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Review

Current status of sentinel lymph node biopsy in solid malignancies

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Abstract

Lymphatic mapping and sentinel lymph node biopsy were first reported in 1977 by Cabanas for penile cancer. Since that time, the technique has become rapidly assimilated into clinical practice. The sentinel node concept has been validated in cutaneous melanoma and breast cancer. However, follow-up data of patients from randomised trials is needed to establish the clinical significance of sentinel lymph node biopsy before accepting the procedure as a standard of care. This technique has the potential to be utilised in all solid tumours like colon, gastric, oesophageal, lung, gynaecologic, and head and neck cancer. This paper reviews the current status of sentinel lymph node biopsy in solid tumours.

Background

The sentinel lymph node is defined as the first node in the lymphatic basin into which the primary tumour drains. Therefore, if the sentinel lymph node (SN) is not involved with metastatic disease, the remainder of the lymph nodes should also be negative. Likewise, if the SN is positive, there is a risk that higher order nodes may be involved with metastatic disease.

Cabanas [1] introduced the concept of the "sentinel node" in 1977 when he used lymphangiograms performed via dorsal lymphatics of the penis to demonstrate the existence of specific node or group of nodes associated with the superficial epigastric vein that predicted the nodal status of penile carcinoma. In 1992, Morton and colleagues [2] described lymphatic mapping utilising an intradermal isosulfan blue dye injection technique for malignant melanoma and were the first to employ this concept to localise SNs in patients with malignant melanoma. The authors demonstrated a high success rate in identifying a SN and in achieving low false-negative rate. In 1993, Alex and Krag [3] introduced the use of a radioactive tracer ^{99m}Technetium sulphur colloid, injected intradermally around a primary melanoma site, followed by imaging and subsequent intraoperative use of a gamma probe to localise and extirpate the SN. In recent years, lymphoscintigraphy and blue dye have been used to trace the regional SN in many tumours.

This simple yet revolutionary concept has raised the possibility that all solid malignancies might be amenable to the diagnostic and potential therapeutic benefits of SN identification and staging, and to the diminished surgical morbidity of radical lymphadenectomy. The following article reviews the current status of the application of SN identification in solid malignancies.

Melanoma

The management of the regional lymphatic basin in patients with cutaneous melanoma and no palpable

lymphadenopathy has long been a controversial topic. No prospective randomised trial has shown an overall survival benefit for those patients undergoing routine elective complete lymph node dissection (ELND) [4-6]. The surgeon cannot accurately predict the nodal basin unless the dermal tumour lies on an extremity. Even in this situation in-transit nodes might be missed in the epitrochlear and popliteal spaces in 5% of the population [7]. This finding raises significant concern regarding the original randomised trials evaluating the efficacy of elective lymph node dissection (ELND) versus observation for intermediate thickness melanomas. It is estimated that one-third of the patients in the ELND arms had incorrect nodal basin dissected [8-10].

With the emergence of sentinel node technology, melanoma patients can be staged histopathologically using lymphatic mapping and selective lymphadenectomy, and spared the morbidity associated with ELND. Studies have established that sentinel lymph node biopsy (SNB) is safe, accurate, and reproducible when undertaken by an experienced multidisciplinary team of professionals from nuclear medicine, surgical oncology and pathology. Overall, the success rate of harvesting the SN by blue dye alone is 82%, by radioactive mapping alone is approximately 94%, and by a combination method is 98% [2,11-13]. Whether the choice of SN localisation method, by radioactivity or blue dye is of any clinical significance is undetermined at this time. Patients whose sentinel nodes are tumour free require no additional lymph node dissection. For patients whose sentinel nodes contain metastatic melanoma, however, a complete regional lymph node dissection is necessary. As yet, however, no prospective randomised trial has shown that this results in a survival benefit for patients with any tumour type compared to delay of ELND until the presence of palpable nodes.

Two major studies are examining the utility of SNB in melanoma. The Multicenter Selective Lymphadenectomy Trial (MSLT) [14], compares wide excision and SNB to wide excision alone in patients with clinical stage I melanoma (localised disease). Patients with intermediate (1–4 mm) thickness melanoma who have not had a wide excision (with >1.5 cm margins), a skin graft, or any other procedure that would alter the lymphatic drainage are eligible. Selective completion lymph node dissection is performed only when lymphatic drainage fields contain tumour positive sentinel nodes. The purpose of this study is to determine the therapeutic benefit of SNB and the true accuracy of the technique at multiple international melanoma centres. The experience from the MSLT has shown that the combined blue dye and radiopharmaceutical technique seems to work best for SNB. Patient accrual for this trial was completed in 2002. The outcome of the trial will determine whether SNB eventually becomes the standard of management for patients with clinical stage I melanoma, making conventional ELND unnecessary and providing better outcome than the alternative 'wait and see' approach.

A second randomised trial, the Sunbelt Melanoma Trial [15], examines the efficacy of SNB as treatment for tumour positive regional lymph nodes. This study compares patients with one tumour positive lymph node determined by conventional haematoxylin and eosin (H&E) or immunohistochemical techniques (followed by complete lymph node dissection) to observation or treatment with adjuvant interferon-α. A second group of patients who have a tumour positive sentinel by reverse transcriptase polymerase chain reaction (RT-PCR) alone are randomised to observation, complete lymph node dissection and interferon-α. The organizers of this study anticipate that the results of this trial will provide further insights into the therapeutic value of SNB for patients with a single tumour positive lymph node identified by either routine techniques or RT-PCR.

It would be ideal to determine the tumour status of the sentinel node intraoperatively, so that subsequent regional node dissection can be carried out immediately. Unfortunately, frozen section examination of the sentinel node cytology has been shown to be unreliable [16]. Sentinel lymph nodes can be investigated by more extensive pathologic evaluation. Pathologic examination of 1 or 2 lymph nodes, rather than 20 or 30, allows for a more thorough and focused pathologic evaluation of the submitted tissue. H&E is able to identify one tumour cell in a background of 10,000 normal cells; immunohistochemical (IHC) staining identifies one tumour cell in a background of 100,000 normal cells. Serial sectioning and IHC (with monoclonal antibodies against HMB-45 and S-100) raise the sensitivity some 10–20% [17]. The reverse transcriptase polymerase chain reaction (RT-PCR) is an extremely sensitive and specific technique to establish the presence of messenger RNA from melanoma cells. RT-PCR can detect one melanoma cell in a background of 1 million normal lymphocytes. However, there is no data from randomised trials on the clinical significance of micrometastatic disease detected with IHC, serial sectioning or even RT-PCR. It is not known whether this low burden of disease can be adequately managed by the patient's immune system, especially if the SN bearing isolated tumour cells is removed.

Although it is tempting for the oncologic community to assume that the SNB will alter the ultimate outcome for patients, we must not change our management approaches until the results of the ongoing randomised clinical trials are available.

Table 1: Ongoing trials evaluating the role of sentinel node biopsy in breast cancer

Study[23,24]	**Start date**	**Sample size**	**Design**
Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC)	2000	1260	Randomise to: ALND or sampling vs. SN biopsy
After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS)	2001	3485	If SN positive randomise to: ALND vs. RT
German Clinical Interdisciplinary Sentinel Study (KiSS)	2000	1912	If SN negative randomise to: ALND vs. no ALND
French Randomised Sentinel Node Study (Fransenod)	NA*	446	SN biopsy patients randomised to peritumoural injection vs. periareolar injection
International Breast Cancer Study Group Trial (IBCSG 23-01)	2001	1960	If SN positive for micrometastases(IHC), randomise to: ALND vs. no ALND
American College of Surgeons Oncology Group (ACOSOG-Z0010)	1999	5300	IHC positive SN patients(H&E negative) observed to determine prognostic significance; bone marrow also assayed for micrometastasis to determine incidence and significance
American College of Surgeons Oncology Group (ACOSOG-Z0011)	1999	1900	If SN positive(H&E) randomise to completion ALND vs. observation
National Surgical Adjuvant Breast and Bowel Project(NSABP-B-32)	1999	4500	If SN negative randomise to: completion ALND vs. no additional axillary treatment
Royal Australasian College of Surgeons Sentinel lymph Node biopsy versus Axillary Clearance (RACS SNAC)	2001	1000	SN negative patients randomised to completion ALND vs. no additional axillary treatment

ALND, Axillary lymph node dissection; SN, sentinel lymph node; RT, radiotherapy; IHC, immunohistochemical staining; H&E, haematoxylin and eosin. *Not available

Breast

Axillary lymph node dissection (ALND) involves considerable use of resources (longer surgical procedures under general anaesthesia), and increases the risk of acute and late morbidity that may adversely affect the patient's health related quality of life. The complications may include lymphoedema, pain, numbness and limited shoulder movements [18-21]. SNB is emerging as a minimally invasive alternative to axillary dissection in the staging of patients with breast carcinoma. It has the potential to identify those patients most likely to be helped by axillary dissection (i.e. those with positive nodes) and to spare node-negative patients. The recently published Milan trial [22] reported decreased postoperative morbidity in patients undergoing SNB. However, no data exist from randomised trials, focusing on the relapse free and overall survival following SNB alone. Therefore, results from randomised trials validating the sentinel node biopsy in breast cancer are required before accepting the procedure as the standard of care. Table 1 summarises the ongoing randomised trials, which will resolve several important issues.

Numerous studies have reported identification of the SN in more than 90% of breast cancer patients, with false-negative rates for prediction of axillary nodal status of less than 10% [25,26]. Patient factors shown to increase the likelihood of not finding the SN include increasing age and body mass index [25,27,28]. No factors other than surgeon experience have been found to influence the false-negative rate.

The data show that there is a definite learning curve for sentinel node biopsy that cannot be ignored [29-31]. The ALMANAC study group has shown that standardised training programme of in-house operative training can decrease the learning curve [26]. The number of procedures of the learning curve cannot be fixed for all surgeons. Until compelling evidence to suggest otherwise is available, surgeons should perform minimum of 20 cases. Only after documentation of a successful localisation rate of $\geq$ 90% and false-negative rate of $\leq$ 10% should full ALND be omitted for patients with negative sentinel nodes. If statistical certainty is required to achieve a low false negative rate, then Tanis et al. [32] have calculated that over 300 cases would be required to establish a false negative rate of <5%.

The technique of injecting the radioisotope colloid and blue dye has been a matter of great debate. The combination technique appears to be the most accurate in identifying all SNs [33]. It also appears that there is often more than one SN. In the ALMANAC validation phase, the false negative rate was 10.1% if a single SN was removed versus 4.9% if multiple SNs were removed. This data demonstrates that all SNs must be removed in the initial operation.

The various injection techniques include intraparenchymal, dermal or subdermal, and subareolar plexus. All three techniques have been shown to be reliable in experienced hands. The dermal technique has been shown by McMasters et al [34] to identify the SN in the axilla with increased frequency as compared to the peritumoural injection technique (98% vs. 90%). The dermal technique results in significantly higher counts in the SN and compares favourably with the peritumoural injection for concordance and false negatives. The subareolar technique offers many of the advantages of the dermal injection: it is easy, it avoids the need for image guided injection and it increases the distance of the tumour to the SN, thus eliminating shine through from upper outer quadrant lesions. The transit time is also quicker than the peritumoural technique [35]. In spite of the many advantages of the dermal or subareolar technique, some institutions continue to utilise an intraparenchymal injection, because this is the only technique that will identify internal mammary lymph nodes. Additional questions regarding the optimal mode of injection will be answered by the Fransenod study (French Randomised Sentinel Node Study; Study Chair, Dr Jean-Francois Rodier). Patients are randomised to one of the treatment arms: 1) Patients receive peritumoural injections of Patent BlueV dye and technetium Tc99m sulphur colloids 2) Patients receive periareloar injections as in arm 1. The Fransenod trial closed in January 2003 after recruiting 446 patients.

Interest in evaluating internal mammary nodes (IMNs) has recently been rejuvenated with the advent and widespread acceptance of lymphatic mapping and SNB in breast cancer. It has been established, contrary to traditional thinking, that IMN drainage is not limited to tumours of the medial quadrant [36]. The significance of IMN involvement is controversial, and the current practice ignores the internal mammary nodes. Most surgeons do not intend to perform internal mammary lymph node biopsies, even if lymphatic mapping demonstrates drainage to this site. Determination of IMN involvement may alter adjuvant therapy. Fortunately, this represents only a small number of patients as the number of instances in which an internal mammary SN contains metastatic cancer when the axillary SN does not is small. Moreover, many patients these days are receiving adjuvant therapy based upon tumour characteristics, even if node negative [36].

The issue of mapping for patients with a diagnosis of ductal carcinoma in situ (DCIS) remains controversial. All would agree that patients with DCIS have an excellent long-term prognosis (98% survival). 19%–36% of patients with DCIS on core biopsy will be found at definitive surgery to have an invasive cancer [37]. More importantly, there is no way to predict preoperatively which patients with DCIS will be upstaged to invasive cancer at the time of definitive surgery. Lymphatic mapping is less reliable after a lumpectomy and impossible after a mastectomy. If the SNB is not performed at the time of the definitive operative procedure, a significant number of patients will be found to have an invasive cancer, which will require a second operative procedure and in all likelihood ALND. The majority of these patients will be found to have a negative axilla, yet miss out on all the advantages of SNB if not performed initially.

The role of IHC staining of the SNs also remains an area of significant controversy. SNB and a focused pathologic evaluation have resulted in upstaging of approximately 10%–20% of breast cancer patients. The question is whether this detectable disease is clinically significant. All the present literature is retrospective in nature and the results are very inconclusive. Prospective studies are ongoing to evaluate the prognostic significance of micrometastases (IBCSG 23-01 trial, ACOSOG Z0010 trial) (Table 1). Therefore, until we have good data, clinical decisions should not be made based on inadequate studies.

The need for completion ALND in patients with a positive SN who will receive systemic cytotoxic therapy is also controversial. This important clinical question is being addressed by the ACOSOG Z0011 trial. In this trial, patients with a positive SN are randomised to completion ALND or no additional axillary therapy.

Colon

As a result of the success of SNB in melanoma and breast tumours, the technique is now being applied to other solid tumours in the gastrointestinal tract. In breast cancer and melanoma, most patients are found to be node negative, and avoiding radical lymphadenectomy decreases the morbidity of the procedure. In colon cancer, the aggressiveness of the resection is unaffected by the decision to perform a SNB, and therefore, morbidity is unchanged. The SN theory for colorectal cancer, however, has the potential for detecting previously unrecognised disease and provides better nodal staging. Up to 30% of node-negative patients with colorectal cancer develop a recurrence and die of distant metastasis. It is postulated that this group of patients may have occult lymph node micrometastasis not identified at the time of colon resection and conventional pathologic evaluation. Methods have been developed to help enhance the detection of lymph node metastasis, including serial sectioning, IHC staining, and RT-PCR. All of these techniques remain too expensive and impractical to perform on all lymph nodes. SNB aims to facilitate staging by identifying the lymph nodes most likely to harbour metastases for thorough pathological evaluation. It may be an efficient method of upstaging patients at high risk for recurrence who should

be offered adjuvant therapy. However, the true significance of micrometastases detected by these techniques remains unclear.

Many reports of SNB in colorectal cancer are emerging [38-47]. Presently, there is no standardisation; both single- and combined-agent injection techniques have been utilised, such as subserosal and submucosal injection, in vivo and ex vivo injection methods, and in vivo and ex vivo SN identification. Success rates vary from 58%–98% of patients, with false-negative rates from 0%–60%. One of the reasons for the difference in the false-negative rates is the definition of false negative. If IHC staining and RT-PCR are used, then the false-negative rate is much lower. The mean number of SNs identified varies from a low of one to surgeons arbitrarily choosing to count only the first four blue lymph nodes as SNs. These results would appear to represent a steep learning curve for a new technique.

The mapping agent should be injected near the tumour with as little mobilisation of the colon as needed prior to injection. When the colon is significantly mobilised and when lymphatic mapping has been performed *ex vivo*, lymphatics may be disrupted and aberrant lymphatics might never be identified. The concordance between a submucosal and subserosal injection is unknown. Colonoscopy for submucosal injection must be performed intraoperatively or a day prior and results in colonic distension, patient inconvenience, and increased expense. It is not known whether single agent is better than two agents.

Drainage to aberrant lymphatics outside the field of a standard oncological mesenteric resection has been reported in 0%–10% patients [40,48,49]. In some cases, this aberrant lymph node has been found to be the only positive lymph node. However, there is no data to support a more extensive procedure be performed to remove SNs outside the standard field of resection.

The results to date suggest that lymphatic mapping and SNB in rectal cancer is not as successful as its application in colon tumours [38,41,44,45,47]. Identification of sentinel nodes below the peritoneal reflection may be difficult [49]. Also, the mesentery of the rectum should not be disturbed until the pathologist has assessed the lateral margins. This limits the utility of this technique for primary rectal tumours, and many surgeons are using this as a contraindication for mapping.

SNB in colorectal cancer is still in its infancy. Prospective randomised studies are required to determine the true significance of micrometastases in colorectal cancer. Sentinel node mapping may assist in this process by guiding both surgeon and pathologist to the node most likely to harbour micrometastases. Should micrometastases prove to have a prognostic impact, sentinel node mapping may have a role to play in selecting patients for adjuvant therapy. Based on the limited data at this time we cannot recommend systemic cytotoxic chemotherapy to the upstaged patients.

Other solid cancers

A number of reports have examined the feasibility of sentinel lymph node biopsy in gastric, oesophageal, lung, gynaecologic, head and neck cancer. However, the technical aspects of the procedure remain to be perfected and verified and the topic in general remains controversial.

Conclusion

Sentinel node biopsy is a promising new medical technique that is gaining popularity before the medical community has had time to provide adequate training and put the procedure into practice in a safe and organised manner. SNB is minimally invasive and can reduce morbidity and cost. SNB is able to provide the pathologist with a limited number of lymph nodes to allow a focused analysis. However, the clinical relevance of tumour cells identified by immunohistochemical staining or even more sensitive testing, such as polymerase chain reaction technology in the SN, remains unclear.

For melanoma and breast cancer, ongoing clinical trials are in progress to determine the clinical significance of sentinel node biopsy. Defining the role of SNB in other malignancies remains in its infancy, but available data suggest this approach is feasible. While the trials are underway and outstanding questions are being answered, surgeons should resist commercial pressure and media-driven patient requests for performing SNB outside clinical trials or validated training programmes.

Competing interests

None declared.

Authors' contributions

Both authors (AG and RM) contributed to the drafting and editing of the article. All authors read and approved the final manuscript.

References

1. Cabanas RM: **An approach for the treatment of penile carcinoma.** *Cancer* 1977, **39:**456-466.
2. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ: **Technical details of intraoperative lymphatic mapping for early stage melanoma.** *Arch Surg* 1992, **127:**392-399.
3. Alex JC, Krag DN: **Gamma-probe guided localization of lymph nodes.** *Surg Oncol* 1993, **2:**137-143.
4. Balch CM, Soong SJ, Bartolucci AA, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Ross MI, Jewell WR, Mihm MC, Barnhill RL, Wanebo HJ: **Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger.** *Ann Surg* 1996, **224:**255-263.

5. Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH: **A prospective randomised study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. Preliminary results.** *Cancer* 1978, **41:**948-956.
6. Veronesi U, Adamus J, Bandiera DC, Brennhovd IO, Caceres E, Cascinelli N, Claudio F, Ikonopisov RL, Javorskj VV, Kirov S, Kulakowski A, Lacoub J, Lejeune F, Mechl Z, Morabito A, Rode I, Sergeev S, van Slooten E, Szcygiel K, Trapeznikov NN: **Inefficacy of immediate node dissection in stage I melanoma of the limbs.** *N Engl J Med* 1977, **297:**627-630.
7. Uren RF, Howman-Giles R, Thompson JF, Shaw HM, Quinn MJ, O'Brien CJ, McCarthy WH: **Lymphoscintigraphy to identify sentinel lymph nodes in patients with melanoma.** *Melanoma Res* 1994, **4:**395-399.
8. Godellas CV, Berman CG, Lyman G, Cruse CW, Rapaport D, Heller R, Wang X, Glass F, Fenske N, Messina J: **The identification and mapping of melanoma regional nodal metastases: minimally invasive surgery for the diagnosis of nodal metastases.** *Am Surg* 1995, **61:**97-101.
9. Kamath D, Rapaport D, DeConti R, Cruse CW, Wells K, Glass F, Messina J, Fenske N, Brobeil A, Berman C, Puleo C, Reintgen D: **Redefining cutaneous lymphatic flow: the necessity of preoperative lymphoscintigraphy in the management of malignant melanoma.** *J Fla Med Assoc* 1997, **84:**182-187.
10. Uren RF, Howman-Giles RB, Shaw HM, Thompson JF, McCarthy WH: **Lymphoscintigraphy in high-risk melanoma of the trunk: predicting draining node groups, defining lymphatic channels and locating the sentinel node.** *J Nucl Med* 1993, **34:**1435-1440.
11. Albertini JJ, Cruse CW, Rapaport D, Wells K, Ross M, DeConti R, Berman CG, Jared K, Messina J, Lyman G, Glass F, Fenske N, Reintgen DS: **Intraoperative radio-lympho-scintigraphy improves sentinel lymph node identification for patients with melanoma.** *Ann Surg* 1996, **223:**217-224.
12. Krag DN, Meijer SJ, Weaver DL, Loggie BW, Harlow SP, Tanabe KK, Laughlin EH, Alex JC: **Minimal-access surgery for staging of malignant melanoma.** *Arch Surg* 1995, **130:**654-658.
13. Leong SP: **The role of sentinel lymph nodes in malignant melanoma.** *Surg Clin North Am* 2000, **80:**1741-1757.
14. Morton DL, Thompson JF, Essner R, Elashoff R, Stern SL, Nieweg OE, Roses DF, Karakousis CP, Mozzillo N, Reintgen D, Wang HJ, Glass EC, Cochran AJ: **Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group.** *Ann Surg* 1999, **230:**453-463.
15. McMasters KM: **The Sunbelt Melanoma Trial.** *Ann Surg Oncol* 2001, **8:**41S-43S.
16. Tanis PJ, Boom RP, Koops HS, Faneyte IF, Peterse JL, Nieweg OE, Rutgers EJ, Tiebosch AT, Kroon BB: **Frozen section investigation of the sentinel node in malignant melanoma and breast cancer.** *Ann Surg Oncol* 2001, **8:**222-226.
17. Cochran AJ: **The pathologist's role in sentinel lymph node evaluation.** *Semin Nucl Med* 2000, **30:**11-17.
18. Warmuth MA, Bowen G, Prosnitz LR, Chu L, Broadwater G, Peterson B, Leight G, Winer EP: **Complications of axillary lymph node dissection for carcinoma of the breast: a report based on a patient survey.** *Cancer* 1998, **83:**1362-1368.
19. Velanovich V, Szymanski W: **Quality of life of breast cancer patients with lymphedema.** *Am J Surg* 1999, **177:**184-187.
20. Roses DF, Brooks AD, Harris MN, Shapiro RL, Mitnick J: **Complications of level I and II axillary dissection in the treatment of carcinoma of the breast.** *Ann Surg* 1999, **230:**194-201.
21. Hack TF, Cohen L, Katz J, Robson LS, Goss P: **Physical and psychological morbidity after axillary lymph node dissection for breast cancer.** *J Clin Oncol* 1999, **17:**143-149.
22. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, Intra M, Veronesi P, Robertson C, Maisonneuve P, Renne G, De Cicco C, De Lucia F, Gennari R: **A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.** *N Engl J Med* 2003, **349:**546-553.
23. Mansel RE, Goyal A: **European studies on breast lymphatic mapping.** *Semin Oncol* 2004 in press.
24. **National Cancer Institute clinical trials database** [http://www/nci.nci.gov/clinicaltrials/]. Accessibility verified April 2, 2004
25. McMasters KM, Wong SL, Chao C, Woo C, Tuttle TM, Noyes RD, Carlson DJ, Laidley AL, McGlothin TQ, Ley PB, Brown CM, Glaser RL, Pennington RE, Turk PS, Simpson D, Edwards MJ: **Defining the optimal surgeon experience for breast cancer sentinel lymph node biopsy: a model for implementation of new surgical techniques.** *Ann Surg* 2001, **234:**292-299.
26. Clarke D, Newcombe RG, Mansel RE, ALMANAC Trialists Group: **The learning curve in sentinel node biopsy: The ALMANAC experience.** *Ann Surg Oncol* 2004, **11(2 Suppl):**2115-2155.
27. Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, Feldman S, Kusminsky R, Gadd M, Kuhn J, Harlow S, Beitsch P: **The sentinel node in breast cancer – a multicenter validation study.** *N Engl J Med* 1998, **339:**941-946.
28. Tafra L, Lannin DR, Swanson MS, Van Eyk JJ, Verbanac KM, Chua AN, Ng PC, Edwards MS, Halliday BE, Henry CA, Sommers LM, Carman CM, Molin MR, Yurko JE, Perry RR, Williams R: **Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye.** *Ann Surg* 2001, **233:**51-59.
29. Tafra L, McMasters KM, Whitworth P, Edwards MJ: **Credentialing issues with sentinel lymph node staging for breast cancer.** *Am J Surg* 2000, **180:**268-273.
30. Simmons RM: **Review of sentinel lymph node credentialing: how many cases are enough?** *J Am Coll Surg* 2001, **193:**206-209.
31. Morrow M, Rademaker AW, Bethke KP, Talamonti MS, Dawes LG, Clauson J, Hansen N: **Learning sentinel node biopsy: results of a prospective randomized trial of two techniques.** *Surgery* 1999, **126:**714-720.
32. Tanis PJ, Nieweg OE, Hart AA, Kroon BB: **The illusion of the learning phase for lymphatic mapping.** *Ann Surg Oncol* 2002, **9:**142-147.
33. Goyal A, Newcombe RG, Mansel RE: **Relative value of blue dye and isotope in sentinel node localization for breast cancer in a multicentre trial [abstract].** *Eur J Cancer* 2004, **2(suppl 3):**78-79.
34. McMasters KM, Wong SL, Martin RC, Chao C, Tuttle TM, Noyes RD, Carlson DJ, Laidley AL, McGlothin TQ, Ley PB, Brown CM, Glaser RL, Pennington RE, Turk PS, Simpson D, Cerrito PB, Edwards MJ: **Dermal injection of radioactive colloid is superior to peritumoral injection for breast cancer sentinel lymph node biopsy: results of a multiinstitutional study.** *Ann Surg* 2001, **233:**676-687.
35. Kern KA: **Lymphoscintigraphic anatomy of sentinel lymphatic channels after subareolar injection of Technetium 99m sulfur colloid.** *J Am Coll Surg* 2001, **193:**601-608.
36. Mansel RE, Goyal A, Newcombe RG: **Internal mammary node drainage and its role in sentinel node biopsies: the initial ALMANAC experience.** *Clin Breast Cancer* 2004 in press.
37. **The UK NHS Breast Screening Programme 2001/2 statistics** [http://www.cancerscreening.nhs.uk/breastscreen]. Accessibility verified April 2, 2004
38. Gandy CP, Biddlestone LR, Roe AM, O'Leary DP: **Intra-operative injection of Patent Blue V dye to facilitate nodal staging in colorectal cancer.** *Colorectal Dis* 2002, **4:**447-449.
39. Bendavid Y, Latulippe JF, Younan RJ, Leclerc YE, Dube S, Heyen F, Morin M, Girard R, Bastien E, Ferreira J, Cerino M, Dube P: **Phase I study on sentinel lymph node mapping in colon cancer: a preliminary report.** *J Surg Oncol* 2002, **79:**81-84.
40. Feig BW, Curley S, Lucci A, Hunt KK, Vauthey JN, Mansfield PF, Cleary K, Hamilton S, Ellis V, Brame M, Berger DH: **A caution regarding lymphatic mapping in patients with colon cancer.** *Am J Surg* 2001, **182:**707-712.
41. Esser S, Reilly WT, Riley LB, Eyvazzadeh C, Arcona S: **The role of sentinel lymph node mapping in staging of colon and rectal cancer.** *Dis Colon Rectum* 2001, **44:**850-854.
42. Paramo JC, Summerall J, Wilson C, Cabral A, Willis I, Wodnicki H, Poppiti R, Mesko TW: **Intraoperative sentinel lymph node mapping in patients with colon cancer.** *Am J Surg* 2001, **182:**40-43.
43. Waters GS, Geisinger KR, Garske DD, Loggie BW, Levine EA: **Sentinel lymph node mapping for carcinoma of the colon: a pilot study.** *Am Surg* 2000, **66:**943-945.
44. Joosten JJ, Strobbe LJ, Wauters CA, Pruszczynski M, Wobbes T, Ruers TJ: **Intraoperative lymphatic mapping and the sentinel node concept in colorectal carcinoma.** *Br J Surg* 1999, **86:**482-486.

45. Cserni G, Vajda K, Tarjan M, Bori R, Svebis M, Baltas B: **Nodal staging of colorectal carcinomas from quantitative and qualitative aspects. Can lymphatic mapping help staging?** *Pathol Oncol Res* 1999, **5:**291-296.
46. Merrie AE, van Rij AM, Phillips LV, Rossaak JI, Yun K, Mccall JL: **Diagnostic use of the sentinel node in colon cancer.** *Dis Colon Rectum* 2001, **44:**410-417.
47. Saha S, Bilchik A, Wiese D, Espinosa M, Badin J, Ganatra BK, Desai D, Kaushal S, Singh T, Arora M: **Ultrastaging of colorectal cancer by sentinel lymph node mapping technique – a multicenter trial.** *Ann Surg Oncol* 2001, **8:**94S-98S.
48. Paramo JC, Summerall J, Poppiti R, Mesko TW: **Validation of sentinel node mapping in patients with colon cancer.** *Ann Surg Oncol* 2002, **9:**550-554.
49. Bilchik AJ, Nora D, Tollenaar RA, van de Velde CJ, Wood T, Turner R, Morton DL, Hoon DS: **Ultrastaging of early colon cancer using lymphatic mapping and molecular analysis.** *Eur J Cancer* 2002, **38:**977-985.