as it moves into the SNs.[35]

In summary, SNB in colorectal cancer patients is a technically demanding procedure with variable success rates. Although MRD assessment can lead to profound upstaging, there is no clear evidence that it should affect adjuvant treatment decisions. Still, in some countries colorectal cancer patients with sentinel node micrometastases are receiving systemic adjuvant therapy. Optimization of SNB and MRD assessment techniques may lead to more tailored adjuvant treatment.

CONCLUSION

Limiting the extent of surgery in the treatment of solid tumors through SNB is technically feasible. However, comparison of the studies reveals variations in patient

TABLE 4. *An overview of the sentinel lymph node (SLN) biopsy studies in colorectal cancer*

References	No. of patients	Identification time (min)	Success rate (%)	Average no. of SLNs (range)	Upstaging methods	False-negative rate (%)
Joosten et al.[58]	50	15	70	3	IHC	60
Wiese et al.[59]	83	5–10	99	1.9	SS and IHC	9
Feig et al.[60]	48	—	98	2.6	IHC	38
Wong et al.[61]	26	2–5	92	2.8	SS and IHC	6
Saha et al.[62]	203	1–5	98	(1–4)	SS and IHC	6
Merrie et al.[63]	26	20[a]; 26–106[b]	88	3 (0–8)	RT-PCR	45
Esser et al.[64]	31	—	58	—	—	33
Broderick-Villa et al.[65]	51	—	92	1.5	IHC	50
Wood et al.[66]	100	—	97	2	SS and IHC	11
Bilchik et al.[67]						
Fitzgerald et al.[68]	26	5–10	88	2.5	SS and IHC	40
Paramo et al.[69]	55	5	82	1.9	SS and IHC	7
Kitagawa et al.[35]	56	120	91	3.5	—	18

IHC, immunohistochemistry; SS, serial sectioning; RT-PCR, reverse transcriptase polymerase chain reaction; Tc, 99m technetium.
[a] Blue dye.
[b] Tc.

selection and in the type, volume, and injection site of tracers. These variations complicate trial comparison, which hampers application of SNB in daily practice. Minimal residual disease assessment by serial sectioning, immunohistochemistry, and RT-PCR is possible and may lead to considerable upstaging. The results from studies addressing the prognostic role of micrometastases are often contradictory, which might be due to the use of different examination techniques, markers, antibodies and differences in sample size and length of follow-up. This variation in techniques of SNB and MRD assessment will delay the development of evidence-based diagnostic and therapeutic guidelines in the near future. Quality control leading to standardization of SNB and MRD assessment is necessary to enable reliable comparison of different studies. Only in this way can we determine the prognostic role of MRD and tailor adjuvant treatment on the basis of MRD assessment of lymph nodes retrieved after limited surgery.

ACKNOWLEDGMENTS

The acknowledgments are available online in the full-text version at www.annalssurgicaloncology.org. They are not available in the PDF version.

REFERENCES

1. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 2001;19:157–63.
2. Camp RL, Rimm EB, Rimm DL. A high number of tumor free axillary lymph nodes from patients with lymph node negative breast carcinoma is associated with poor outcome. *Cancer* 2000; 88:108–13.
3. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* 2003;21:2912–9.
4. Herr HW, Bochner BH, Dalbagni G, et al. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2002;167:1295–8.
5. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949–55.
6. Wong SL, Edwards MJ, Chao C, et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. *J Am Coll Surg* 2001;192:684–9.
7. Dowlatshahi K, Fan M, Snider HC, et al. Lymph node micrometastases from breast carcinoma: reviewing the dilemma. *Cancer* 1997;80:1188–97.
8. Noguchi M. Therapeutic relevance of breast cancer micrometastases in sentinel lymph nodes. *Br J Surg* 2002;89:1505–15.
9. Dowlatshahi K, Fan M, Bloom KJ, et al. Occult metastases in the sentinel lymph nodes of patients with early stage breast carcinoma: a preliminary study. *Cancer* 1999;86:990–6.
10. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; 220:391–8.
11. Cody HS III. Sentinel lymph node mapping in breast cancer. *Oncology (Huntingt)* 1999;13:25–34.
12. Schwartz GF, Giuliano AE, Veronesi U. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19–22, 2001, Philadelphia, Pennsylvania. *Cancer* 2002;94:2542–51.
13. Sasako M, McCulloch P, Kinoshita T, et al. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg* 1995;82:346–51.
14. CJH van de Velde, KCMJ Peeters. The gastric cancer treatment controversy. *J Clin Oncol* 2003;21:2234–6.
15. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;345:745–8.
16. Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996;347:995–9.
17. Aikou T, Higashi H, Natsugoe S, et al. Can sentinel node navigation surgery reduce the extent of lymph node dissection in gastric cancer? *Ann Surg Oncol* 2001;8:90S–3S.
18. Noguchi S, Hiratsuka M, Furukawa H, et al. Detection of gastric cancer micrometastases in lymph nodes by amplification of keratin 19 mRNA with reverse transcriptase-polymerase chain reaction. *Jpn J Cancer Res* 1996;87:650–4.
19. Liefers GJ, Cleton-Jansen AM, van de Velde CJ, et al. Micrometastases and survival in stage II colorectal cancer [see comments]. *N Engl J Med* 1998;339:223–8.
20. Mori M, Mimori K, Ueo H, et al. Clinical significance of molecular detection of carcinoma cells in lymph nodes and peripheral blood by reverse transcription-polymerase chain reaction in patients with gastrointestinal or breast carcinomas. *J Clin Oncol* 1998;16:128–32.
21. Rosenberg R, Hoos A, Mueller J, et al. Prognostic significance of cytokeratin-20 reverse transcriptase polymerase chain reaction in lymph nodes of node-negative colorectal cancer patients. *J Clin Oncol* 2002;20:1049–55.
22. Noura S, Yamamoto H, Ohnishi T, et al. Comparative detection of lymph node micrometastases of stage II colorectal cancer by reverse transcriptase polymerase chain reaction and immunohistochemistry. *J Clin Oncol* 2002;20:4232–41.
23. Tsavellas G, Patel H, Allen-Mersh TG. Detection and clinical significance of occult tumor cells in colorectal cancer. *Br J Surg* 2001;88:1307–20.
24. Cutait R, Alves VA, Lopes LC, et al. Restaging of colorectal cancer based on the identification of lymph node micrometastases through immunoperoxidase staining of CEA and cytokeratins. *Dis Colon Rectum* 1991;34:917–20.
25. Jeffers MD, O'Dowd GM, Mulcahy H, et al. The prognostic significance of immunohistochemically detected lymph node micrometastases in colorectal carcinoma. *J Pathol* 1994;172:183–7.
26. Greenson JK, Isenhart CE, Rice R, et al. Identification of occult micrometastases in pericolic lymph nodes of Duke's B colorectal cancer patients using monoclonal antibodies against cytokeratin and CC49. Correlation with long-term survival. *Cancer* 1994;73: 563–9.
27. Adell G, Boeryd B, Franlund B, et al. Occurrence and prognostic importance of micrometastases in regional lymph nodes in Dukes' B colorectal carcinoma: an immunohistochemical study. *Eur J Surg* 1996;162:637–42.
28. Broll R, Schauer V, Schimmelpenning H, et al. Prognostic relevance of occult tumor cells in lymph nodes of colorectal carcinomas: an immunohistochemical study. *Dis Colon Rectum* 1997;40: 1465–71.
29. Sasaki M, Watanabe H, Jass JR, et al. Occult lymph node metastases detected by cytokeratin immunohistochemistry predict recurrence in "node-negative" colorectal cancer. *J Gastroenterol* 1997; 32:758–64.
30. Oberg A, Stenling R, Tavelin B, et al. Are lymph node microme-

tastases of any clinical significance in Dukes Stages A and B colorectal cancer? *Dis Colon Rectum* 1998;41:1244–9.
31. Yasuda K, Adachi Y, Shiraishi N, et al. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. *Ann Surg Oncol* 2001;8:300–4.
32. Choi HJ, Choi YY, Hong SH. Incidence and prognostic implications of isolated tumor cells in lymph nodes from patients with Dukes B colorectal carcinoma. *Dis Colon Rectum* 2002;45:750–5.
33. Wood TF, Tsioulias GJ, Morton DL, et al. Focused examination of sentinel lymph nodes upstages early colorectal carcinoma. *Am Surg* 2000;66:998–1003.
34. Tsioulias GJ, Wood TF, Morton DL, et al. Lymphatic mapping and focused analysis of sentinel lymph nodes upstage gastrointestinal neoplasms. *Arch Surg* 2000;135:926–32.
35. Kitagawa Y, Watanabe M, Hasegawa H, et al. Sentinel node mapping for colorectal cancer with radioactive tracer. *Dis Colon Rectum* 2002;45:1476–1480.
36. Nwariaku FE, Euhus DM, Beitsch PD, et al. Sentinel lymph node biopsy, an alternative to elective axillary dissection for breast cancer. *Am J Surg* 1998;176:529–31.
37. Borgstein PJ, Pijpers R, Comans EF, et al. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. *J Am Coll Surg* 1998;186:275–83.
38. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer–a multicenter validation study. *N Engl J Med* 1998;339:941–6.
39. Hill AD, Mann GB, Borgen PI, et al. Sentinel lymphatic mapping in breast cancer. *J Am Coll Surg* 1999;188:545–9.
40. Veronesi U, Paganelli G, Viale G, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. *J Natl Cancer Inst* 1999;91:368–73.
41. Winchester DJ, Sener SF, Winchester DP, et al. Sentinel lymphadenectomy for breast cancer: experience with 180 consecutive patients: efficacy of filtered technetium 99m sulphur colloid with overnight migration time. *J Am Coll Surg* 1999;188:597–603.
42. Bass SS, Cox CE, Ku NN, et al. The role of sentinel lymph node biopsy in breast cancer. *J Am Coll Surg* 1999;189:183–94.
43. 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.
44. Fraile M, Rull M, Julian FJ, et al. Sentinel node biopsy as a practical alternative to axillary lymph node dissection in breast cancer patients: an approach to its validity. *Ann Oncol* 2000;11:701–5.
45. Kollias J, Gill PG, Chatterton BE, et al. Reliability of sentinel node status in predicting axillary lymph node involvement in breast cancer. *Med J Aust* 1999;171:461–5.
46. Tafra L. The learning curve and sentinel node biopsy. *Am J Surg* 2001;182:347–50.
47. Nano MT, Kollias J, Farshid G, et al. Clinical impact of false-negative sentinel node biopsy in primary breast cancer. *Br J Surg* 2002;89:1430–4.
48. Hiratsuka M, Miyashiro I, Ishikawa O, et al. Application of sentinel node biopsy to gastric cancer surgery. *Surgery* 2001;129:335–40.
49. Yasuda S, Shimada H, Ogoshi K, et al. Preliminary study for sentinel lymph node identification with Tc-99m tin colloid in patients with esophageal or gastric cancer. *Tokai J Exp Clin Med* 2001;26:15–8.
50. Ichikura T, Morita D, Uchida T, et al. Sentinel node concept in gastric carcinoma. *World J Surg* 2002;26:318–22.
51. Kitagawa Y, Fujii H, Mukai M, et al. Radio-guided sentinel node detection for gastric cancer. *Br J Surg* 2002;89:604–8.
52. Miwa K, Kinami S, Taniguchi K, et al. Mapping sentinel nodes in patients with early-stage gastric carcinoma. *Br J Surg* 2003;90:178–82.
53. Maehara Y, Oshiro T, Endo K, et al. Clinical significance of occult micrometastasis lymph nodes from patients with early gastric cancer who died of recurrence. *Surgery* 1996;119:397–402.
54. Cai J, Ikeguchi M, Maeta M, et al. Micrometastasis in lymph nodes and microinvasion of the muscularis propria in primary lesions of submucosal gastric cancer. *Surgery* 2000;127:32–9.
55. Morgagni P, Saragoni L, Folli S, et al. Lymph node micrometastases in patients with early gastric cancer: experience with 139 patients. *Ann Surg Oncol* 2001;8:170–4.
56. Fukagawa T, Sasako M, Mann GB, et al. Immunohistochemically detected micrometastases of the lymph nodes in patients with gastric carcinoma. *Cancer* 2001;92:753–60.
57. Lee E, Chae Y, Kim I, et al. Prognostic relevance of immunohistochemically detected lymph node micrometastasis in patients with gastric carcinoma. *Cancer* 2002;94:2867–73.
58. Joosten JJ, Strobbe LJ, Wauters CA, et al. Intraoperative lymphatic mapping and the sentinel node concept in colorectal carcinoma. *Br J Surg* 1999;86:482–6.
59. Wiese DA, Saha S, Badin J, et al. Pathologic evaluation of sentinel lymph nodes in colorectal carcinoma. *Arch Pathol Lab Med* 2000;124:1759–63.
60. Feig BW, Curley S, Lucci A, et al. A caution regarding lymphatic mapping in patients with colon cancer. *Am J Surg* 2001;182:707–12.
61. Wong JH, Steineman S, Calderia C, et al. Ex vivo sentinel node mapping in carcinoma of the colon and rectum. *Ann Surg* 2001;233:515–21.
62. Saha S, Bilchik A, Wiese D, et al. Ultrastaging of colorectal cancer by sentinel lymph node mapping technique–a multicenter trial. *Ann Surg Oncol* 2001;8:94S–8S.
63. Merrie AE, van Rij AM, Phillips LV, et al. Diagnostic use of the sentinel node in colon cancer. *Dis Colon Rectum* 2001;44:410–7.
64. Esser S, Reilly WT, Riley LB, et al. The role of sentinel lymph node mapping in staging of colon and rectal cancer. *Dis Colon Rectum* 2001;44:850–4.
65. Broderick-Villa G, Ko A, O'Connell TX, et al. Does tumor burden limit the accuracy of lymphatic mapping and sentinel lymph node biopsy in colorectal cancer? *Cancer J* 2002;8:445–50.
66. Wood TF, Nora DT, Morton DL, et al. One hundred consecutive cases of sentinel lymph node mapping in early colorectal carcinoma: detection of missed micrometastases. *J Gastrointest Surg* 2002;6:322–9.
67. Bilchik AJ, Nora D, Tollenaar RA, et al. Ultrastaging of early colon cancer using lymphatic mapping and molecular analysis. *Eur J Cancer* 2002;38:977–85.
68. Fitzgerald TL, Khalifa MA, Al Zahrani M, et al. Ex vivo sentinel lymph node biopsy in colorectal cancer: a feasibility study. *J Surg Oncol* 2002;80:27–32.
69. Paramo JC, Summerall J, Poppiti R, et al. Validation of sentinel node mapping in patients with colon cancer. *Ann Surg Oncol* 2002;9:550–4.