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SENTINEL NODE BIOPSY: CONCEPTS AND CURRENT STATUS

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1. ABSTRACT

One of the major routes for spread of cancer is via lymphatic vessels to local lymph nodes. For this reason, local lymph nodes are removed to prevent further spread of tumors. Over the years, surgery has evolved from therapeutic lymphadenectomy for involved nodes to elective lymphadenectomy when the risk of harboring metastasis was high. Two major problems encountered with such an approach included the morbidity of the procedure and a high proportion of nodes being negative on pathologic examination. For these reasons, a new approach has been developed - Sentinel node biopsy (SNB). SNB is an *in vivo* assessment of the nodal involvement in early disease. During surgery, the sentinel node is identified by the injection of a blue dye, a radio-colloid substance or both which has been show to have fewer false negatives. This procedure is now standardized during surgery of breast carcinoma or melanoma. However, its use in other types of tumors is still considered investigational at present.

2. INTRODUCTION

Tumors have no primary lymphatics. Cancer cells presumably gain access to the lymphatic system at the invasive tumor periphery through clefts between lymphatic endothelial cells or through lymphoinvasion much similar to angioinvasion. These afferent lymphatics join a marginal sinus in the cortex of individual lymph nodes (LN). From there, tumor cells later invade the medulla and join the efferent channel. These efferents drain into a next echelon LNs and finally end in one of the three terminal collecting trunks – thoracic, subclavian and right lymphatic ducts through which it drains into the venous system. The filter-barrier theory proposed that LNs served as mechanical and biologic filters in which phagocytosis assists the mechanical phase of particulate trapping. Contradicting this are studies where the tumor cells traverse LNs while the LNs themselves are not affected implying that the LNs are ineffective barriers. Some other studies have shown that LNs act a barrier for a limited time – 3 weeks and after a certain threshold these cells pass to general circulation (1-4). It is now believed that the properties of tumor cells per se rather than the filtration capacity of the nodes which determine whether the cells are trapped.

In the early part of 1900s, it was believed that nodal metastasis occurred by permeation which resulted in the concept of en bloc resections in cancer (5). It was later found that cancer cells could be detected in the nodes without tumor involvement of intervening lymph vessels. However in certain situations like tumor recurrence, blockade of normal lymphatics or in tumors involving certain sites like floor of mouth, the permeation concept is still applicable. It is now generally accepted that the lymphatic spread is largely by embolization. Traditionally, it was thought that tumor cells gain access to blood stream only through the terminal collecting lymph trunks like the thoracic duct. But, many other lymphovenous communications exist. Cells deposited in the subcapuslar sinuses may lodge permanently in the nodes, may egress through the efferent lymphatics, or may egress to the hematogenous system through lymphovenous communications. At times, the cells may completely bypass the lymphatic system to enter systemic circulation (6, 7). Occasionally, tumor cells can bypass the nearest regional LN and proceed to a remote LN, a phenomenon termed 'skip metastases'. Current thinking questions this concept and attributes the remote LN involvement to variable lymph drainage rather than the inability of the nearest node to trap the tumor cells making the concept of 'skip metastases obsolete. Lymphatic channels form as buds from venous structures, a common embryologic origin that creates the potential for lymphovenous anastomoses under conditions of increased lymph pressure and flow (8, 9). The many opportunities for lympho-venous, venous-lymphatic and interlymphatic communication prevent any rigid discrimination between hematogenous and lymphatic metastasis. The significance of these shunts under physiological and pathological circumstances is unknown although obstruction is not a pre-requisite for such a shunt to be active (10).

A controversial area is the role of regional LNs in the immune response to tumors. In animal experiments it has been shown that LN removal or irradiation in the early period after tumor implantation resulted in decreased resistance and increased metastasis. The same did not occur after node removal later (11, 12). The response of LN cells to cancer may be different over time and location of the primary tumor. Loco-regional LNs could exhibit anti-tumor activity while distant uninvolved nodes may not (7). The accepted implication of such experiments is that regional nodes are important in host defense against early cancer during which time they potentiate systemic immunity. The same nodes are defunct when tumor burden increases. This was shown in the preliminary results of Reiss in breast cancer (13). Contradicting this claim, it has been demonstrated that immune response is not generated exclusively in regional LNs demonstrating that the lymphocytic response is systemic and not limited to regional LNs (14). The occurrence of large nodal disease with small undetectable primary is seen occasionally and suggests that regional LNs may be a 'fertile soil' for tumor growth than destruction. Recent reports indicate that there is down-modulation of immune function in the sentinel nodes (SLN) (15). This could be due to factors released from the primary and related to the mechanism of micrometastasis (16). Recent studies have pointed toward the importance of dendritic cells in initiating the immune response to malignancy. Dendritic cell maturation, likely from passage of these cells from the skin to the regional lymph nodes, causes changes in the function of these cells from antigen processing to presentation. There is upregulation of co-stimulatory molecules which is necessary for T cell activation. The maturation of dendritic cells and T cells is thought to be instrumental in the T-cell-driven response to tumor presentation (17). Further evaluation in this direction could throw light on the mechanism of metastasis. To date, the role of regional LNs has not been defined exactly with conflicting evidences. Primary melanoma produces immunosuppressive factors that affect the regional LNs (15). Hence it is likely that SLN are more immunosuppressed than the non SLN. Once the malignant cell metastasizes to the node, further immunosuppression in the SLN occurs; which in turn results in immunosuppression of non SLN nodes and later to systemic immunosuppression. Hence those likely to benefit from removal of these nodes include patients in whom the tumor cells are 'incubating' in the nodes – the micro-metastatic disease. Those least likely to benefit are those with large nodal disease and systemic disease (18).

It is now accepted that regional LNs are indicators of the ability of primary tumor to metastasize than an instigator of distant metastasis. Regional LNs can also contribute to distant metastasis but is less important in clinical practice. The metastatic regional LNs (N+) status indicates the host condition permissive for development of metastasis and presence of LN metastasis decreases chances of survival by about 50%. Another interesting concept of nodal metastasis proposed is the LN avid and LN avoidant patterns. In a sub-set of cancer patients, the lymphatic system appears to be the only or at least the first route of dissemination – the LN avid situation (19). Nodal dissection in this situation would prevent further metastatic cascade and hence could result in cure (20). An example

would be long term survivors of breast cancer patients who had LN metastasis in the Halstedian era (21), while another would be a situation of neck nodal metastasis with unknown primary. Colon cancers with hepatic metastasis reveal that at least 50% of them are node negative. An autopsy study of head and neck cancers showed that 37% of patients had distant metastasis while neck LNs was uninvolved (22). This would represent a LN avoidant pattern of dissemination. These concepts are for theoretical discussion and perhaps have little utility in the clinical setting of a given patient.

The metastatic nodes are addressed by therapeutic lymphadenectomy wherever feasible. The intent of such a procedure is towards local control and staging while the curative nature is unclear. One of the common areas addressed by lymphadenectomy is the axilla in breast cancer. Some authors believing that axillary dissection does not increase survival but that it is important as a staging procedure only (23). Others believe that improved loco-regional control results in superior overall survival (24). The management of regional nodal basins which are N0 is much more controversial. Extending this concept of therapeutic lymphadenectomy, excision of occult nodal metastasis as in elective lymph nodal dissection (ELND) should not contribute to cure and would not be a useful manoeuvre for reducing metastatic ability. Theoretically, ELND would be curative in a setting of regional nodes harboring micro metastasis and regional nodes being the only site of metastasis. Certain unresolved issues include significance of occult nodal disease, their immunologic significance and whether they actually indicate systemic disease (at the stage of occult metastasis) amongst others. Superimposed on this controversial area of tumor biology, another hotly debated area is whether such regional nodes should be addressed with surgery or with radiation with each modality claiming superiority over the other.

The presence of occult metastases in the lymph nodes, bone marrow, or both of these compartments may not only define patients who are at higher risk for recurrence and death but also may identify biologically distinct mechanisms of tumor spread (e.g., lymphatic vs. vascular dissemination). Use of techniques to detect occult metastases may also allow the identification of a biologically important population of cells, i.e., those cells constituting the earliest metastatic population of tumor cells. Thus, techniques that identify occult metastases may be valuable in furthering our understanding of the events regulating tumor dissemination (25)

Theoretically, patients who are likely to benefit from an ELND are those in whom the primary is under control but later develop metastatic nodes which are not salvageable; and those who die of distant metastasis where the nodal disease is the origin of metastasis. The category of patients who would not benefit from ELND include those who would never develop LN metastasis, those who are successfully treated after developing LN metastasis, those in whom primary tumor is uncontrolled, those who die due to ELND and those in whom distant metastasis arise as a result of non-lymphatic dissemination. To address this benefit ratio, there appears to be a general consensus of ELND in neck for occult metastasis from head and neck cancers exceeding 15% - 20% (26). This can presumably extrapolated to other organs which result in ELND for almost all organs. However, morbidity of the procedure remains and unnecessary nodal dissections would be done in 50% - 80%. One of the important areas addressed by the sentinel node biopsy (SNB) is avoiding an unnecessary nodal dissection for this large group.

3. THE SENTINEL NODE MAPPING AND BIOPSY

3.1. The beginning and evolution of SNB

Gould, in 1960 reported the concept of 'sentinel node' during parotidectomy (27). In the late 1970's, Cabanas popularized the concept of SNB for penile carcinoma (28). However, Braithwaite used the term to study in lymphatic drainage much earlier in 1923 (29). He described the existence of a SLN near the superficial epigastric artery by a series of lymphangiograms. In addition, he showed that groin dissection could be avoided if this SLN was negative. Over the years, this procedure was not widely practiced as there were varying results and controversy surrounded the exact location of this node. The static approaches of Cabanas were not reproducible and did not take into account the inter-individual variability of lymphatic drainage and hence did not receive enough support for the concept at that time. Later, there were attempts to define sentinel node in retroperitoneum for testicular tumor and in the axilla for the breast. However, the most remarkable breakthrough in defining the sentinel node was by Morton (30). The work of his group at the John Wayne Cancer Institute initiated one of the most interesting recent developments in surgical oncology. They used cutaneous lymphoscintigraphy with colloidal gold since 1977 to identify the lymphatic drainage pattern of melanomas located at ambiguous sites. In addition to this preoperative procedure, they also developed a technique for intra-operative mapping to selectively remove lymph nodes on the direct drainage pathway from the primary melanoma. This technique of identifying the SLN by scintigraphy was individualized and was different from the anatomic-fixed location of the sentinel node defined by Cabanas although the concept of SLN remained the same.

The concept of SNB is based on two basic principles: the existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin, and the functioning of a first lymph node as an effective filter for tumor cells. The sentinel node concept is actually based on the Halsted theory that stressed the importance of locoregional cancer treatment because of the step-wise spread. This was investigated in a laboratory study (31).The SLN is defined as the first node in the lymphatic basin into which the primary tumor drains. The primary afferent lymphatic first drains into the SLN of the respective basin. Therefore, the status of the SLN(s) should accurately reflect the entire basin. If the SLN is not involved with metastatic disease, the remainder of the lymph nodes should also be negative. Likewise, if the SLN is positive, there is a risk of higher order nodes being involved with metastatic disease. Underlying this

hypothesis is the assumption that the surgeon can correctly and consistently identify this node (i.e., the sentinel node) (32). It also assumes the existence of a therapeutic window during which the metastatic cascade can be arrested by removal of tumor-involved regional lymph nodes (18).

Lymphatic mapping utilizing an intradermal isosulfan blue dye injection technique for malignant melanoma was employed to localize SLNs in patients with malignant melanoma (30). The authors demonstrated a high success rate in identifying an SLN and in achieving low false-negative rate. This technique was reproduced at other institutions demonstrating similar findings. Similarly, intraparenchymal blue dye lymphatic mapping to the nodal evaluation of breast cancer was reported (33). The two major disadvantages of using vital blue dyes in melanoma are that the dissection of the lymphatics can sometimes be technically difficult and that the dye may pass rapidly through the sentinel node and stain several nodes in the lymphatic basin. Perhaps more importantly, the position of the sentinel node in this disease is not always predictable, interfering with the planning of an appropriate incision and risking inaccurate sentinel node identification (34). For these reasons lymphatic mapping using lymphoscintigraphy and a gamma probe was developed. Development of the hand-held gamma radiation detectors was later used for localizing SLN in breast cancer using intraparenchymal ^{99m}Tc sulfur colloid as a mapping agent to localize the SLN in breast cancer (35). Likewise, lymphoscintigraphy for SLN localization was described which incidentally also demonstrated routes of spread not described in conventional teachings (36). A combined radiocolloid and blue dye technique for mapping both melanoma and breast cancer patients was subsequently developed (37).

3.2. Clinical nodal disease – importance

It is apparent from the earlier discussion that nodes are one of the most important predictors of metastatic disease and hence metastatic nodes are very important prognosticators. In addition, regional nodes are the common initial site of metastatic disease in a solid tumor. Regional nodal staging therefore needs to be accurate. Many decisions on loco-regional or systemic therapy is based on the knowledge of regional nodal involvement. The low negative predictive value of various instrumentation or tumor targeting agents (magnetic resonance, gamma-scintigraphy, and positron emission tomography [PET]) is particularly worrisome when staging cancer patients (38). Sentinel node biopsy (SNB) is a minimally invasive staging technique that may allow improved precision in the evaluation and management of many newly diagnosed cancer patients. On average it takes 18 to 24 months for microscopic nodal metastases to grow to a clinically palpable size (39). This interval may be a critical window of time that may make a difference between curative and palliative treatment in some cancers. Regardless of whether complete lymphadenectomy is therapeutic, removing nodal metastases at the same time as the primary cancer achieves maximum disease control and may spare patients a second course of surgical treatment in the subsequent months or years. In diseases in which lymphadenectomy is regarded as having staging value only, SNB may lower the overall morbidity of surgical staging with complete lymphadenectomy (39).

3.3. Other methods to identify nodal disease

The aim at addressing nodal disease is to treat only metastatic nodes while avoiding therapy to node negative disease. All investigations including SNB are aimed in this direction. Most of the following discussion pertains to axilla in breast cancer and may as well be applicable to other organs. Although some imaging modalities are surprisingly effective, good results are usually dependant on local expertise and are difficult to reproduce in a more general setting (40). The high sensitivity demanded for the evaluation of nodal disease can frequently be achieved only by compromises in specificity. In reality the likelihood of any imaging modality having the ability to detect very small nodal metastases, and indeed micro metastases, is small.

Magnetic resonance imaging (MRI): One study showed that MRI had a sensitivity of 90%, specificity of 83%, positive predictive value (PPV) of 86% and negative predictive value (NPV) of 88% (41). Another group has tried to predict axillary involvement by evaluation of primary (42). With very few studies addressing the issue of nodal evaluation by MRI comparing with pathologic status, it is premature to comment on the usefulness of the investigation.

Positron emission tomography (PET) most frequently uses positron emitting radiopharmaceutical 18-fluor labeled 2-deoxy-D-glucose (18F-FDG), a radioactively labeled glucose analog. 18F-FDG accumulates predominantly in the tumor tissue and can be visualized by a PET camera. Some investigators doubt that 18F-FDG–PET is capable of accurately assessing the nodal status of breast cancer patients and others believing that a noninvasive PET scan could replace SLN biopsy at predicting the disease status of the axillary lymph nodes. Sensitivity of PET for axillary disease has been reported to be as low as 79% (43). The series that have reported very high sensitivity have done so at the expense of poor specificity and low PPV (44, 45). PET scanning does not currently have the adequate spatial resolution to detect both micro and small macro-metastatic disease in axillary lymph nodes of patients with breast cancer. Therefore, currently PET scanning cannot serve as a non-invasive alternative to SLN biopsy (46).

All series of scintimammography using ^{99m}Tc-sestamibi are small and performed in single centres. The results are disappointing with sensitivity in the larger series generally less than 85% and as low as 62%. One large series evaluating 100 patients showed a sensitivity of 79%, specificity of 85%, PPV of 83% and NPV of 81% (47).

The role of CT scanning must currently be considered uncertain with low sensitivity, specificity and PPV (48, 49). Recently however a technique of SNB using computed tomography-lymphography using iopamidol has been described for breast cancer which allowed quick localization of SLN (50, 51).

The results of ultrasound are operator dependant and generally poor, with sensitivity as low as 56% reported in patients not having the nodes assessed with fine needle aspiration cytology. The echo pattern of the node returns a low sensitivity but high specificity and PPV, whereas considering size alone improves sensitivity but compromises specificity and PPV. Ultrasound-guided fine needle aspiration biopsy (FNAB) had a sensitivity of 80% and a specificity of 100% and detected metastases in 63% of node-positive patients. Although FNAB is an easy, reliable, inexpensive method for identifying patients with positive nodes, in the case of negative findings, other diagnostic procedures to exclude lymph node metastases, such as SNB, could be performed (52).

Radiolabeled monoclonal antibodies directed against tumour associated antigens have been investigated as diagnostic tools in breast cancer. To date, an adequately sensitive and specific antibody has not been identified and until one is forthcoming this technique must remain experimental. (53, 54)

3.4. The sentinel node biopsy - considerations

The development and validation of staging method by sentinel node technique has been rapid over the past several years and clearly provides a minimally invasive method of cancer staging. Clinical investigations have demonstrated the value of SLN in management decisions for patients with clinically negative regional LNs and its value as an entry qualification of patients participating in clinical trials. The technique also offers new biological insights into the role of lymphatics in cancer metastases (39). Success of the technique depends on the coordinated efforts of the surgeon, pathologist and the physician in nuclear medicine emphasizing the multi-disciplinary team effort. As the technique is evolving, there are variations in experience and reported results in the same as well as different sites. The utility of SLN is accepted in melanoma and breast cancers while the exploration of SLN with other types of cancer is still in relatively early stages of evaluation. The results demonstrate that the principle of lymphatic drainage patterns to a predictable SLN is applicable for many, if not most, anatomical sites. If results are confirmed as experience grows and techniques are standardized, then this technique may have broad value in more precisely defining the stage of disease and enhancing the treatment decision-making process for a wide variety of cancers (39).

3.5. The technique of identification of the sentinel node

There are two main techniques to identify the sentinel node. One uses vital dyes which color the node. The second uses radioactive isotopes and their localization to sentinel node is detected by a hand held gamma camera. However, combination of both techniques yields optimal and accurate nodal localization with false negatives being very low. The following description of SNB is what is practiced for either melanoma or breast cancers as the techniques for these two cancers are reasonably standardized. In general, even with significant variations in methodology, reasonably consistent results are obtained.

3.5.1. The dye

Dyes used for SLN identification include isosulfan blue, patent blue, indocyanine green, indigocarmine and methylene blue (33, 37, 55-57). Ionizable groups (sulfonic acids) that are present in the structure of dyes are directly involved in dye–protein binding. At the molecular level, there is a sulfonation reaction between sulfonic acid dyes and amino groups on the protein surface to form sulfonamide complexes. This reaction shows how the soluble dyes Evans blue and Patent blue are trapped in lymph after subdermal injection during the sentinel node biopsy procedure (58). Isosulfan blue is the monosodium salt of 2,5-disulphonated triphenyl methane, while patent blue violet is a triphenylethane similar in structure to isosulfan blue. Biochemically, they are essentially the same agents, and no difference has been observed in their ability to identify SLNs (30). Due to availability and preference, isosulfan blue is more commonly used in the United States while patent blue is used in the Europe. Dyes other than isosulfan blue including patent blue, indigocarmine and indocyanine green have been used in Japan. No prospective study has been conducted comparing these dyes, but the SLN identification rates in Japan show no difference between the dyes (59). Presumably, a reasonable level of success could be expected with all the dyes. However, methylene blue, having no sulfonic acid groups in this structure, clearly was not bound to plasma proteins, consistent with the literature that this dye is not taken up by lymph, and that follows the expected course of inert soluble compounds by diffusing directly into blood capillaries after subdermal injection (58). In addition, methylene blue should be avoided as one of the known complications of injecting this drug is fat necrosis in patients who have had breast conservation surgery (60). Recent studies however have used and recommended methylene blue (61). Rarely, allergic reactions have been described (0.9%) which have responded to steroids (62).

Blue dye traverses the lymphatics rapidly. Depending upon the position of the primary, a leash of stained lymphatic vessels leading to a stained sentinel node can usually be found in the axilla between 3 and 10 min after injection (63) When the dye is administered intradermally or peritumorally in breast cancer or melanoma, the blue dye may stain one or more than one node. The sentinel node may not always be the nearest staining node to the primary tumour. Dissection of the node can be at times, technically more difficult since the position of the sentinel node is not always predictable. This could lead to creation of tissue flaps and risk of infection or necrosis (64). The node or nodes hence defined by the blue dye is then excised and evaluated by histopathology.

3.5.2. Lymphoscintigraphy

The alternative to the use of blue dye is a radiolabelled colloid. After the injection of colloid, gamma cameras can be used to obtain both early dynamic images and later static images of the axilla. Once the ‘hot area’ is visualized in the lymphoscintigram, the location can be marked on the patient’s skin. In the operating theatre

handheld gamma-detectors can then be used to confirm the pre-operative localization or to orientate more precisely the skin incision in the area of the "hot spot" or to isolate the sentinel node if it was not identified preoperatively (40). Different colloids with varying characters are available which makes the choice rather controversial. The rate of migration of a colloidal particle in the lymph is inversely related to its size (65). This is one of the major variables responsible for diverse behaviors of various pharmaceuticals. Uptake is nonspecific and does not infer nodal metastasis per se. In fact, heavily invaded nodes may not accumulate the tracer and so remain undetected. Macrophages in the nodes determine the uptake and retention of the radiopharmaceutical. Theoretically, the particle size should be such that the migration in the lymph vessels is rapid but is taken up by the macrophages and retained long enough to be identified as a 'hot spot'. Hence the particle need to be small enough for the lymph vessel but large enough for the macrophage. Meeting both the requirements and achieving best results are those particles in the range of 200 – 1000 nm (66). Generally, particles smaller than 50nm pass through the sentinel node and reach second and third echelon nodes very rapidly, while those more than 500nm pass very slowly through the lymph vessels and hence take prolonged period for nodal accumulation (40). In the United States, the commonly ^{99m}Tc Sulfur colloid is commonly used. The size of the particle is however larger than some others used in Europe. Hence, certain investigators have tried to modify the size by using 0.1 and 0.22 micrometer filters (67). Rapid accumulation in nodes could result due to reduction in particle size (68). A non-randomized trial compared the two ^{99m}Tc Sulfur colloids and concluded that unfiltered was superior to filtered (69). ^{99m}Tc nano colloid and ^{99m}Tc antimony sulfide are commonly used in Europe. Au^{198} colloid has a good nodal uptake with very little extra nodal escape. A major drawback precluding its use is the high radiation burden (70, 71)**.** Among the newer tracers, Rhenium sulfide has shown promise (72). Doses of radioisotope ranges from 7 – 370 MBq and volumes ranging from 0.2 to 4 ml have been used (56, 73, 74). Although higher doses could yield better sentinel node identification (75), reasonable success can be achieved over a wide range of dose and volume as followed by various investigators. Attempts have been made to increase detection rate by enhancing nodal contrast by methods such as graded shield technique (76). As stated earlier, tracer retention in SLNs is performed by nonspecific trapping mechanisms. There is renewed effort to develop tracers with active, receptor-mediated trapping. The most promising so far is ^{99m}Tc-labeled diethylenetriamine penta-acetic acid mannosyl dextran (77).

Pre-operative lymphoscintigraphy was not found to be beneficial when added to intraoperative localization in one study (78). But contradicting opinion is expressed by others. It is argued that SLN sometimes contains so little radioactivity it cannot be identified with a probe through the intact skin. In addition, sometimes the sentinel node cannot be picked up with the probe because of a location so close to the primary lesion site (where the bulk of the radioactivity stays behind) that its counts are overwhelmed by shine-through from the injection site. This particular problem was encountered in 26% of patients in one study (79). Yet another reason proposed is the situation of SLN outside the usual nodal basin; with pre-surgical lymphoscintigraphy being useful to identify these. However the advantage of intra-operative use of a handheld probe is that it particularly aids identification of nodes situated outside the axilla. These locations include internal mammary chain, within the breast or supraclavicular fossa. In addition, use of a gamma probe avoids the risk of losing the way to the sentinel node which could be due to damage of the blue stained lymphatic duct (40). This is particular hazard during early part of the learning curve. Various studies show that the SLN is visualized in 75% to 98% using lymphoscintigraphy (79). With experience, the localization has been consistently above 90%.

3.5.3. Dye or radiocolloid?

Good results have been obtained with blue dye alone without isotope study. The SLN retrieval rate increased from 65% in mid 1990s to 88% in late 1990s (33, 80) with one study showing a retrieval of 93%, accuracy of 100% and no false negatives (81). Instances where the blue dye stained node has not been shown on isotope localization have been reported. One such series reported such an incidence in 32% cases (57). A small randomized study comparing dye alone versus dye in combination with radioactive isotope did not show significant difference in SLN identification (82). Other studies have shown that radioactive isotope localization alone is better than dye alone but the combination of both results in low false negatives of 7.2% (37, 78). Currently, though dye technique is considered the gold standard, both these techniques are to be considered as complimentary (83). The current recommendation is to use the combination of dye and radioisotope. This should be able to identify SLN in 96% of patients in order to reduce false negatives (61, 84). Some authors advocate pre-operative lymphoscintigraphy in addition to intraoperative 'blue dye' staining of SLN and a hand held gamma camera for accurate localization – 'the triple technique' (85). The recent results from NSABP-32 trial shows that the identification of sentinel node is successful in 96.2% of cases with a false negative rate of 6.7% (86). Cumulative results of SNB in breast showed an overall identification rate of 90%. The identification rates were 92%, 81% and 93% for isotope localization, dye localization and with combined technique respectively. The false negatives ranged from 5% to 9% while the overall accuracy was 96% to 98% depending on the technique used (87).

3.6. Sentinel node biopsy – technical issue

When a combination technique is used, four peritumoral (or subareolar as per institutional practice) injections of tracer are given around the tumor and at the depth of the center of the tumor. They are placed at 12, 3, 6, and 9 o'clock with 1 ml syringes with 5 to 10 MBq of ^{99m}Tc-antimony sulfide colloid solution (or other radiotracers) in a volume of 0.2 ml for each injection. The aim is to place the injection in normal breast tissue immediately adjacent to the tumor and not to inject the tumor itself. After injecting the patient a sterile pad is

placed over the injection site, and the patient is asked to perform gentle massage over the tumor in a rotary fashion for 5 minutes using the opposite hand (88). An early image is then obtained at 10 minutes to visualize any dominant lymph channels. Delayed scans are preformed 2 to 3 hours later and the SLN is then marked on the skin. This procedure can be scheduled on the day prior to surgery. The radiotracer is retained by the node for more than 24 hours. Blue dye (3-5ml) is injected just prior to surgical exploration in the way very similar to the tracer (some surgeons prefer the dermal injection). The hand held gamma camera now is put to use. The pre operative marking, the blue staining of the lymph channels and the node, aided by the skin marking done previously help identify the SLN with small skin incision/s.

3.7. The injection site

Morton first described an intra-dermal injection of 1.4 ml of lymphazurin on the side of the primary skin lesion nearest to the lymph node basin most likely to contain the sentinel node (30). Intra-dermal injection seems appropriate for the identification of the SLN in melanoma but the most appropriate site of injection in breast cancer is debated. Some investigators inject intra-dermally or sub-dermally whereas others advocate injection of dye directly into the tumor or peri-tumorally (33). In general, epithelial cancers do not have an efficient lymphatic system of their own. Tumor lymphangiogenesis is grossly dysplastic, exhibiting some or all of the following patterns: Prelymphatics do not link with lymphatics, basal lamina and flattened endothelium are inconsistent and often incongruous, and interconnection of stroma with blood vessels and lymphatic structures is often abnormal (89). Experimental evidence emphasizes either the absence or inefficiency of structured lymphatic drainage from most solid tumors, including breast cancer. This makes the use of intratumoral injections less logical than that of peritumoral or subdermal injections. The interstitial fluid leaving the tumor bed has to follow the lymphatic spaces and pathways of the normal tissues surrounding the tumor (38). Owing to its embryologic origin in the ectoderm, the mammary gland is, in a sense, an organ of the skin; therefore, its lymphatic drainage mostly parallels lymph flow from the overlying skin. In fact, the breast is situated between the lymphatics of the overlying dermis and the deep lymphatic collectors of the underlying fascial plane, being intimately connected with both sets of lymphatic structures (38, 90). Complex architecture deriving from common embryologic origin explains why most of the mammary gland and of overlying skin can be considered as a single biologic unit sharing a common centrifugal lymphatic pathway to the same axillary nodes (38). Hence a sentinel node identified by intra- or sub-dermal injection of dye into the skin overlying the site of the primary tumor is likely to correlate with the sentinel node draining from the breast parenchyma of the tumor itself (91, 92). Moreover, data suggests higher more successful SLN localization with intra dermal injection compared to intraparenchymal injection in the breast (91). Contrasting data suggesting significant variation between the lymphatic drainage of the skin of the breast and the glandular tissue below has been reported (93, 94). They concluded that there is no physiological basis for the use of intra-dermal or sub-dermal injections and they recommended peri-tumoral injection. This technique would certainly appear more appropriate for tumors deep within a large breast or for impalpable tumors detected by mammography alone, in which case dye can be injected through a needle localized radiologically. In addition, deeper injection of blue dye avoids skin discoloration which in some cases could persist for several months (81). Intra-patient comparisons of the two injection sites have been performed (95). In this study, peritumoral injection identified SLN more frequently than the intradermal injection. Another observation is that intradermal injection fails to identify SLN in the internal mammary area and it requires a peritumoral injection to do so (95, 96). In conclusion, both intradermal injection and peritumoral injections are practiced with comparable false-negative rates. Subareolar injection is as accurate as peritumoral injection. Peritumoral injection is desirable when internal mammary node localization is required.

3.8. Controversy in defining the sentinel node

The first node in the pathway to receive the tumor lymphatic drainage is the SLN. There is some confusion on the interpretations during identification of SLN. This is despite the fact that there is neither ambiguity in understanding the concept nor is there a different aim. People from different backgrounds are involved and everyone views this new development from his or her own perspective. The National Cancer Institute (NCI) describes sentinel lymph node mapping as: “The use of dyes and radioactive substances to identify the first lymph node to which cancer is likely to spread from the primary tumor.”

3.8.1. Node in the direct drainage pathway

One definition is that sentinel node is a node on the direct drainage lymphatic pathway from the primary tumor. It is the initial node into which the primary tumor drains (30). However in experience, it is found that nodes in remote areas away from the usually defined nodal basin are the first ones to receive the drainage.

3.8.2. Node closest to primary

The definition of the sentinel node as the lymph node closest to the primary lesion disregards the physiology of lymph drainage. This is illustrated by the observation that most melanomas of the lower leg and foot have their sentinel node in the groin and not in the popliteal fossa, which is much closer. The node closest to the primary tumor is the first one to be involved only when it receives drainage directly from the primary lesion site (97).

3.8.3. First node on scintiscan

Investigators in the field of nuclear medicine define the sentinel node as the first lymph node that becomes visible on the lymphoscintigraphy images. The first node that lights up is a sentinel node. Late lymphoscintigraphy images may depict more than one node, but they do not visualize the lymphatic channels. Early images do visualize the lymphatic channels and thereby delineate the order of drainage. When multiple nodes are shown, some investigators define the sentinel node as the first lymph node that becomes visible on the

lymphoscintigraphic images. However, there may be more than one sentinel node as there may be two lymphatic ducts originating in the primary tumor running to two different lymph nodes in the same basin. Because of a preferential flow, one node may be appearing on the scintigraphy images earlier than the other. This does not mean that only the first node is a sentinel node. On the contrary, the decreased flow to the other node may in fact be caused by a tumor deposit at the entrance of its lymphatic duct. Too few nodes could be labeled "sentinel" nodes, and metastases may be missed (79). When more than one sentinel node was identified, the involved node was not the most radioactive node in about 20% (97, 98). However if the node contains large metastatic disease, it is likely that such a node is palpable intra-operatively or is identifiable on ultrasound (99)

3.8.4. Blue node or radioactive node

Another definition is that sentinel node as either a blue node or a radioactive node (73, 100, 101). Hence every blue node or every radioactive node is a sentinel node. This definition disregards the fact that some of the tracer tends to pass through the first-tier lymph node and lodges in secondary nodes that are not directly at risk of harboring metastatic disease. Hence this definition is too broad and leads to the situation where too many nodes are removed. Removal of secondary nodes is of no additional value and the primary aim of limiting the nodal dissection is lost. Another factor to be contended is the differential behavior of nodes to uptake of dye versus radioisotope. In about 15% to 30% the sentinel nodes are only blue and not radioactive. These would hence be missed if only radioisotope is used (57, 102).

3.8.5 Node count rate versus others or background and the hottest node

If the images show multiple nodes, each with its own afferent channel from the injection site the definition can still be applied. However, the definition cannot be applied if multiple nodes are depicted without lymphatic channels. In that situation some people define the sentinel node as the hottest node (103). Other investigators use the number of counts, sometimes compared to the count rate in another lymph node or in the background, to decide whether a node is a first-echelon node (35, 37, 74, 104). A problem with this definition is that the amount of radioactivity that travels to a lymph node varies with the type of colloid particles that are used, their size and stability, their surface characteristics, the size of the lymph node, and the lymph flow rate and the whole procedure is not standardized (105). The hottest node is most often but not always the first to receive tumor cells. Sometimes the tracer may pass through a sentinel node and move on to subsequent second echelon nodes with more active macrophages resulting in more radioactivity than the first echelon node. Another factor that determines the accumulated tracer apart from its position of drainage is number of lymph channels that enter the node and the rate of flow of lymph. The sparse flow could also be due to obstruction by metastatic disease as stated earlier. Another factor that determines the brightness on the scan is the distance of the node to the gamma camera. If two nodes containing an equal amount of a radionuclide are situated at a different depth, the node closest to the gamma camera will be depicted as the hottest. The probe cannot distinguish first echelon and second echelon nodes. It is suggested that all blue nodes and those with 10% or higher of the *ex vivo* radioactive count of the hottest sentinel node should be harvested for optimal detection of nodal metastases (106).

By the methods currently used, it may not be possible to distinguish accurately the real sentinel nodes from the second or third echelon nodes in some cases.

3.9. False negatives

There can be three credible definitions of a false-negative finding in sentinel node procedures as applicable in breast cancer (97). The first of these definitions is what is routinely meant. The node (SLN) is identified by lymphoscintigraphy, a probe, or blue dye. The result of this procedure would be falsely negative if this sentinel node is disease-free at initial pathology evaluation but a tumor is identified in any axillary lymph node at any time. Second definition applies when the procedure is truly positive if, in addition to the tumor-free SLN found during the standard procedure, an additional node is identified that proves to be tumor-positive. Here, the other node is positive while the SLN is false negative. The third definition would be to state that the results of a sentinel node procedure falsely negative only if an axillary recurrence develops during follow-up, an extension of the first definition.

Different factors can influence sentinel node identification with possible mechanisms being involved in erroneous identification of the sentinel node (107). The first error results from the surgeon's inability to adequately identify and remove all the sentinel lymph nodes. The end result is a technical failure which could be due to various reasons including the dye, isotope, drug quantity injected, site of injection, duration between the injection and identification of the node etc. The inexperience of the team including the surgeon, the nuclear medicine physician and the pathologist contribute to this. The team must attain a certain level of accuracy before abandoning routine nodal dissection although the learning curve is steep showing that learning could be reasonably rapid. Failure to adhere to guidelines results in high false negatives. The second error results from the secondary spread of tumor to the nodal basin from a local recurrence or an in-transit node and is a biological failure. SNB could carry with itself an inaccuracy inherent to the procedure itself. In view of cancer being such a complex disease and with varied biology, this is not surprising. But it must be realized that as long as false negatives persist, these patients continue to receive sub-optimal therapy (40). The third is a pathological failure which occurs when the occult disease present in the sentinel node is not detected by the analysis. This has been partly addressed as technical failure. Lastly, it could be possible for some lymphatics to carry the lymph for certain periods of time and other lymphatics during certain other periods much akin to parts of kidney or lung 'taking rest' for some periods of time during the day. This could be perhaps one of the causes of inherent failure ascribed to the procedure itself.

For SNB to be an alternative to nodal dissection, the false negative rate must be very low. This appears to be the fact in breast and melanoma with ability to identify the SLN being above 90% in most instances. In early disease when SNB concept is applied, many of the nodal basins are negative in any case. Hence, false negative statistics must be applied to node positive basins where SNB has failed to localize the node. This would considerably increase the statistics of false negatives. Most of the studies do not address this. Another flaw is that in many studies, SLN assessed by step sectioning and IHC is compared with non-sentinel nodes which are assessed by routine H&E resulting in low false negative (40). Two retrospective studies showed that by applying such criteria, the sensitivity of SNB is only marginally decreased but there is an increase of non-SLN metastasis by 15% (108, 109). However, with current practices, false negatives are reasonably low in breast and melanoma.

3.10. Radiation exposure

Lymphatic mapping using radiolabelled colloid exposes both the patient and staff involved to external radiation. The isotope used (and its half life) as well as the dose administered determine the level of exposure (110). In one study patients received between 10 and 15 MBq of ^{99m}Tc-labelled colloidal albumin and the effective dose to the patient was 0.021 mSv/MBq, with a mean breast dose of 0.72 mGy/MBq (111). Although these doses are moderate, the radiation risk is low relative to the effective dose administered in many other imaging investigations. In the same study a mean whole body dose of 0.34 mSv was received by the surgical staff per procedure, with a mean finger dose of 0.09 mSv. Studies have concluded that precautions have to be exercised, that exposures are low and the risk to both patient and team carrying out the procedure is negligible (111, 112) .

3.11. The learning curve

The importance of the learning curve in SNB was emphasized in Morton's first publication (30). He suggested that 60-80 procedures need to be performed to attain efficiency. Other authors have suggested between 20 and 25 procedures are required before standard axillary dissection can be abandoned in case of breast cancers (113-115). It is established that a 'learning curve' exists for SNB. It has also been shown that dye localization learning is more protracted than radiocolloid for attaining accuracy. The need for a training program is emphasized in the Philadelphia consensus statement (116). However two issues need to be addressed. One is the surgical localization while the other is the pathologic analysis of the node with equal emphasis on both. The former is represented by the localization rate which is expected to be in excess of 90% (34) while the latter is represented by the false negative rate which is variable and difficult to quantify. The ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) trial provided a structured multidisciplinary program involving the surgeons, pathologists, nuclear medicine physicians and the radiologists. They found that apart from the failure in the first procedure which was not proctored, the learning curve is not statistically demonstrable. They concluded that the surgeon would be capable of performing SNB satisfactorily much earlier than the stipulated 40 procedures in that trial (117).

3.1.2 Pathology

Some institutions delay the processing of nodal specimen due to radiation concerns (57, 112). However, tissues can be processed immediately without fear of radiation exposure as the radiation received is less than that of the surgeon and is within the accepted limits while the tissues can be stored in formalin stored within lead covered containers (118). Radiation doses received by pathology staff were predominantly below measurable levels and were deemed likely to be negligible unless primary specimens from a large number of studies were all analyzed promptly upon their excision (111). Pathologic evaluation performed intraoperatively of the SLN specimen can confirm that the specimen is a lymph node and can also exclude the possibility of extravasated blue dye or radiocolloid in adipose tissue (119). Most importantly, intra operative pathologic examination can identify metastasis in SLN tissue, allowing the surgeon to undertake complete nodal dissection during the same procedure. In contrast, there are concerns over false negative results (34, 73), in which case another procedure needs to be performed should the SLN turn out to harbor metastasis. Although frozen section (FS) including immunohistochemical studies (IHC) have been successfully performed, an intra operative study seems to be useful for tumors in the breast when the size is greater than 1cm (118). FS alone had a higher chance of missing micrometastasis (120). Complete step section FS has a negative predictive value of 96% while the same procedure with IHC added would result in a 100% negative predictive value (121). However the procedure requires 40-50 mins which is would be a major disqualification. Imprint cytology is another study claiming success similar to that of FS with a negative predictive value of 90% to 97% compared to routine pathologic examination (118, 122-124). Rapid IHC could be useful in enhancing the results further for both FS and imprint cytology but as yet such a procedure is not suitable for general use. At present there is no consensus on the role of intra-operative pathologic examination. Another procedure, the reverse transcriptase-polymerase chain reaction (RT-PCR) is a highly sensitive technique for detecting metastatic breast carcinoma cells in lymph nodes, blood, or bone marrow (118, 125). Molecular biology staging offers the most sensitive methods of detecting nodal metastases (126). In contrast to IHC, molecular markers allow analysis of the entire lymph node in one reaction, thus reducing the time needed for screening. The limitations include the lack of marker specificity, standardization of assay procedures, and morphologic correlation of a positive signal RT-PCR. In addition, the procedure requires fresh or frozen SLN. Well designed clinical trials are needed to determine the role of molecular techniques in the diagnostic evaluation of the SLN.

The initial evidence of nodal metastasis is frequently seen in the subcapuslar sinus where small foci of tumor cells are seen at the junction of the afferent lymphatic vessel (127, 128). Small metastatic foci are

classified as isolated tumor cells and micro-metastasis. The former is defined as isolated cells or small clusters of cells not greater than 0.2mm in largest diameter without stromal invasion or malignant activity. Micro-metastasis is defined as those that do not fit in the above but measure 0.2 to 2 mm in size (128). Gross sections of the SN needs to be no thicker than 2 mm for optimal results (129). The blue dye used would not interfere with detection of metastasis if any.. The importance of metastasis detected by IHC continues to be debated although certain data supports its clinical significance (130, 131). Contradicting opinions are also expressed where it is argued that sentinel lymph node metastases detected by IHC only do not mandate complete axillary lymph node dissection in breast cancer (132). The question of the clinical relevance of IHC-detected "metastases" will soon be answered by the ACOSOG Z0010 trial. Among the patients who has SNB positive, 34% of them had non sentinel nodes harboring metastasis (in axilla for breast cancer) detected on routine histopathology (133). In melanoma, the overall survival rates at 5, 10, and 15 years were 70%, 65%, and 65%, respectively, for patients with IHC-positive SLNs compared to overall survival rates of 89%, 83%, and 81% respectively with IHC-negative SLNs (134). The sentinel node technique has provided the surgeon with a precise tool that can stage for the presence or absence of regional metastases down to a threshold of 10^5 to 10^6 cells with an accuracy of 95%. With serial step sections and IHC, there is an increase in node positivity by as much as 20% to 50% due to improved staging, compared with the conventional method of examining a single section of a bivalved lymph node solely with routine staining (39, 118). The European Working Group for Breast Screening Pathology recommends that use of IHC is optional and the use of molecular markers should not be routine and confined to research work at present (135). In addition it was also observed that FS was useful for single stage procedures and that imprint cytology was a better option.

3.13. Utility of SNB in tumors arising from various Organs

Apart from breast and melanoma where the procedure of SNB is accepted, other solid tumors where SNB is tried include gastrointestinal cancers, head and neck cancers, lung cancer, gynecologic cancers, urologic cancers, merkel cell carcinoma and sarcomas (136, 137). SNB for breast results in a less invasive surgery. However, in the case of esophagus, SNB does not result in less surgical invasion and is neither simple because of widespread location of sentinel nodes. Although the concept of sentinel node is appealing, its utility may be organ dependent and needs to be individualized. The role of SNB outside melanoma and breast is as yet undefined. Hence SNB should not be the standard of care and at present remains an active area of investigation. Results of future trials may help define the exact role of SNB in these areas. Some of the ongoing major trials are listed in table 1 along with a brief objective. Though its role has yet to be defined, surgeons are hoping this minimally invasive technique may serve as a means to improve staging, better predict prognosis and utilize adjuvant therapies and decrease morbidity by avoiding unnecessary major lymphadenectomies (138).

3.13.1. Breast

Axillary lymph node dissection (ALND) has been an integral part of breast cancer management since Halsted introduced radical mastectomy. Although the impact of ALND on survival is currently a subject of controversy, accurate assessment of axillary nodal status provides the most important prognostic information for patients with primary breast cancer apart from achieving local control. Axillary nodal status is one of the important parameters that determine the necessity and type of adjuvant therapy. ALND with the histopathology of the specimen is the standard assessment of axilla. Axillary dissection is associated with a low local recurrence rate and a low false negative rate (23). However, both acute and chronic complications including lymphedema may reach 20% to 30% (139). Clinical examination alone is inaccurate in about 30% and random axillary sampling results in 40% false negativity. On the other hand, only about one third of patients with clinically negative axillae have histopathologic evidence of metastases in the ALND specimen, routine ALND places a significant number of patients at risk for operative morbidity without certain benefit (23). SNB has the potential to spare a proportion of patients this morbidity and also to improve the accuracy of lymph node staging. In one study, 206 patients out of 208 breast cancers had a negative sentinel lymph node. With a median follow-up of 26 months, there have been 3 axillary recurrences with a clinical SLN false negative rate of 1.4% (140). Another study showed one axillary recurrence, one supraclavicular metastasis and two cases with second primary breast cancer in opposite breast in a 3 year follow up of SNB alone without ALND (141). Today, in experienced hands, when the team has progressed through the learning curve with a low false negative rate, it is perhaps feasible to avoid ALND when SLN is negative. The exact number of SNB procedures with ALND necessary before performing SNB alone is controversial, but the goal should be to achieve a false negative rate 0.5% and an identification rate of >90% (116). However, this statement must be applied with caution and should not be interpreted as a blanket justification to forgo ALND in inexperienced hands. In addition, long-term outcome of sentinel node surgery without axillary dissection has not been established. To that extent the therapeutic outcome of sentinel node surgery is unknown. Hence clinical trials results are necessary to answer these questions.

The identification of a single sentinel internal mammary node makes assessment of this lymphatic basin feasible without incurring significant additional morbidity. Internal mammary node is found on SLN mapping in about 10% of patients. Majority opinion is that these nodes are of prognostic significance and is an independent predictor of survival (142). At the present time this option has not been widely taken-up, with many surgeons electing to ignore sentinel nodes located medially.

In breast, attempts have been made to stratify the risk groups for non-sentinel disease by combining the pathologic factors of the primary tumor and sentinel node metastasis. It has been shown that in patients with invasive breast cancer and a positive SLN, extranodal extension or

Table 1. Ongoing studies world wide on sentinel node biopsy

	STUDY	PATIENTS	TRIAL OBJECTI VES
B R	**RMNHS – 1631 ***	150+50	Compare sentinel node biopsy vs axillary dissection in determining axillary nodal status in patients with resectable stage I or II breast cancer
	ACOSOG – Z0010*	5300	Estimate the prevalence and evaluate the prognostic significance of sentinel lymph node micrometastases detected by immunohistochemistry in women with stage I or IIA breast cancer. Estimate the prevalence and evaluate the prognostic significance of bone marrow micrometastases detected by IHC in these patients. Evaluate the hazard rate for regional recurrence in women whose sentinel nodes are negative by hematoxylin and eosin (H&E) staining. Provide a mechanism for identifying women whose sentinel nodes contain metastases detected by H&E so that these women can be considered as candidates for ACOSOG-Z0011.
	ACOSOG-Z0011 *	1900 (950 per arm)	Determine whether axillary lymph node dissection (ALND) improves overall survival in women with stage I or IIA breast cancer. Quantify and compare surgical morbidities associated with sentinel lymph node dissection with or without ALND in these patients.
	IBCSG-23-01 †	13000	Compare disease-free survival of women with clinically node-negative breast cancer with sentinel lymph node micrometastases treated with surgical resection with or without axillary dissection. Compare overall survival of patients treated with these regimens. Compare quality of life of patients treated with these regimens. Compare the incidence of reappearance of disease in the undissected axilla, sites of first failure, and short- and long-term surgical complications in patients treated with these regimens. Correlate pathological features of disease with outcome in patients treated with these regimens.
	NSABP – B-32†	5400	Compare the long term control of regional disease by sentinel node resection vs sentinel node resection followed by conventional axillary dissection in women with breast cancer who are clinically node negative and pathologically sentinel node negative. Compare the effect of these two regimens on the overall and disease-free survival of these patients. Compare the morbidity associated with these two regimens in these patients. Compare the prognostic value of these two regimens in patients who are sentinel node negative or positive by pathology. Determine whether a more detailed pathology investigation can identify a group of patients with a potentially increased risk of systemic recurrence who are node negative by pathology. Determine the technical success rate of sentinel node dissection and the variability of technical success rate in a broad population of surgeons. Determine the sensitivity of the sentinel node to determine the presence of nodal metastases in these patients. Objectives of quality of life questionnaire in sentinel node-negative patients: Compare the severity of self-assessed symptoms and activity limitations of patients treated with these two regimens. Compare the severity of self-assessed symptoms and activity limitations after breast cancer surgery in patients whose surgery was on the dominant side vs patients whose surgery was on the non-dominant side. Compare the impact of arm edema, range of motion, and sensory neuropathy on self-assessed measures of daily functioning, symptoms, and overall quality of life of patients treated with these regimens.
	STRAUSS-FRANSENOD *	450	Determine the optimal mode of injection (peritumoral vs periareolar) of patent blue V dye and technetium Tc 99m sulfur colloid in patients with stage I or II breast cancer undergoing sentinel lymph node identification. Determine the reduction of morbidity associated with breast cancer surgery, in terms of local control and survival, in patients undergoing sentinel lymph node identification with these drugs. Determine the evolution of disease in patients who have undergone this procedure and do not show histological invasion of the sentinel lymph node.

	FRE-FNCLCC-96008 *	200	Determine whether the concept of a sentinel lymph node within the axillary nodal basin is valid in staging breast cancer. Determine the sensitivity of combined methods of identification of sentinel lymph nodes by patent blue V dye and gamma probe detection in these patients.
	04-C-0114 †	60	This is a pilot study which examines the role of sentinel lymph node (SLN) mapping, and of primary tumor gene expression profiling, for determining the incidence of axillary lymph node metastases in women with breast cancer after neoadjuvant chemotherapy
	EORTC-10981 †	3485 1394 SN+ve 2091 SN-ve	Compare the regional control of the axilla obtained by complete axillary lymph node dissection vs axillary radiotherapy in sentinel lymph node-positive women with operable invasive breast cancer. Determine whether local and regional axillary control can be obtained without axillary lymph node dissection in sentinel lymph node-negative women. Compare the axillary 5-year recurrence-free survival of these patients treated with these regimens. Compare the morbidity of patients treated with these regimens. Compare the quality of life of these patients treated with these regimens.
	RACS SNAC Trial,	1000	Principal objective of the SNAC trial is to determine whether SNB (with ALND only if the SNB specimen is positive) results in less morbidity than immediate ALND and produces equivalent cancer-related outcomes for women with early breast cancer. The trial compares (1) axillary morbidity; (2) observer ratings and self-ratings of arm swelling, symptoms, and function; (3) axillary recurrence rates; (4) other aspects of quality of life; (5) overall survival and disease-free survival (local, distant, and both); (6) use of adjuvant therapies; and (7) number of surgical episodes and total number of days in hospital.
	ALMANAC		planned axillary surgery to either have SLNB or standard treatment. The primary endpoints of the study are axillary morbidity and quality of life, but the study also compares health economic issues between the different procedures. With longer follow-up, the study will also address the issue of axillary recurrence
	AMAROS	3400	Phase III trial to assess treatment of the axilla. Principal aim of the trial is to assess morbidity between surgery and radiation to axilla. A secondary endpoint will be morbidity after SLNB only.
COLON CANCER	**RPCI-DS-96-57 ‡**	10	Confirm that injection of isosulfan blue into the mucosa or serosa immediately adjacent to a colorectal cancer results in the lymphatic transport of that agent initially to a specific regional lymph node that can readily be identified on visual inspection, dissected, and histologically evaluated for the presence or absence of metastatic disease.
	MCC-11785, NCI-G00-1780 *	10	Determine the feasibility of lymphatic mapping and sentinel lymph node biopsy in patients with stage I, II, or III colorectal cancer. Evaluate technetium Tc 99m sulfur colloid as a mapping agent in this patient population. Identify patients with histologically negative nodes but have positive nodes on further detailed examination
LUNG CANCER	**CALGB-140203 †**	57-150	Determine the feasibility and accuracy of intraoperative sentinel lymph node mapping using technetium Tc 99 sulfur colloid in patients with stage I non-small cell lung cancer. Determine the percentage of patients in which at least 1 positive sentinel lymph node is identified using this procedure. Determine the percentage of patients undergoing this procedure who are found to have positive sentinel lymph nodes with no metastases in other intrathoracic lymph nodes.

MELANOMA	**UAB-9735 ***	3000	Compare the efficacy of regional lymphadenectomy with or without adjuvant high-dose interferon alfa-2b on disease-free survival and overall survival of patients with invasive cutaneous melanoma with early or submicroscopic sentinel lymph node metastasis detected by histology or immunohistochemistry or by polymerase chain reaction (PCR). Compare the effect of lymphadenectomy vs observation on disease-free survival and overall survival of patients with submicroscopic sentinel lymph node metastasis detected only by PCR. Determine the recurrence rate and survival of patients with submicroscopic sentinel lymph node metastasis detected only by PCR. Determine the positive and negative predictive value of reverse transcriptase PCR analysis of sentinel lymph nodes and peripheral
	UCCRC-9308 §	30	Determine the feasibility of performing reverse transcriptase-polymerase chain reaction (RT-PCR) for five different tumor antigen genes using lymph node samples or peripheral blood from patients with melanoma. Determine the ability of PCR-positive lymph nodes or peripheral blood to predict relapse of disease in these patients. Determine the correlation of positive PCR results from peripheral blood with disease stage.
	UVACC-MEL-38 †	56	Compare the effects, specifically on cells at and around the tumor site and in the lymph node that drains the tumor, of sargramostim (GM-CSF) alone vs Montanide ISA-51 alone vs GM-CSF and Montanide ISA-51 vs placebo in patients with stage I or II melanoma
	MSLT I & II	3500	Determine whether SLN mapping followed by completion lymphadenectomy (CLND) is superior to SLN mapping alone in patients with evidenceof metastases in the SLNs by histopathological or molecular techniques. Follow-up of patients in MSLT-I, which has completed accrual, will determine whether there is a survival benefit of CLND for all patients who have histopathological evidence of micrometastases in the SNs at the time of LM/SL.
	SUNBELT MELANOMA TRIAL	3000	Prospective randomized trial to evaluate the role of lymph node dissection and adjuvant interferon alfa-2b for patients with early lymph node metastases.
GYNEC CANCERS	**GOG-173 †**	40-630	Determine the negative predictive value of a negative sentinel lymph node in patients with invasive squamous cell carcinoma of the vulva. Determine the location of the sentinel node in these patients
	GOG – 0206 †	295-590	Determine the sensitivity of the sentinel lymph node in the determination of lymph node metastases, using combined preoperative and intraoperative lymphatic mapping, in patients with stage IB1 cervical cancer. Determine the false-negative predictive value of the sentinel lymph node in the determination of lymph node metastases in these patients.
HEAD & NECK CACNCERS	**NYU – 9917 NCI-G01-1915 ‡**	25	Evaluate the sensitivity of lymphoscintigraphy and isosulfan blue in localization of sentinel lymph nodes in patients with previously untreated squamous cell carcinoma of the oral cavity or oropharynx. Determine evidence of micrometastases in histologically normal sentinel lymph nodes resected from these patients. Assess the clinical significance of micrometastases in lymph nodes resected from these patients.
	ACOSOG-Z0360†	161	Determine whether a negative hematoxylin and eosin finding from the lymphatic mapping and sentinel node lymphadenectomy procedure accurately predicts the negativity of the other cervical lymph nodes in patients with stage I or II squamous cell carcinoma of the oral cavity. Determine the extent and pattern of disease spread in the nodal bed in these patients. Obtain data on the use of immunohistochemistry to assess nodes in these patients

* No longer recruiting patients, † Currently recruiting patients, ‡ Trial completed § Trial suspended

macrometastasis within the SLN were both independent predictors of non-SLN involvement (143). Risk categorization has also been attempted. Low-risk groups include patients who have T1 primary tumors plus SLN micrometastases and patients who have T2 tumors without lymphovascular invasion, plus SLN micrometastases. They

have less than 10% rate of tumor-positive non-SLNs by H&E. An intermediate-risk group comprises patients who have T1c primary tumors with lymphovascular invasion, plus SLN micrometastases and have approximately 22% rate of tumor-positive non-SLNs by H&E. High-risk groups include any patient with SLN macrometastasis (144). In a recent multivariate analysis of 1228 patients, non SLN involvement was associated with type, size, number of SLN involved, occurrence of peritumoral and perivascular invasion (145). In this study, despite favorable factors, non SLN involvement was about 13%. Due to this and other factors, at present ALND is advised outside trials when SLN is metastatic (146).

With SNB being successful, newer areas in breast cancer are being tested. A number of areas are considered contraindications for SNB (147). When each of them is analyzed separately, it becomes clear that some of them are relative contraindications while some are not actually contraindications. Clinically positive axilla could have path metastatic nodes and hence lymph channels of the node could be blocked. This could result in the actual SLN not being identified. A recent study points out that clinical exam of axilla is inaccurate in 30% of cases. After evaluating such patients, they suggest that if palpation combined with image guided needle aspiration is negative SNB could be attempted (148). However SNB is contraindicated at present in the setting of a palpable axillary node. Traditionally SNB is not attempted in a patient who has received neoadjuvant chemotherapy. However, preliminary report supports the use of SNB. SLN mapping has been performed in patients receiving preoperative chemotherapy for breast cancer with successful identification in 86% (149, 150). More data is required before SNB can be applied for all patients receiving neoadjuvant chemotherapy. When tumor size is considered, most studies have been performed for T1 tumors. However studies on T1 versus T3 show no difference as long as the axilla does not harbor a palpable node and SNB can be technically performed (151, 152). Tumor multicentricity is considered by many as a contraindication for SNB. Most areas of breast were thought to drain into subareolar plexus based on fetal studies. The current thinking is that most areas of the breast drain straight to the nodal basin which is the axilla in majority of the instances. A small study indicates success with SNB in the setting of multicentric disease showing greater than 97% identification rate and a 0% false negative rate (153). Although preliminary data suggests that SNB could be useful larger studies required. By definition, ductal carcinoma in situ (DCIS) should not harbor axillary nodal metastasis. However, as it is impractical for the pathologist to see every area of the tumor, small foci of invasion could be missed. In such situations, like those with large mass suspicious of nodal disease SNB can be useful (154). Isosulfan blue is not tested and should not be used in pregnancy. Lymphoscintigraphy with technetium can be done with low radiation exposure (155). While no age is contraindication for SNB, it is more difficult in women older than 50 (92, 100, 156, 157). A controversial area is the applicability of SNB by injecting dye into the walls of the biopsy cavity in patients who have undergone lumpectomy. If biopsy was performed prior to SLND, dye is injected into the breast parenchyma adjacent to the biopsy cavity (32). The surgical procedure can undoubtedly disrupt the local lymphatic anatomy and particularly when a large tumor has been removed. SLN identification may prove difficult and there is some evidence to suggest that larger excision biopsies are associated with a higher rate of false negative results (158). Contradicting this, studies have shown no significant affect on SNB after excision biopsy of breast lump (159). Previous biopsy is no longer a contraindication. Two multi-institutional studies have shown SNB is successful in these patients (156, 157). Prior axillary surgery is said to be a contraindication to SNB because lymphatics draining the breast are disrupted and successful axillary lymphatic mapping is not possible. One small study showed SLN were identified in 75% of patients overall, but in 100% of those whom had recently undergone axillary surgery for breast cancer (160). More data is required before any conclusions are reached. Prior radiation to axilla or breast is also considered a contraindication for SNB.

Detection of micrometastases in sentinel nodes and bone marrow may provide more information, but the clinical significance still needs to be confirmed by ongoing large trials. Possibility of SNB or detection of bone marrow micrometastasis replacing traditional axillary lymph node dissection is being evaluated by trials (161).

Despite the enthusiasm of some practitioners, evidence for its safety and benefit has not yet been generated by large multicenter randomized trials. SNB has been accepted without evaluating the main end point – overall survival. Reports suggesting that there is no increase in axillary recurrence is reassuring for small tumors of 2cm or less (162, 163). The study also showed that skip metastases are rare. The accuracy was 96.9% with false negative of 8.8%. In addition, it raised the issue that the possibility of occult metastasis would never become clinically evident if the axilla is left intact.

3.13.2. Melanoma

ELND procedures for melanoma have now been abandoned in all major melanoma treatment centers around the world, not only because of the morbidity associated with these procedures but, more importantly, because of the failure of clinical trials to demonstrate any associated improvement in overall survival (164). Overall, the success rate of harvesting the SLN by blue dye alone is 82%, by radioactive mapping alone is approximately 94%, and by a combination method is 98% (30, 165, 166). Information provided by staging that is at least as accurate as that provided by ELND can be obtained by SNB. While the outcome for patients with melanomas no thicker than 0.75 mm is excellent following wide local excision only, about 20% of those with thicker melanomas develop regional lymph node metastases (167). Most of these metastases can be detected in micro stages by SNB and by thorough histological and IHC evaluation of the SLNs. The Augsburg Consensus, summarizing the basic standards for the application of SLN techniques in dermato-oncology was the result of the symposium on SLN in cutaneous

Table 2. Classification of microscopic nodal involvement in melanoma

Earlier classificiation		**Current recommended classification**	
S0	Absence of detectable melanoma cells	S0	Absence of detectable melanoma cells
S1	($1 \leq n \leq 2$ and $d \leq 1$ mm) is a localized peripheral tumor cell deposit	SI	≤ 0.3mm
S2	($n > 2$ and $d \leq 1$ mm) is a more extended or multi-focal peripheral involvement,	SII	0.31-1mm
S3	$d > 1$mm	SIII	> 1mm

'n' is number of melanoma involved SLN slices 'd' is depth of invasion towards centre of lymph node measured with an ocular micrometer from the interior margin of the lymph node capsule

malignancies (168). Standard of SLN evaluation is a pragmatic compromise between diagnostic accuracy and feasibility under routine circumstances. The formalin fixed SLN is cut parallel to its longest axis into 1-mm slices, each of which provides three paraffin sections, one for hematoxylin and eosin and two for IHC with anti-S-100 and -HMB-45. If the node is found to harbor melanoma cells, two morphometric parameters 'n' and 'd' are recorded – table 2. Attempts have been made to evaluate the predictive value of the 'S' classification for the status of regional non SLNs involvement. The frequency of non SLN positivity was zero in SI cases, approximately 20% in SII cases, and approximately 60% in SIII cases. Although this correlation between S classification and non SLN status was highly significant, there was no significant relation between the T categories and non SLN metastases (169). They opined that In SI cases, the need for a completion lymphadenectomy is questionable and should be clarified by a randomized prospective multicenter trial versus SNB alone. In addition, S factor was found to be an independent prognosticator for distant metastasis and survival. In patients with SIII metastases in their SLNs more than 50% of these individuals have additional metastases in non SLNs, and more than 50% develop distant metastases within 5 years (167). SNB is more than a highly sensitive staging tool in melanoma. It is key for the early elimination of a major source of systemic metastasis (170). The most efficient principles of melanoma therapy—early diagnosis and timely surgical removal are thus successfully extended to the regional lymph nodes. Conversely, loco-regional interventions will usually fail when systemic micro dissemination is already underway. This complication, however, appears to be relatively rare if neither the primary melanoma nor the SLN metastases have reached advanced stages (167).

In one study, at median follow-up of 37 months, recurrence (at any site) occurred in 47% of SN-positive patients but only 12% of SN-negative patients. 30% of SLN-positive patients died of melanoma, but only 6% of SLN-negative patients died. Although sentinel lymphadenectomy provides accurate staging and important prognostic information, its therapeutic significance has yet to be determined in clinical trials (171). 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 randomized 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. However, unpublished report of MSLT 1 shows survival benefit for SNB arm. Since only 20% of patients with primary melanoma have SLN metastases, the proportion of patients with primary melanoma who might benefit from early SNB and therapeutic complete lymph node dissection needs to be evaluated. The overall therapeutic benefit from SNB is probably no more than 4% to 7%, depending upon the thickness of the primary melanoma. Therapeutic trials of SNB must be quite large to detect such a small benefit (18).

3.13.3. GIT

It is claimed that lymphatic mapping can identify the SLN(s) that drains a GI neoplasm without adding significantly to the time, cost, or morbidity of the primary surgical procedure (172). In addition, lymphatic mapping can identify aberrant lymphatic drainage, which may alter the extent of resection. The status of the SLN accurately reflects the tumor status of the entire regional node basin in 96% of cases, excluding rectal neoplasms. It must be emphasized that lymphatic flow from lesions in the GI tract is complicated and multidirectional (173) and this complicates the concept, study design, evaluation and interpretation of SNB. Focused examination of the SLN based on serial sectioning and IHC further increases staging accuracy. The value of such a procedure is as yet not defined. Application of SNB in gastrointestinal tumors must be confined to investigative protocols at present.

3.13.3.1. Esophagus

The SNB concept seems to be applicable according to recent reports (174-176). A dye-guided method is not applicable for esophageal cancer because of its anatomical situation. It is impossible to trace the flow of blue dye without destruction of the lymphatic network. As the esophagus extends from neck to abdomen, lymphoscintigraphy appears essential and dye method would appear less useful. Another issue which needs to be addressed is the fact that unlike breast cancer, sampling of multiple sentinel nodes across the length of esophagus is not a minimally invasive procedure. At present, performing a local resection when sentinel nodes are negative does not seem practical. Individualized selective nodal dissection based on sentinel node appears more reasonable approach and if found useful could replace the three field lymphadenectomy which is being uniformly applied to all esophageal cancers (177).

3.13.3.2. Stomach

Sentinel node mapping for these tumors was pioneered in Japan because of the high prevalence of gastric and esophageal cancers in Asia. The application of this technique, especially in early gastric cancer as seen in

Japan, has led to the use of sleeve resection with selective lymphadenectomy in SLN negative patients. This has drastically altered the paradigm of gastric cancer surgery from radical lymphadenectomy to minimally invasive gastric surgery (178). The success of mapping of SLN has ranged from 94% to 100%, with false negatives ranging from 8% to 18% (179). 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.

3.13.3.3. Hepatobiliary and pancreatic

Nodal metastasis in hepatocellular carcinoma is a rare and late event. It is unlikely that SNB would be useful in this situation (177). For pancreatic cancer, a dye method has been used to demonstrate that the sentinel nodes are situated posterior pancreaticoduodenal area and have even recommended para aortic dissection based on this technique (180).

3.13.3.4. Colorectal

The extent of surgery in colorectal cancers is primarily defined by the location and size of the primary tumor. Hence the identification of SLNs would not initially influence the extent of surgery. But a more detailed histological approach to those nodes that are the most likely sites of metastases would be feasible (181). It was initially thought that these small metastatic foci in the nodes were missed on routine histopathology and was the cause of treatment failure in a significant proportion of node negative tumors (181, 182). The nodes classified as pericolic, intermediate and principal based on anatomic concept of nodal spread is not true for all cases. Radioguided or dynamic dye guided studies with immediate identification of the SLNs are the optimal methods and the procedure is satisfactory in early disease. Skip metastasis where the principal or apical node harbors metastatic disease in absence of pericolic or intermediate nodal involvement is reported in up to 10% of patients (183, 184). In addition to skip metastasis, nodal metastases have been reported in locations outside the traditional field of resection. These nodal metastasis have been reported in nodes at splenic flexure for a right colonic disease (185, 186) and larger series suggest 4% to 8% of unexpected nodal drainage (182, 187). These findings could alter the surgical plan. However certain other issues need to be resolved. Serial sectioning and IHC leads to upstaging of disease in 7% to 33% and the value of such micrometastasis is uncertain with some reports claiming it to be good and others bad prognostically (188). It is still not clear whether or not SNB with a targeted intensive pathology assessment can lead to greater insight into the biological relevance of micrometastases and isolated tumor cells. Currently, there are unacceptably high false negative rates, despite some optimistic results. Contradicting reports of usefulness of SNB in colonic cancer are reported by two multi institutional trials. One concluded that that SLN sampling in patients with colon cancer is not useful as a means of determining the optimal extent of lymphadenectomy or facilitating the examination of micrometastatic disease while the other claimed that the procedure is simple, cost effective, and upstages about 14% of colonic cancers (189, 190). From the above discussion it is apparent that while SNB can reduce the extent of regional lymph node dissection in breast cancer and melanoma, the primary purpose of SNB in colorectal cancer is to upstage tumors whose metastasis would remain undetected by conventional pathological means. It is still controversial whether SNB in colon yields this desired result.

For rectal cancer, radio-guided method is essential because the anatomical situation is the same as esophageal cancer (191). Preoperative scintigraphy is also essential for mapping in rectal cancer. In particular, 10% of the cases with lower rectal cancer showed sentinel nodes in the lateral area. There is a risk of aberrant distribution of sentinel nodes beyond the extent of total mesorectal excision. Node mapping with scintigraphy is useful for effective sampling of sentinel nodes in unexpected areas and for accurate staging without extensive lymph node dissection (177).

A refining of work up of anal canal cancers by SNB has been proposed. Inguinal nodal metastasis was detected in 42% of these cases and IHC was useful to detect two of them. A decision on irradiating the inguinal area could be planned based on SNB (192).

3.13.4. Head and neck

One of the most crucial management decisions in head and neck as in any other area is the absence or presence of nodal metastasis for the purposes of staging, treatment, and prognosis. Traditionally, patients with metastatic neck nodes have been treated by neck dissection. For patients with no metastasis detected in the neck (N0) the neck is generally addressed with an elective neck dissection (END) when the chances of metastasis exceed 15% to 20% (193). When the neck is N0, END stages and prognosticates. In addition, if the neck nodes harbor metastasis, END is also considered therapeutic. A SNB assisted END determines tumors with bilateral drainage and targets the SLN. Additional pathological study like the IHC may be performed apart from routine studies. This would perhaps be the most accurate assessment of the neck. A further step is to evaluate whether SNB alone without END is adequate if SNB is negative. A multi-centre study on the applicability of SNB for head and neck cancers with N0 status showed that the technique is feasible for oral cavity and oropharyngeal cancers (194). Another recent 10 year study shows that it SLN mapping is feasible in head and neck (195). At present SNB technique is difficult and less sensitive for floor of mouth cancers. SNB upgrades nodal pathology in the neck in about 44% and the technique holds promise (196, 197). SNB has not yet been demonstrated to possess the same level of utility seen in SNB in melanoma and breast cancer patients. As a consequence, the application of SNB to head and neck cancers remains an experimental technique—one which has not yet acquired the status of the standard of patient care (198).

3.13.5. Gynecology

Sentinel nodes have been identified for vulvar cancers with an accuracy of near 100% by the combined

Table 3. Comparison of plus and minus of SNB

Possible Advantages	Concerns
Provides a minimally invasive way to detect nodal metastases, thus defining a group of node-negative patients who may be spared radical lymphadenectomy	Frozen section has mixed results. Requires experience. Addition of IHC enhances positivity. Tissue loss occurs at IHC. Procedure takes long time. Requires second surgery in false negatives
May provide earlier recognition of nodal metastases compared with clinical or radiological assessment and thus facilitate therapeutic lymphadenectomy because of lower volume of disease.	There is concern about 'false negatives'. Some inherent failures are known. Procedure applicable only when consistent low false negatives are recorded
Is likely to improve the accuracy of staging, both because of the opportunity to detect sentinel nodes located outside of conventionally defined lymph node basins and also because of our ability to detect micrometastases by thorough evaluation of the sentinel node.	Second surgery is required if SNB is positive
It may improve the accuracy, interpretability, and comparability of cancer clinical trials because of the ability to define more homogeneous trial groups.	There is a well defined learning curve. This includes training of multidisciplinary team. Another concern would be the cost.
It provides a new and powerful tool for examining the biology of lymphatic metastasis.	There are no guidelines on adjuvant therapy for micrometastases detected on SNB
	Other nodal areas – like internal mammary when found raises more questions than answers
	Radiation exposure for the team
	Long term effects of SNB – trial results awaited
	Definition of a sentinel node itself is controversial (per-op identification)
	Morbidity of SNB itself if the nodal basin does not harbor metastasis

dye and isotope method with a negative predictive value of 100% (199, 200). For cervical cancers, the idea is to offer surgery for sentinel node negative and radiochemotherapy for node positive cases after detection by laparoscopy. A mean negative predictive value of 97% and a false negative of 3% to 11% has been reported (200). There is very little evidence of SNB for endometrial cancer and in those blue dye was used.

3.13.6. Sarcoma

Majority of sarcomas metastasize hematogenously and hence SNB evaluation has not been investigated. Regional nodal metastasis can occur in 3% to 10% of patients with localized disease (201). The overall incidence of nodal metastasis is quite low and confined to certain high grade and pathologic sub-types like rhabdomyosarcoma, epitheloid sarcoma, clear cell sarcoma, synovial sarcoma and some vascular sarcomas (201). Hence in a vast majority of cases do not merit SNB. In addition, apart from the general unanswered questions of SNB, the prognostic information obtained from nodal involvement of these sarcomas and the benefit of adjuvant systemic therapy in these patients is less clear than for other malignancies (138).

3.13.7. Lung

Studies on the lung with SNB have been performed for both primary and even for metastasis (202). Unlike in breast and melanoma the idea of SNB is not primarily for limiting the morbidity of nodal dissection. An important potential role may be directing pathologic examination to specific sentinel nodes and applying more sensitive techniques on a limited amount of tissue to detect occult micrometastatic disease. With the sentinel node procedure, non small cell lung cancers were upstaged 5.5% (203). Studies have used dye and or radioactive isotope either pre or intraoperative (204-206). Although the sentinel node technique may not ever be used to distinguish patients who require a full mediastinal node dissection from those in whom a sampling or no dissection is adequate, the information gained from mapping the nodal drainage of each tumor will blur the lines between N1 and N2 disease, calling for reconsideration of the staging of single-site skip-pattern metastases (203).

3.13.8. Thyroid

Preliminary studies indicate an detection rate of 96%, sensitivity of 90% and accuracy of 95% suggesting that it may discriminate between true node negative and those with non palpable metastasis (207, 208). However, the significance of occult metastasis in thyroid is controversial with an argument that many may not be clinically significant. The value of SNB in thyroid remains unresolved.

3.13.9. Urologic

The feasibility of SNB for penile, urinary bladder and prostatic cancer has been evaluated (209-212). Occult nodal metastasis has been detected with a sensitivity of 80%. The significance of SLN method to detect metastasis outside the obturator fossa needs to be evaluated in bladder cancers. It could probably facilitate proper patient selection for radical prostatectomy in future if the procedure is standardized. SNB for penile cancers may lead to a more

accurate staging and avoid morbidity of groin dissection in SLN negative patients. A recent report indicated a false negative rate of 16%(213).

3.14. Advantages and concerns in SNB

In a clinically node negative patient, SNB offers certain distinct advantages (39). There are some advantages, some disadvantages and some unanswered questions about SNB. The possible advantages of SNB along with certain unanswered areas and certain negatives of SNB are listed in table 3. Another endpoint in evaluation of SNB is the quality of life (QOL). In a prospective study in breast cancer, QOL was evaluated (214). It showed that patients recovered sooner after SNB compared to ALND. Arm pain was significantly less at 36% compared to 68% after ALND. Numbness was reported in only 4% as against 19% after ALND. In another study, arm morbidity was lower with SNB (215).

4. PERSPECTIVE

Involvement of nodes in malignancy is one of the very important prognosticators. With increasing awareness and advances in the field of diagnosis, cancers are being detected in clinically early stages. Many such patients are detected when the nodes are clinically not involved. Traditionally these nodes were addressed by ELND when the chance of harboring metastasis was considered significant. This would result in over treatment of 50% to 80% of patients. The problem of nodal dissection included morbidity associated with such surgeries. In addition, for melanomas situated in midline and around umbilicus, there could be multiple nodal basins where the tumor could drain resulting in difficulty to plan therapy. SNB is an *in vivo* assessment of tumor spread. The combination procedure using dye and radiocolloid is well established for breast and melanoma. The initial objective in melanoma was to define the nodal basin and then identify the SLN. With its success in melanoma, the procedure gained acceptance in breast around the same time. In these malignancies, the morbidity of nodal dissection in a large group could be avoided if SNB is negative. When positive, the prognostic information provided by ELND can be obtained by the SNB alone. With success of the procedure, additional benefits were identified which included focused pathology on these nodes with detailed step sectioning, IHC and probably by molecular markers. This benefit is the focus of SNB being applied to other solid tumors. Another surprising development has been the identification of nodes 'outside' the defined nodal basins for a particular organ or site. This has resulted in re-writing the surgical anatomy of the lymphatic drainage.

SNB results in avoiding the morbid nodal dissection for breast cancers and melanomas if it is negative. There are some studies which are attempting to predict non-SLN metastasis and thereby avoid SNB even in some sub-categories of SNB positive patients. Admitting that the procedure holds a lot of promise and excitement, evidence is still lacking to permit its general usage. If node is the only site of metastasis and such macrometastatic node is resected by SNB then this should result in a cure. Then is SNB a curative modality for very early disease? At the other extreme is the question whether this improves the survival. At present, we do not have answers for both. We have to await the results of the ongoing trials before any recommendations are made. Another new area which we have ventured into is the detection of occult and micro-metastasis in the nodes. Many of the new detections could be with IHC or with molecular techniques. The clinical importance of such metastasis is unknown. Hitherto adjuvant therapy was planned based on hematoxylin and eosin studies. Planning of adjuvant therapy based on these results would the challenge for the future. In a small but significant number of patients, nodes outside the defined basins are identified by SLN techniques. A positive outcome is that the surgeon could address these areas at surgery. But whether such a procedure benefits the patient remains unanswered.

In conclusion, 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 randomized clinical trials are available. In the case of breast cancers and melanoma, SNB alone could be adopted in experienced hands who have consistently demonstrated low false negative rates. Others need to pass through the learning curve and till such time must complete the nodal dissection. SNB in the rest of solid tumors is investigational. Abandonment of nodal dissection or planning therapy shall not be based on SNB in these organs.

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