

## Techniques that accurately identify the sentinel lymph node in cancer

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### Abstract

Sentinel lymph node (SLN) biopsy has become the gold standard for patients with melanoma and breast cancer but its clinical application in other solid tumor types such as cancers of the esophagus, stomach, colon and rectum, head and neck, penis, uterine cervix and endometrium has been somewhat limited. Commonly used mapping techniques utilizing the combination of radiocolloid and blue dye may result in reduced SLN detection and increased false negative rates when applied to cancers with more complex lymphatic drainage patterns. Novel localization techniques including

near infrared fluorescence, high resolution imaging and molecular targeted agents have been developed to address the limitations of conventional SLN detection practices in many solid tumor types. This article reviews the indications, techniques and detection rates for SLN biopsy in several different solid tumor types as well as the promising novel techniques created to address the contemporary limitations of this procedure.

**Key words:** Sentinel lymph node biopsy; Carcinoma; Radionuclide; Blue dye; Techniques; Imaging

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**Core tip:** Novel localization techniques including near infrared fluorescence, high resolution imaging and molecular targeted agents have been developed to address the limitations of conventional sentinel lymph node (SLN) detection practices in many solid tumor types. This article reviews the indications, techniques and detection rates for SLN biopsy in several different solid tumor types as well as the promising novel techniques created to address the contemporary limitations of this procedure.

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### THE SENTINEL LYMPH NODE: PAST AND PRESENT

The modern understanding of cancer metastasis from primary tumors to regional lymph nodes originated from the observations of anatomists and pathologists. In the mid-19<sup>th</sup> century, Sappey illustrated breast

lymphatics travelling in the subareolar plexus towards the axilla *via* lymph collecting vessels<sup>[1]</sup> forming the theoretical basis of the subareolar injection of dye and isotope in the contemporary sentinel lymph node biopsy (SLNB). In 1860, Virchow<sup>[2]</sup> observed that an axillary node in breast cancer can be diseased for a long period of time without affecting adjacent nodes or distant organs. He postulated that node functioned as a filter that did not permit harmful particles to travel systemically until the node's barrier function had become insufficient or the node itself had become a new source of independent metastases<sup>[2]</sup>.

One of the first operations based on knowledge of the lymphatics and importance of regional lymph node status was the radical mastectomy, thought to effectively control the orderly, translymphatic contiguous extension of tumor<sup>[3,4]</sup>. Radical operations for rectal, uterine, pancreatic, colon, stomach, and lung cancers adopted the same principle of removing the primary tumor, the organ from which it arose and regional lymph nodes en bloc<sup>[5-8]</sup>. Even early operations for melanoma described removal of the primary tumor, the regional lymph nodes and a long strip of contiguous skin and subcutaneous tissue thought to contain the lymphatics<sup>[9]</sup>. The morbidity of these resections drove surgeons to consider less invasive operations based on increasing knowledge of lymphatics and cancer metastasis<sup>[10]</sup>.

Cabanas, an American-trained urologist, recognized the devastating complications of inguinofemoral lymphadenectomy for the treatment of penile cancer and devised an operation based on the identification and evaluation of the first echelon node draining the penis. By injecting contrast material *via* the dorsal lymphatics of the penis<sup>[11]</sup>, he was able to reliably identify the first lymph node to drain the primary tumor, which he termed the "sentinel lymph node (SLN)". If the SLN was negative for cancer, it followed that cancer had not metastasized to the locoregional nodal basin and the patient would not benefit from inguinofemoral iliac dissection.

The sentinel node era continued to move forward by animal and human studies designed to explore the mechanisms of metastasis. The function of lymph nodes in the spread of cancer was investigated by injection of small particles into afferent lymphatics of animal models<sup>[12-15]</sup>. Observations from these experiments contradicted both the "filter function" postulated by Virchow and the Halstedian model of contiguous cancer spread, giving rise to new understandings and differing hypotheses of SLN function<sup>[16]</sup>. Fisher and Fisher observed that the node was not a "filter" that prevented dissemination of tumor cells but that metastatic disease in the lymph node was a "marker" for the presence of systemic disease<sup>[13-15]</sup>. Hellman proposed locoregional metastasis to be on a "spectrum" of the disease process that was relative to growth and progression of the primary tumor<sup>[17]</sup>. The subsequent "incubator" hypothesis described by Morton considered the unique immunologic interrelationship between the tumor and

host, suggesting immunosuppressive factors released by the primary tumor allow for the growth and cloning of tumor cells in the SLN until the tumor reaches a critical mass, allowing it's movement to upper eschelon nodes or systemic dissemination<sup>[18]</sup>. By the 1990's, the SLNB had become a valid technique in staging malignant tumors of the skin and breast<sup>[19-23]</sup>.

Accurate identification of the SLN documenting presence of occult regional node metastasis has helped to avoid complete lymphadenectomy in certain patients and may allow upstaging in others. The ideal tracer for SLN identification and lymphatic mapping should be standardized, easily acquired, require minimal preparation, nontoxic, have prompt translocation into the peritumoral lymphatics with reliable rate of travel, be taken up into the first encountered lymph node (SLN) in high amounts with high retention without lingering of radioactive signal in the primary injection site, creating a high signal to noise ratio and minimal "shine through"<sup>[24,25]</sup>.

This ideal tracer does not yet exist, but knowledge of the size and chemical characteristics of clinically available agents can be used to optimize intraoperative, preoperative or postoperative use. Small sized contrast agents (< 5-10 nm) have fast uptake into the lymphatics, leaving only a brief window of SLN visualization before diffusion into upper eschelon nodes occurs. Medium sized agents (50-200 nm) have a slower transport rate through lymphatics but provide a longer imaging window. Larger particles (> 500 nm) tend to migrate very slowly after having been taken up by macrophages and dendritic cells<sup>[26]</sup> (Table 1).

This article will review the indications, techniques and detection rates for SLN biopsy in several different solid tumor types as well as the promising novel techniques created to address the contemporary limitations of this procedure.

## MELANOMA

Indications for lymphatic mapping and subsequent SLNB in melanoma continue to evolve based on the recent results of landmark trials. The Multicenter Selective Lymphadenectomy Trial- I was the largest trial to address the role of lymphatic mapping with SLNB in determining prognosis and survival<sup>[27]</sup>. Ten year follow-up results confirmed the role of lymphatic mapping and SLNB guided lymphadenectomy as a prognostic tool that improves disease specific survival compared to observation in intermediate thickness (1.20 to 3.50 mm) and thick (> 3.50 mm) melanomas<sup>[28]</sup>. Current National Comprehensive Cancer Network (NCCN) Guidelines recommend SLN biopsy for melanoma > 1 mm thick or those ≤ 1 mm thick with high risk features including ulceration or mitotic rate ≥ 1 per square millimeter<sup>[29]</sup> (Table 2). The American Joint Committee on Cancer (AJCC) guidelines emphasize lymphoscintigraphy followed by lymphatic mapping and SLNB as important components of melanoma staging that should be used to identify occult stage III regional

**Table 1** Characteristics of common tracers

Blue dyes	<p>Inherent low molecular weight of blue dyes translates into a very rapid migration into and subsequently out of the lymphatics with fairly low SLN retention, relying on surgeon expertise to identify, locate and remove the SLN before the dye spreads to other nodes<sup>[111]</sup></p> <p>Better for localization of superficial lymph nodes</p> <p>Methylene blue (tetramethylthionine chloride, C<sub>16</sub>H<sub>18</sub>CIN<sub>3</sub>S) is a heterocyclic aromatic dye, a member of thiazine dyes<sup>[112]</sup></p> <p>First line of treatment in methemoglobinemias, is used frequently in the treatment of ifosfamide-induced encephalopathy and has applications in the treatment of memory loss<sup>[112]</sup>. Has risk of skin necrosis observed with intradermal injection<sup>[113]</sup>. Excreted primarily in the urine and causes a green-blue discoloration of the urine which can also be observed in saliva and bile that disappears within a few days. Better safety profile when compared to Isosulfan Blue<sup>[114]</sup></p> <p>Patent blue (Isosulfan Blue, Lymphazurin) has a vivid affinity for the lymphatics, with particle size small enough to travel through the lymph vessel but large to be trapped in the lymph nodes<sup>[115]</sup></p>
Radiolabelled colloid	<p>Variable size, from 100-400 nm<sup>[24]</sup></p> <p>Sulphide-based nanoparticles conjugated with Tc-99m are the most commonly used and available<sup>[116]</sup></p> <p>Half life is approximately 6 h<sup>[116]</sup></p> <p>As the radiocolloid emits high energy gamma radiation (140 keV) which is highly penetrating, allowing for its use in variable tissue depth, density and coloration<sup>[116]</sup></p> <p>Gamma detection instruments are needed to localize tracer (hand held gamma probes, gamma cameras, SPECT)</p>
Indocyanine green	<p>ICG is a negatively charged ion tricarboyanine dye belonging to the large family of cyanine dyes</p> <p>ICG fluoresces at about 800 nm and longer wavelengths, confines to the vascular compartment through binding with plasma proteins, has low toxicity and rapid excretion, almost exclusively into the bile<sup>[117]</sup></p> <p>ICG is a low molecular weight contrast agent, and is both rapidly taken up into the lymphatics but also can diffuse from the lymphatics, reducing the local concentrations and contributing to background signal<sup>[116]</sup> and needs to be readministered</p>
Tilmanocept (99mTc, Lymphoseek)	<p>Radiopharmaceutical that accumulates in lymphatic tissues by binding to a mannose-binding protein on the surface of macrophages<sup>[101]</sup></p> <p>The molecule, 99mTc-DTPA-mannosyl-dextran, is composed of a dextran backbone to which multiple units of mannose and DTPA are synthetically attached<sup>[101]</sup></p>

DTPA: Diethylenetriamine pentaacetic acid; SLN: Sentinel lymph node; ICG: Indocyanine green; SPECT: Single-photon emission computerized tomography.

nodal disease among patients with clinical stage I B or II melanoma<sup>[30]</sup>.

### Blue dye

Morton's landmark research validated the clinical use of intraoperative lymphatic mapping for early stage melanoma<sup>[22]</sup>. In his study, patent V blue or isosulfan blue (0.5-1 mL) was injected intradermally with a 25 gauge needle at the site of melanoma, gently massaged and repeated every 20 min throughout the duration of the case. The rate of SLN identification with this technique was 81.8% (194 of 237 subjects) with a false negative rate (FNR) of less than 1% (non-SLNs were the sole site of metastasis in only 2 of 3079 nodes).

### Radiolabelled colloid

Lymphatic mapping was first described with radiolabelled colloidal gold (198-Au) to predict the often ambiguous lymphatic drainage in truncal melanomas. In a pilot study of 57 patients with truncal melanoma, 0.1 mCi of radiolabelled colloid was injected into the dermis of the primary melanoma site and followed by radionuclide scanning a day later. The authors reported no lymph node metastases were found at sites other than those taking up the radiolabeled colloid, providing a promising technique to accurately identify the draining nodal basin of the primary tumor<sup>[10]</sup>.

A recent meta-analysis including 71 studies and 25240 patients demonstrated the proportion of successfully mapped SLN to be 98.1% (95%CI: 97.3%-

98.6%) using scintigraphy with radiolabeled colloid<sup>[31]</sup>. The average dose of radiocolloid was 0.98 mCi.

### Near infrared fluorescence

Recent clinical trials have used near-infrared (NIR) imaging with indocyanine green (ICG) to identify the SLN in melanoma. NIR imaging has high tissue penetration allowing for transcutaneous visualization of the tracer as it migrates from the peritumoral injection site to the regional lymph node basin in real time. Fluorescent lymphangiography using ICG has proven to be an effective method of SLN identification in patients with cutaneous melanoma and when used in combination with radiolabelled colloid, may replace the use of blue dye. In a recent study examining 52 consecutive patients with cutaneous melanoma of the trunk or extremities, rates of SLN detection were 96.2% for technetium-99m sulfur colloid, 59.6% for isosulfan blue, and 88.5% for ICG<sup>[32]</sup>.

### Imaging

Ultrasound relies upon the detection of anatomic changes in nodes with metastatic disease that may not always be apparent until a large nodal tumor burden is present. Loss of the normal fatty hilum and peripheral hypervascularity may indicate presence of nodal metastasis. Ultrasound guided fine needle aspiration performed in the presence of these concerning imaging characteristics increases the sensitivity of ultrasound for the diagnosis of nodal metastasis to approximately 82% with a positive predictive value of 52%<sup>[33]</sup>. In a

**Table 2 National Comprehensive Cancer Network Guidelines for sentinel lymph node biopsy by cancer type**

Melanoma (version 4.2014)	In general, SLN biopsy is not recommended for primary melanomas $\leq 0.75$ mm thick, unless there is significant uncertainty about the adequacy of microstaging For melanomas 0.76-1.0 mm thick, SLN biopsy may be considered in the appropriate clinical context In patients with thin melanomas ( $\leq 1.0$ mm), apart from primary tumor thickness, there is little consensus as to what should be considered "high-risk features" for a positive SLN. Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and LVI, are very uncommon in melanomas $\leq 0.75$ mm thick; when present, SLN biopsy may be considered on an individual basis For melanomas $> 1$ mm thick, discuss and offer SLN biopsy
Breast (version 3.2014)	Performance of SLN mapping and resection in the surgical staging of the clinically negative axilla is recommended for assessment of the pathologic status of the axillary lymph nodes in patients with clinical stage I or II breast cancer. This recommendation is supported by results of randomized clinical trials showing decreased arm and shoulder morbidity (pain, lymphedema, sensory loss) in patients with breast cancer undergoing SLN biopsy compared with patients undergoing standard axillary lymph node dissection. The patient must be a candidate for SLN biopsy and an experienced SLN team is mandatory for the use of SLN mapping and excision Axillary staging following preoperative systemic therapy may include SLN biopsy or level I / II dissection SLN mapping injections may be peritumoral, subareolar, or subdermal. However, only peritumoral injections map to the internal mammary lymph node(s) The performance of a SLN procedure should be strongly considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future SLN procedure In women with a local breast recurrence after breast conserving surgery who had a prior SNB, a repeat SNB may be technically possible. The accuracy of repeat SNB is unproven and the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged The use of blue dye is contraindicated in pregnancy; radiolabelled sulfur colloid appears to be safe for SNB in pregnancy
Esophagus and Esophagogastric Junction (version 1.2014)	No guidelines for SLN biopsy exist
Stomach (version 1.2014)	No guidelines for SLN biopsy exist
Colon (version 3.2014)	Examination of the SLN allows an intense histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. At the present time the use of SLNs should be considered investigational, and results should be used with caution in clinical management decisions
Rectum (version 3.2014)	Examination of the SLN allows an intense histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. At the present time the use of SLNs should be considered investigational, and results should be used with caution in clinical management decisions
Head and Neck (version 2.2014)	SLN biopsy is an alternative to elective neck dissections for identifying occult cervical metastasis in patients with early (T1 or T2) oral cavity carcinoma in centers where expertise for this procedure is available. Patients with metastatic disease in their sentinel nodes must undergo a completion neck dissection while those without may be observed
Penis (version 1.2014)	Dynamic SLN biopsies are recommended only in patients with nonpalpable inguinal lymph nodes treated at tertiary care centers that perform greater than 20 per year
Cervix (version 1.2015)	Consider SLN mapping in stage I A1 (with LVSI), I A2 and I B1 Consider SLN mapping for positive margins or dysplasia or carcinoma on cone biopsy for stage I A1 without LVSI
Endometrium (version 1.2015)	SLN mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration Cervical injection with dye has emerged as a useful and validated technique for identification of LNs that are at high risk for metastasis The combination of a superficial (1-3 mm) and deep (1-2 cm) cervical injection leads to dye delivery to the main layers of the lymphatic channel origins in the cervix and corpus

SLN: Sentinel lymph node; SNB: Sentinel node biopsy; LVSI: Lymphovascular space invasion; LVI: Lymphovascular invasion; DCIS: Ductal carcinoma *in situ*; LN: Lymph node.

feasibility study examining non-invasive staging of melanoma by ultrasound, 325 patients with melanoma underwent preoperative SLN ultrasound before SLN biopsy. Overall, sensitivity of ultrasound was 33.8%, specificity 85.7%, positive predictive value 36.5%, and negative predictive value 84.2%<sup>[33]</sup>. Variable lymphatic drainage patterns and low sensitivity make the routine clinical application of preoperative ultrasound without lymphoscintigraphic localization impractical.

Single-photon emission computerized tomography (SPECT)/computed tomography (CT) is a multimodal imaging technique that combines single photon emission computed tomography with CT. In melanoma, SPECT may allow for greater sensitivity, resolution,

and anatomical localization than conventional lymphoscintigraphy alone, leading to a larger number of metastatic nodes excised (2.40 vs 1.87; 95%CI: 1.93-2.18;  $P < 0.001$ ), decreased local recurrence rates (6.8% vs 23.8%,  $P = 0.03$ ) and prolonged 4-year disease-free survival (93.9% vs 79.2%;  $P = 0.02$ ) in a recent prospective randomized trial<sup>[34]</sup>. SPECT/CT may be of particular value in melanomas of the trunk and head and neck region, where lymphatic drainage is variable<sup>[35]</sup>.

#### **Failure of SLN detection and false negative rates**

Factors that lead to failure of SLN localization in melanoma include inexperience of the surgeon, poor

tracer injection technique or injection away from the biopsy scar, timing of tracer injection, imaging the wrong nodal basin, not imaging all possible nodal basins, and complete replacement of the SLN with neoplastic disease causing the injected tracer to completely bypass the infiltrated node<sup>[22,36,37]</sup>.

The FNR (calculated as number of patients with negative SLN biopsy who recur divided by the number of patients with positive SLN regardless of recurrence combined with the number patient with negative SLN who recur) in a meta-analysis that included data from about 25240 patients in 71 studies was 12.5%<sup>[31]</sup>. Likewise, collaborative groups worldwide have sited relatively high FNR ranging between 5.6% and 21%<sup>[37]</sup>. FNR increased with the length of follow-up ( $P = 0.002$ ) but decreased with greater number of lymph nodes sampled ( $P = 0.001$ ).

### Gold standard

In the meta-analysis mentioned above that included data from about 25000 patients in 71 studies, at least one SLN was extracted in 14481 of 14818 patients, making SLN detection rate approximately 97.5%. All studies in the meta-analysis used scintigraphy, and 89% (63 studies) used blue dye<sup>[31]</sup>. Successful intraoperative SLN identification rates are generally reported to range between 97% and 100%<sup>[38]</sup>, but this number is vastly discordant from the identification rates of the "true" SLN given the high false positive rates reported with melanoma. Most surgeons have adopted the preoperative use of radiolabeled colloid to detect the location of the SLN *via* lymphoscintigraphy and intraoperative use of a hand held gamma probe in conjunction with blue dye for visualization. The combination of techniques may increase the SLN identification rate when compared to a single technique alone but the lack of international guidelines and consensus for preoperative lymphoscintigraphy and intraoperative identification may contribute to the relatively high FNR continued to be reported in melanoma management<sup>[39]</sup>.

## BREAST CANCER

The SLNB has become invaluable in the staging of breast cancer. Although techniques for SLN identification may differ by clinician and institution, the American Society of Clinical Oncology 2014 practice guidelines<sup>[40]</sup> and NCCN guidelines<sup>[29]</sup> be viewed as the evidence based standard of care (Table 2). The SLN biopsy can be offered to women with operable breast cancer who have multicentric tumors, ductal carcinoma *in situ* (DCIS) with simultaneous mastectomy, history prior breast or axillary surgery and to those who will undergo preoperative or neoadjuvant systemic therapy. There continues to be insufficient evidence to recommend SLNB in large or locally advanced breast cancer (T3/T4), inflammatory breast cancer, DCIS when breast conserving surgery is planned and in pregnancy<sup>[40]</sup>.

### Blue dye

The SLNB in breast cancer was pioneered by Guiliano at John Wayne Cancer Institute<sup>[24]</sup>. Applying contemporary techniques used for intraoperative lymphatic mapping of cutaneous melanoma, his landmark paper described using isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Inc., Richmond, VA) to accurately identify the SLN in breast cancer. His technique became standardized to the use of 3 to 5 mL injected in and around the breast tumor with interval wait time of 5 min from injection to exploration. Although a learning curve was observed, the SLN was identified 65.5% of the time (114 of 174 cases) and accurately predicted axillary nodal status in 95.6% (109 of 114 cases). Since its inception, the SLN identification rates with the use of blue dye alone have been reported to be 70%-98%<sup>[41-45]</sup>. Blue dye (methylene blue or isosulfan blue vital dye) is readily available and inexpensive, but the risk anaphylaxis remains a concern. Allergic reaction to the dyes isosulfan blue and patent blue V is rare and the reported incidence varies between 0.07% and 2.7%<sup>[46]</sup>.

### Radiolabelled colloid

The use of radiolabelled colloid in SLN identification was applied to the staging of breast cancer from its use in melanoma. Krag *et al*<sup>[47]</sup> first described the injection of 0.4 mCi technetium sulfur colloid in 0.5 mL saline around the breast lesion and the intraoperative use of a hand-held gamma probe to locate the nodes receiving drainage from the breast. A SLN was identified in 81.8% of consecutive patients (18 of 22) in this pilot study. The availability of radiolabeled colloid has been limited by the cost and departmental infrastructure needed to accommodate its parent isotope. A meta-analysis including over 8000 patients sited overall identification rate of 96% and false negative rate of 7.3% with the use of radiolabeled colloid<sup>[42]</sup>.

### NIR

NIR using ICG creates a real time image penetrable through tissue up to 2 cm, allowing percutaneous visualization of lymphatic channels and has been suggested for SLN mapping and identification. Based on a recent meta-analysis, ICG was shown to be better than blue dye alone but had no difference when compared to radiocolloid alone in terms of improved SLN identification<sup>[48]</sup>. Phase II trials evaluating the accuracy of ICG have demonstrated an increased rate of SLN localization with the combination of ICG and conventional techniques vs blue dye alone. Using both NIR fluorescence and radioactivity, the FNR for SLN mapping was only 1% and the sensitivity of NIR fluorescence for initial localization of SLNs was 98%<sup>[49]</sup>. A multimodal approach of ICG, blue dye and radioisotope vs radioisotope alone demonstrated a significant increase in the average number of SLNs

identified in the multimodal approach group ( $3.4 \pm 1.37$  vs  $2.3 \pm 1.04$ , respectively;  $P < 0.001$ ). Identification of SLNs occurred in all patients (100%) and there were no complications, leading the authors to consider the use of ICG in combination with blue dye and radioisotope safe<sup>[50]</sup>. The use of NIR may compliment the standard of care in SLN detection but head to head randomized control trials and cost analyses are needed.

### Imaging

Imaging modalities including ultrasound (US), US guided SLNB, positron emission tomography (PET)/CT and MRI can identify structural and anatomic atypia in the regional lymph nodes and accurately predict the presence of metastasis in the SLN in breast cancer.

High resolution US is used to identify patients with clinically negative axillae who harbor nodal metastasis and may be candidates for preoperative chemotherapy. Eccentric cortical enlargement, thickening or lobulation, displacement or absence of the fatty hilum, hypoechoic echotexture or round or ovoid nodes are ultrasonographic findings suggestive of nodal metastasis<sup>[51-54]</sup>. In a meta-analysis of 21 studies using axillary US to identify metastasis (4313 patients), mean sensitivity and specificity were 61.4% (51.2% to 79.4%) and 82% (76.9% to 89.0%), respectively<sup>[52]</sup>. The addition of US guided biopsy improved both sensitivity and specificity to 79.4% (68.3% to 89%) and 100%, respectively<sup>[52]</sup>. Pooled data from a 31 study meta-analysis observed a FNR of axillary US with or without image guided biopsy to be 25% (95%CI: 24%-27%)<sup>[55]</sup>. Despite the high FNR, US guided biopsy has become a useful adjunct to the surgical SLN biopsy in the preoperative staging of patients with breast cancer.

A meta-analysis of 26 studies (2591 patients) evaluating diagnostic accuracy of PET or PET/CT in the axillary nodal metastasis, the mean sensitivity was 63% (95%CI: 52%-74%; range 20%-100%) and mean specificity 94% (95%CI: 91%-96%; range 75%-100%). Of 7 studies evaluating PET/CT (862 patients), the mean sensitivity in SLN identification was 56% (95%CI: 44%-67%) and mean specificity was 96% (95%CI: 90%-99%)<sup>[56]</sup>. Despite the application of PET/CT imaging in the evaluation of distant metastasis, evidence suggests that PET-based staging of the axilla in breast cancer is not recommended.

The use of MRI in the evaluation of axillary metastasis is also not supported by current evidence. In a meta-analysis, based on the highest sensitivity and specificity reported in each of the nine studies evaluating magnetic resonance imaging (MRI) (307 patients), mean sensitivity was 90% (95%CI: 78%-96%; range 65%-100%) and mean specificity was 90% (95%CI: 75%-96%; range 54%-100%). Estimates of sensitivity and specificity do not support replacement of SLN biopsy with any current MRI technology in this patient group<sup>[57]</sup>.

### Intraoperative assessment

Measuring intranodal pressure of the SLN and clinical suspicion based on intraoperative palpation has correlated well with the prediction of SLN macro- and micrometastasis in breast cancer<sup>[58]</sup>. The "true SLN" may be firmer and larger than other non-SLNs and highly suspicious for metastasis if it is more round than kidney-bean shaped, larger than usual, firm or matted.

### Failure of SLN detection and false negative rates

Factors leading to the failure of SLN identification include the presence of altered lymphatic dynamics secondary to increased tumor burden in the nodal basin<sup>[59]</sup> and the receipt of preoperative chemotherapy (reported detection rates were 80.1% following chemotherapy)<sup>[60]</sup>. In the ACOSOG Z1071 study, in patients who received neoadjuvant chemotherapy, the use of blue dye alone increased the likelihood of failure to identify the SLN compared to using radiolabeled colloid alone or with blue dye ( $P = 0.006$ ; OR = 3.82; 95%CI: 1.47-9.92). The SLN identification rate in this study cohort was 78.6% with blue dye alone; 91.4% with radiolabeled colloid and 93.8% with dual mapping agents<sup>[61]</sup>.

### Gold standard

The gold standard of SLN identification in breast cancer remains the dual technique of blue dye and radioisotope injection<sup>[48]</sup>. The randomized EORTC AMAROS trial reported a SLN identification rate of 97% (1888 of 1953 patients) for which the majority (1744 patients) had the combined blue dye and isotope technique<sup>[62]</sup>. In the SENTINA trial, the SLN detection rate was 99.1% (95%CI: 98.3-99.6; 1013 of 1022 patients) in patients prior to receiving neoadjuvant chemotherapy<sup>[60]</sup>.

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## ESOPHAGEAL CANCER

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Minimally invasive esophageal resections for cancer have recently been shown to decrease the rate of comorbidities associated with open esophagectomy<sup>[63]</sup>. Prognosis however, remains dependent on extent of lymphatic spread and nodal metastasis<sup>[64]</sup>. The application of the SLNB to esophageal resection might be useful for accurate intraoperative decision making in determining the extent of lymphadenectomy in patients with early stage adenocarcinoma who are high surgical risk or in consideration for endoscopic resection<sup>[65]</sup>.

Accurate identification of SLNs in esophageal cancer is most important in a cancer where direction of metastases is somewhat unpredictable<sup>[66,67]</sup>. The use of radiolabelled colloid (technetium 99m), blue dye and CT lymphoscintigraphy have provided individual detection rates of approximately 97%<sup>[65]</sup>. These tracers are most commonly injected around the tumor with endoscopic guidance. Increased detection rates are seen with smaller, thinner tumors, and adenocarcinoma (when compared to squamous cell carcinoma)<sup>[68]</sup>.

Advocates of the widespread application of SLNB in esophageal cancer site increased ability to tailor and individualize cancer resection. "Ultrastaging" the most important lymph nodes by serial sectioning, immunohistochemistry and/or reverse transcriptase chain reaction, enables the identification of micro-metastatic disease that may guide decision-making in the administration of chemotherapy<sup>[69,70]</sup>.

## GASTRIC CANCER

The widespread application and clinical value of SLNB in gastric cancer is not well established. Gastrectomy with D2 lymphadenectomy remains the standard surgical treatment for gastric cancer worldwide<sup>[29,71]</sup> and a minimum of 15 lymph nodes submitted for pathological analysis has been shown to improve the prognostic ability if the AJCC guidelines to more accurately predict 5 year disease specific and overall survival<sup>[72]</sup>. This resection is not without morbidity, including bleeding, pancreatitis, subdiaphragmatic abscess, lymphorrhea and chylous ascites<sup>[73]</sup>, leading to the application of the sentinel node theory in the management of early stage gastric cancer with the possibility that patients with small primary tumors (T1 or T2, less than or equal to 4 cm), clinically undetectable perigastric nodes (by imaging and endoscopy) with true pN0 gastric cancer may avoid extensive resections.

In a meta-analysis of 26 articles evaluating the FNR of different tracer methods in SLN biopsy in gastric cancer, FNR (defined as number of false negatives divided by number of true positives) were found to be 34.7% (95%CI: 21.2-48.1), 18.5% (95%CI: 9.1-28.0) and 13.1% (95%CI: 0.9-27.2) for blue dye, radiolabelled colloid and a combination of the two techniques, respectively<sup>[74]</sup>. A recent meta-analysis of 38 articles (2128 patients) reported a pooled identification rate of 93.7% (95%CI: 91.1-95.6) with combined tracer methods. Early T stage and submucosal injection resulted in a higher sensitivity but stressed the need for further studies to standardize the procedure and selection criteria<sup>[75]</sup>.

Prospective trials have also demonstrated promising results in SLNB in gastric cancer. A prospective multicenter trial in Japan that included 397 patients with clinical T1N0M0 or T2N0M0 adenocarcinoma of the stomach used a dual tracer method (Technetium 99m labeled colloid and 1% isosulfan blue) to perform SLN mapping<sup>[76]</sup>. On the day prior to surgery, 20 mL of technetium 99m colloid (0.3 mCi) was injected into four quadrants of the submucosal layer of the lesion utilizing endoscopy. Intraoperatively, the gastrocolic ligament was divided to visualize lymphatic flow around the stomach. Isosulfan blue was then injected with the use of intraoperative endoscopy and a hand-held gamma probe was used. SLN detection rate was 97.5%. Pathology revealed four cases of false SLNs that were negative for carcinoma and nonSLN were positive,

three of which were pT2 tumors (> 4 cm). SLNB using ICG has also been described with good detection rates (99.6%)<sup>[77]</sup> but real limitations of this method include the need for multiplanes of visualization, use of imprint cytology and open surgery by experienced surgeons. The JCOG0302 study concluded that the proportion of false negatives (46%) remains too high for the intraoperative "real time" evaluation of SLNs and further improvement on the application of the SLN concept in gastric cancer is needed<sup>[78]</sup>.

## COLORECTAL CANCER

Intraoperative SLN identification techniques have been described in the staging of colorectal cancer but there is no consensus on the application or validity of such practice. Regional lymph-node metastasis represents one of the most important indications for adjuvant chemotherapy in colorectal cancer. The use of blue dye to identify pericolic lymph nodes that would have otherwise been overlooked intraoperatively can provide surgeons with a practical means to improve the staging of node negative patients. Early investigative studies defined SLNs as being those nodes closest to and receiving the most direct drainage from the tumor. When 1 mL of Lymphazurin 1% was injected in the subserosa of the primary tumor circumferentially, the SLN was correctly identified in 98.8% of cases (85 of 86 patients) and may have upstaged 18% of patients from stage I / II to stage III disease<sup>[79]</sup>.

There is no gold standard for this technique, which has been described using different tracers (methylene blue, isosulfan blue, patent blue, technetium 99m, ICG), modes of injection (four quadrant, peritumoral) and stages of surgery (*in situ*, *ex vivo*)<sup>[80]</sup>. A meta-analysis of 1168 patients (912 with colon cancer, 256 with rectal cancer) observed a SLN detection rate of 94% (95%CI: 92-95) with a mean weighted sensitivity of 76% (95%CI: 72-80; range 25-100) and rate of upstaging of 11% (95%CI: 6-22). Because of the potential to improve staging in colorectal cancer and based on the results of this study, the authors suggested that for every patient diagnosed with colon or rectal cancer without clinical evidence of lymph node involvement or metastatic disease, a SLN procedure, in addition to conventional resection, should be considered<sup>[80]</sup>.

## CANCER OF THE HEAD AND NECK

Lymph node status is an important prognostic factor in cancer of the upper aerodigestive tract. It is universally accepted that head and neck squamous cell cancer (HNSCC) with regional metastasis has to be addressed by either surgery with or without adjuvant chemoradiation or by primary chemoradiation, but the management of the clinically node negative neck remains controversial. In 2014, the NCCN guidelines were updated to include the use of SLNB in early (T1/T2) cancers (Table 2)<sup>[29]</sup>. Implementation of SLNB

in clinically node negative disease can potentially spare the morbidity of elective neck dissections and chemotherapy in three-quarters of patients<sup>[81,82]</sup>. In HNSCC, a clinically negative neck must have a negative physical examination and imaging including CT, MRI, ultrasound guided fine needle aspiration, and/or PET or PET/CT according to recent practice guidelines<sup>[83]</sup>. In these guidelines, the SLNB is performed with preoperative lymphoscintigraphy using planar or SPECT/CT followed by intraoperative detection with a portable gamma probe with or without the addition of blue dye. Two recent meta-analyses (1753 patients) examining the diagnostic value of the SLN concluded that SLNB is a valid diagnostic technique with sensitivity of over 90% and detection rates of over 95%<sup>[82,84]</sup>. Lower detection rates and sensitivity, however have been reported in cancers of the floor of the mouth<sup>[85,86]</sup>. SLN should be successfully located in greater than 90% of patients, positive SLN should match that of the observed rate of positive nodes in a formal neck dissections (20%-30%) and rate of false negatives should be < 5%<sup>[81-83]</sup>. Evidence favoring SLNB in T1/T2 HNSCC as a staging tool continues to grow with promising results of trials with longer term follow-up<sup>[85]</sup>.

## PENILE CANCER

Since the landmark work of lymphatic mapping and SLN identification by Cabanas<sup>[11]</sup>, the routine implementation of SLN biopsy in penile cancer still remains in its infancy. NCCN guidelines no longer recommend lymphangiograms due to high reported FNR (over 20%)<sup>[87,88]</sup>. Dynamic SLN biopsies are recommended only in patients with nonpalpable inguinal lymph nodes treated at tertiary care centers that perform greater than 20 of these cases per year<sup>[29]</sup>. This method involves preoperative lymphoscintigraphy by intradermal injection of technetium 99m around the primary tumor and intraoperative use of gamma probe and intradermal blue dye injection. The addition of groin ultrasonography with or without fine needle aspiration preoperatively can potentially identify occult nodal metastases in patients with clinical N0 penile cancer. SLN biopsy alone might miss between 5%-10% of metastases<sup>[89]</sup>. Despite the advent of SLN biopsy in penile cancer leading to decreased inguinal dissection, 5 year disease specific mortality has decreased in clinical N0 disease<sup>[90]</sup>. A recent literature review examining management of inguinal nodes in penile cancer from 1977-2010 concluded that in order to obtain the lowest possible FNRs, performing a SLN biopsy in penile cancer requires urologists, radiologists and pathologists working together as a multidisciplinary team in a high volume center<sup>[91]</sup>.

## CERVICAL CANCER

NCCN guidelines recommend SLN mapping in cervical

cancer for in stage I A1 [with lymphovascular space invasion (LVSI)], I A2 and IB1 and for positive margins, dysplasia or carcinoma on cone biopsy for stage I A1 without LVSI<sup>[29]</sup>. SLN mapping studies have reported greater than 80% of identified SLNs are periliac, contained in the common, external and internal iliac regions<sup>[92,93]</sup>.

Precise detection of the SLN may allow for accurate prediction of pelvic lymph node status<sup>[94]</sup> which is a crucial factor for optimized treatment of cervical cancer. Initial studies using both radiocolloid (technetium 99m injected one day preoperatively in the 3, 6, 9 and 12 o'clock position into the cervix) and blue dye (injected into the same locations intraoperatively) reported SLN detection rates of 78% and established currently used injection protocols<sup>[95]</sup>. SLN detection with ICG seems to have similar detection rates to that of radiocolloid and blue dye<sup>[96]</sup>.

Preoperative SPECT/CT in addition to radiolabeled colloid and intraoperative blue dye has demonstrated better anatomic correlation and improved rates of SLN detection (approaching 100%) compared to planar lymphoscintigraphy<sup>[97]</sup>.

The SENTICOL Study is the largest multi-institutional trial in women with early stage cervical cancer ( I A1 and I B1) who underwent dual tracer guided SLN biopsy (radiocolloid and blue dye) followed by pelvic lymphadenectomy. Detection rates of 97.8% were reported, leading the authors to conclude that SLN biopsy is a highly sensitive and important technique in women with early stage cervical cancer<sup>[98]</sup>.

## ENDOMETRIAL CANCER

Prognosis for endometrial cancer is correlated with lymph node status but complete pelvic lymphadenectomy for all patients regardless of risk is a subject of debate. In a recent multicenter study, SLN biopsy was associated with "ultrastaging" that was helpful in guiding adjuvant therapies<sup>[99]</sup>. Four quadrant cervical injection of technetium sulfur colloid (around the 3, 6, 9 and 12 o'clock) was performed on the day prior to surgery and patent blue dye was injected intraoperatively with a SLN detection rate of 86.4%. In this study, complete pelvic lymphadenectomy was performed in all patients and results recommended the routine use of SLNB in low- and medium-risk patients to guide chemotherapy. The SENTI-ENDO prospective multicenter study also reported the upstaging of 10% of low risk patients and 15% of intermediate risk patients<sup>[100]</sup>. Although it is not the standard of care, implementation of SLNB and subsequent "ultrastaging" in endometrial cancer may lead to more individualized treatment options for these patients.

## DISCUSSION

The SLN biopsy created a paradigm shift away from

invasive, morbid surgical resections and towards more individualized care. Despite the increased use of SLNB in different solid tumor types and improvement in techniques, failure or false detection of the true SLN can still result in poor locoregional control and decreased survival. Further understanding of the molecular mechanisms of lymphatic metastasis has led to the creation of novel tracers and mapping techniques.

Protein receptors on the surface of lymphoid cells have become promising targets in SLN identification. Tilmamcept (99mTc, Lymphoseek) is a synthetic radiotracer that relies on carbohydrate moieties to target the CD206 receptor on the surface of macrophages and reticuloendothelial cells in lymphatics. It has demonstrated highly concordant SLN detection rates compared to traditional tracers<sup>[101-103]</sup> and was recently approved by the Food and Drug Administration for SLNB<sup>[104,105]</sup>. Gold nanoparticles bioconjugated anti-CD45 antibodies demonstrate high affinity for CD45 expressing cells in the lymph node, have rapid lymphatic uptake and significant retention in the nodes after 6 and 24 h<sup>[106]</sup>. The increased binding, uptake and retention of these new immunotracers may allow for their use in solid tumors that are in close anatomical proximity to their SLN or in those tumors with unpredictable or multiple nodal drainage patterns.

Novel imaging techniques have been studied to increase the *in vivo* detection rates of the SLN as well. The use of intradermally injected microbubbles containing sulphur hexafluoride gas and high resolution contrast enhanced US have allowed for real time identification of lymphatic channels that can be traced up to the draining nodal basin. This technique has been shown to facilitate accurate SLN identification and targeted SLNB in pre-operative breast cancer patients<sup>[107]</sup>. The use of MRI with peripherally injected iron oxide nanoparticles has been shown to successfully identify the SLN but has failed to gain wide acceptance in clinical practice<sup>[108,109]</sup>.

US-guided spectroscopic photoacoustic imaging of molecularly activated plasmonic nanosensors can detect lymph node metastasis as small as 50 microns with high sensitivity in animal models, suggesting promising clinical applications for the detection of SLN micrometastasis in the future<sup>[110]</sup>.

As more is known about the unique molecular identity of the SLN itself, the peritumoral and intervening lymphatics, and the cells involved in lymphatic metastasis, tracers can be formulated to identify and irreversibly bind those unique biochemical targets, allowing for more accurate identification of the SLN and ultimately, patient individualized SLN guided lymphadenectomy in more solid tumor types.

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