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Sentinel lymph node biopsy in oncologic care: a review

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ABSTRACT

Sentinel lymph nodes (SLNs) have for centuries been recognized as reliable and effective filters of foreign material, including tumor cells. Since the mid-20th century, this principle has been applied to oncologic care through sentinel lymph node biopsy (SLNB), which detects and quantifies the extent of regional metastasis. First pioneered in parotid tumors, the technique has since expanded to many branches of oncology including breast, melanoma, head and neck, gastrointestinal, and gynecologic tumors. Across these varied pathologies, SLNB has repeatedly demonstrated non-inferiority to traditionally more extensive lymphatic dissections, which are associated with higher rates of infectious, lymphatic, and neuropathic complications. In an era of ever-increasing management options, this technique also provides prognostic and predictive information key to therapeutic selection. This paper reviews the history of the practice of SLNB and its evolution over the decades in a number of oncologic disciplines.

Keywords: Sentinel lymph node biopsy, scintigraphy, breast cancer, melanoma, oncology.

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History

The sentinel lymph node (SLN), the first lymph node reached by metastasizing tumor cells, can be biopsied as a minimally invasive technique to pre- or intra-operatively identify patients with occult regional metastasis. The technique of sentinel lymph node biopsy (SLNB) was first applied by Gould et al. [1], when a certain lymph node at the junction of the anterior and posterior facial veins was by chance observed to contain metastasis even in benign-appearing primary tumors. The technique was left largely unexplored for several decades, until Chiappa et al. [3] and Cabanas et al. [2] identified the SLN for testicular and penile cancers, respectively. The validity of SLNB relies on two key principles. The first is anatomical, and has been described since Scientific Revolution anatomists such as Gassendi and Bartholin mapped the course of the lymphatic system; primary tumors in a given location drain in a reliable and predictable fashion to regional lymph nodes [4,5]. The second principle is physiologic, and dates to Rudolf Virchow's observation that a sailor's tattoo ink was retained in a local lymph node at autopsy: the SLN is an effective filter for infiltrating tumor cells [6]. Despite this strong foundation, anatomic variation in lymphatic drainage patterns between individuals severely limited

the applicability of a traditional single biopsy approach. Unlike in parotid or genital tumors, where the available primary sites and lymphatic drainage pathways are few, the diverse lymphatic anatomy of other tissues such as breast or skin required more expansive and precise sampling techniques., Morton et al. [7,8] at the John Wayne Cancer Institute introduced a more dynamic and physiologic method of SLN identification by intradermally injecting isosulfan blue at primary melanoma sites and resecting the identified draining lymphatics. The inclusion of Technetium-based radionuclide dye to allow lymphoscintigraphy in addition to visual observation further advanced the technique. Shortly thereafter at the same institution, Giuliano et al. [9] applied blue dye mapping to breast cancer lymph node dissection, and since then, SLN has all but replaced the complete axillary lymph node dissection (cALND) that had accompanied mastectomy since the days of Halsted [10]. Now a key tool in surgical oncology, particularly in the treatment of melanoma and breast cancer, SLNB has reduced morbidity and informed staging without reducing short- or long-term survival [11-13]. The use of SLNB continues to evolve also in the care of patients with head and neck, gynecologic, and gastrointestinal malignancies.

Radiopharmaceuticals

Many molecules have been developed for lymphoscintigraphic SLN localization, but currently technetium-labeled colloid-based radiopharmaceuticals are the most commonly used, having largely replaced the vital blue dye used at the birth of the technique due to higher detection rates [14]. Ideally, an SLN mapping agent would exhibit many pharmacokinetic attributes including rapid injection site clearance, rapid SLN accumulation, sustained SLN retention, and of course, an appropriate safety profile [15]. Many radiopharmaceuticals have been investigated, but technetium-labeled colloid-based products have led the industry due to their higher affinity for chemical modification, unlike sulfur and antimony compounds. Technetium has been paired with several molecules, including human serum albumin, which has demonstrated good definition of lymphatic channels but faster washout resulting in less efficient SLN accumulation for nodal identification [16]. Moreover, use of human serum albumin requires costly screening for viral contamination of protein products. In 2013, the US Food and Drug Administration approved Tc-99m tilmanocept as a novel radiotracer for SLNB procedures for breast cancer and melanoma patients. This tracer is only 7 nm in size and is receptor-based, resulting in rapid injection site clearance, high SLN identification and extraction, and low distal node accumulation [17]. Despite these theoretical advantages, no actual advantages of tilmanocept have been demonstrated over Tc-99m sulfur colloid labeled procedures: both products perform similarly in terms of both total and diseased number of SLNs identified [14,18]. The only advantage found is decreased pain on injection of tilmanocept as compared to Tc-99m sulfur colloid injection, perhaps due to the smaller size of the nanoparticle [19]. Pain can also be mitigated by inclusion of lidocaine with injection, without compromising detection rate [20]. Due to the lack of present consensus on optimal radiopharmaceutical for SLNB, the choice of agent among technetium-labeled colloid-based options largely depends on regional availability, provider preference, and material cost.

Melanoma

Melanoma is the fifth most common cancer in the United States and the leading cause of skin cancer-related mortality, with incidence on the rise [21]. Surgical treatment has been the mainstay since William Norris in 1857 introduced wide local excision, in order to eradicate discontinuous nests of tumor cells in adjacent dermal lymphatics [22]. Over time, margins have been reduced from William Handley's original 5 cm to 1 or 2 cm depending on Breslow depth, without increasing risk of local recurrence [23]. The role of lymphatics in metastatic melanoma was recognized early, and in 1892 Herbert Snow suggested that complete lymph node dissection (CLND) should be performed prophylactically to prevent tumor spread [24,25].

Although sound in principle, multiple randomized clinical trials demonstrated no benefit to immediate versus delayed CLND [26]. This failure has been retroactively attributed to other more powerful prognostic factors, chiefly Breslow depth and mitotic index, and anatomic variations in lymphatic drainage. In fact, at that time, CLND was effective in identifying only 20% of metastatic lymph nodes [27,28]. SLNB, with the combined "triple technique" of pre-operative lymphoscintigraphy, perioperative blue dye, and intraoperative gamma-probe-guided localization, was developed to achieve the same survival benefit and staging information with a lower risk of infection and lymphedema. Published in 2006, SOLISM-Italian Melanoma Intergroup trial was the first multicenter non-randomized trial to demonstrate the utility of SLNB in the operative treatment of melanoma [29,30]. Pre-operative lymphoscintigraphy successfully identified an average of 2 SLNs for all but 8 of 1,313 (99.3%) patients, most commonly in the axilla (52.5%). Positivity was 16.9%, and false-negative rate at 31 months was 14.7%. The use of three or more radiocolloid injections was associated with higher reliability in the number of SLN identification. Multicenter Selective Lymphadenectomy Trial (MSLT)-I was the seminal randomized controlled trial for the use of SLNB in melanoma, reporting a 96% correct classification in 2,001 patients [31]. SLN identification rate was 99.4%, while positivity rate was 20.8% and correlated with Breslow depth. False-negative rate was 20% and attributed to variations in technique, particularly the use of blue dye alone, throughout the life of the study. For patients receiving CLND following SLN involvement, 10-year disease-free survival was significantly higher (71% vs. 65% for intermediate thickness and 51% vs. 41% for thick melanomas, $p = 0.01$), but there was no difference in melanoma-specific survival. Presence of nodal metastasis was the most powerful negative prognostic factor, corresponding to a 2.5-fold higher risk of recurrence or death from melanoma. MSLT-II delved further into the benefit of CLND for 1,939 melanoma patients with positive SLNB [32]. Although CLND improved disease-free survival at 3 years (68% vs. 63%, $p = 0.05$), once again there was no difference in the primary endpoint, melanoma-specific survival at 3 years (86% vs. 86%, $p = 0.42$). Conversely, CLND increased the rate of lymphedema complications (24% vs. 6%, $p < 0.001$). These results suggested that the survival benefit of early CLND applies only to disease limited to the SLNs. Non-SLN metastasis was a poor prognostic factor, but earlier timing of CLND did not improve survival for that subgroup. Careful observation with nodal ultrasonography was deemed safe for melanoma with SLN metastasis. CLND did improve regional control and recurrence in addition to providing staging information from non-SLN metastasis, but did not improve survival in any subgroup and increased morbidity. Further clarification of the role of early CLND should

be forthcoming after the 2022 completion of MSLT-II. Largely similar results were obtained in Dermatologic Cooperative Oncology Group Sentinel Lymph Node Trial, where 473 SLN-positive melanoma patients underwent the same randomization, and no overall survival or disease-free survival benefit was observed, with lymphedema rate of 8% [33]. SLN tumor load greater than 1 mm was found to be a poor prognostic factor for 3-year mortality (hazard ratio 2.96, 95% CI 1.98-4.42), and it was consequently recommended that CLND not be performed for SLN micrometastasis. The use of SLNB has expanded from a therapeutic to a prognostic role for patients with melanoma without clinical evidence of metastasis. CLND remains standard of care in palpable or radiographic nodal disease, as well as for patients who cannot be closely monitored for regional recurrence [34]. Such efforts have tangible indirect effects on survival, as is implied by the two most recent American Joint Commissions on Cancer staging systems: in the 2009 edition, where SLN biopsy was not universally applied, 10-year survival for stage II melanoma was 55%, while by the 2017 edition, where SLN biopsy was used for all stages, survival was 82% [35,36]. In light of recent advances in targeted chemotherapy and immunotherapy, the predictive value of SLNB may continue to be critical for patient care in the selection of appropriate adjuvant regimens. Though SLNB has been established as an accurate, minimally invasive staging procedure, extending to CLND in the presence of SLN metastasis has not improved survival in any observed subgroup. The additional prognostic information may be pursued for the well-informed patient seeking maximal tumor characterization for adjuvant selection, a process that may be superseded by up-and-coming genetic and immunological techniques.

Breast Cancer

Breast cancer is the second most common cancer worldwide, and the most common among women, with a lifetime risk of 12.4% [37]. The fifth leading cause of cancer mortality, it accounts for approximately 400,000 deaths annually. Surgical resection has been a mainstay of treatment, and has evolved dramatically since the day of William Halsted's 1882 radical mastectomy, which involved removal of the whole breast, pectoralis major and minor, and axillary and supraclavicular lymph nodes [38]. This procedure dramatically reduced local recurrence to just 6% compared to the contemporary rate of 56%-81%, and became the operative standard. The radical mastectomy, however, did not considerably improve overall survival and involved substantial morbidity including debilitating lymphedema and subsequent risk of angiosarcoma. As chemo- and radiotherapy advanced and mammography detected earlier and smaller tumors, breast-conserving surgery began to replace radical mastectomy in the 1970's and 1980's [39]. Several trials in the 1990's and 2000's

demonstrated non-inferiority of SLNB with lumpectomy compared to the traditional radical mastectomy with cALND, especially in patients with low SLN tumor burden [40-44]. Lumpectomy with SLNB exhibited comparable overall and disease-free survival as well as reduced complications including lymphedema, infection, and neuropathy [45]. Comparable survival despite considerably reduced resection is largely attributable to the rate of non-SLN metastasis: in a meta-analysis of 10,454 patients from 69 studies, only 53% of patients with SLN involvement had further metastasis beyond the SLN on cALND [46]. In patients with lower SLN tumor burden, the rate of non-SLN metastasis further decreased to 20% for SLN micrometastasis and 12% for isolated tumor cells in the SLN. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial provided compelling support for the existing trend to omit cALND in select patients, especially those with small-volume metastases. A total of 891 patients treated with whole breast irradiation and found to have one or two metastatic SLNs were randomized to SLNB or cALND. Non-SLN metastases were found in 27.3% of cALND patients, and only 10% of patients with micrometastatic SLN were found to have non-SLN disease. At a median follow-up of 6.3 years, no difference was observed in overall or disease-free survival. These results confirmed that for a specific population, namely women with T1 or T2 clinically node-negative breast cancer who undergo breast-conserving surgery and whole breast irradiation and have one or two positive SLNs, cALND is not required and can be safely omitted. Similar results were later replicated in populations not well represented in ACOSOG Z0011, including invasive lobular carcinoma [47] and SLN burden greater than three nodes [48]. In order to better assess the need for cALND in populations still not well characterized by clinical trials, various models have been developed. One such nomogram from MD Anderson, comprised of number of SLNs, SLN size, tumor size, extranodal extension, and histology, correctly predicts non-SLN metastasis with an area under the curve of 0.74% and false negative rate of 4% [49]. These methods can be applied to inform operative management for patients not included in existing trials, though these will still be required for definitive recommendations on the utility of cALND in such SLN-positive patients.

Head and Neck

With approximately 66,000 cases and 14,600 deaths annually, head and neck cancer accounts for 3% of malignancies [50]. Though SLNB was first performed in head and neck cancers, it soon fell out of favor after its development. Standardization of the technique in breast cancer and melanoma, technological advancements in radio-tracers and imaging, as well as further realization of the importance of lymphatic metastasis for prognosis, use of SLNB have risen in head and neck malignancies in the

past two decades.[51] Technically, procedures for head and neck are performed similarly to breast cancer and melanoma patients. The anatomy and proximity of nodes to the primary site, however, may decrease the efficacy of preoperative planar imaging. Therefore, single-photon emission computed tomography is often preferred for better localization and less obscuring of nodes by the primary site [52]. As reviewed by Moncayo et al. [53], data support the use of SLNB rather than elective neck dissection in the surgical management of early stage (T1 or T2) oral and oropharyngeal squamous cell carcinoma. Several large trials have demonstrated satisfactory negative predictive value of SLNB in this population, ranging from 86% to 98% [54-56]. Moreover, SLNB offers the additional advantage of identifying contralateral nodes not included in the typical ipsilateral dissection, which may be as prevalent as 12% [55]. It is estimated that SLNB may obviate the need for elective lymph node dissection in 60-70% of patients with head and neck cancer, thus reducing the morbidity of such dissections.

Gastrointestinal

The most extensive experience with SLNB in gastrointestinal malignancies originates in Japan and Korea, where incidences of gastric cancer as high as 30 to 40 per 100,000 have powered trials assessing the prognostic value of SLNB [57]. In this context, SLNB may be helpful in the management of gastric cancer not only for possible multi-modal therapy, but also for possible surgical management, which is referred to as Sentinel Node Navigation Surgery [58]. However, use of SLNB in gastric cancer is not universally accepted, as anatomic variations and heterogeneity of SLNB practice likely contribute to unacceptably high false negative rates in this population [59]. Colorectal cancer accounts for approximately 135,000 cases and 50,000 deaths annually, the third most common cause of cancer-related mortality in the United States [60]. This high burden of disease has led to considerable experience with SLNB in colon cancer in the United States. Preoperative techniques for SLN localization have been more successful (93%) as compared to intraoperative localization (89%) [54]. Early stage (pT1-T2) cancers in particular may benefit from SLNB, where assessment of aberrant lymph nodes can extend surgical resection in as many as 22% of patients [61]. Low sensitivity and high false negative rates, however, as well as mapping results discordant with pathologic staging have not supported the widespread adoption of SLNB in colon cancer. Although the technique is rather conserved across cancer operations, the more extensive and variable lymphatic drainage of the gastrointestinal tract has been a limitation of its application for these tumors. As in gastric cancer, standardization of practice and further development of micrometastatic techniques will be key to optimizing the practice for gastrointestinal cancers.

Gynecologic Malignancies

The fourth most common cancer in American women, endometrial cancer occurs in 66,500 women and accounts for 13,000 deaths annually [50]. Gynecologic malignancies have proven yet another context where SLN status is a key prognostic indicator, and SLNB has been applied with considerable success to endometrial, cervical, and vulvar cancer. Sentinel Node and Endometrial Cancer trial, the first large randomized controlled trial assessing SLNB in endometrial cancer, described in 2015 a SLN detection rate of 88.8% and a metastasis prevalence of 17% in the pelvis and 5% in para-aortic nodes, as well as 97% sensitivity and 84% negative predictive value. SLNB upstaged 10% and 15% of low- and intermediate-risk cancers, respectively [62]. A few years later, the febrile infection-related epilepsy syndrome trial similarly demonstrated good diagnostic accuracy, with sensitivity of 97.2% and negative predictive value of 99.6%. As a result of these trials, SLNB can now be safely offered to the exclusion of pelvic lymphadenectomy for lower risk endometrial cancer [63]. Cervical cancer accounts for approximately 15,000 cases and 4,000 deaths annually in the United States [50]. SLNB has demonstrated similar performance in early-stage cervical cancer; a meta-analysis of 67 studies reported detection rate of 89.2% and sensitivity of 90%, with false negative rates increasing proportionately to tumor burden [64]. Here, SLNB offers the additional advantage of locating otherwise inaccessible SLNs outside of the classical area of detection, such as parametrial nodes. Further clarification on the optimal application of SLNB to cervical cancer is forthcoming in large multi-center trials such as sentinel lymph node biopsy in patients with early stages cervical cancer and Ganglion Sentinelle dans le Cancer du Col. One of the more rare gynecologic malignancies, approximately 6,000 cases and 1,500 deaths attributable to vulvar cancer is recorded annually [50]. Here too, SLNB can play a key role, considering that up to two-thirds of early-stage patients do not have lymph node metastasis, and could be spared the morbidity of inguinofemoral lymphadenectomy. As in other cancers, the performance of SLNB is inversely correlated with tumor size and stage; several trials, such as GROningen INternational Study on Sentinel nodes in Vulvar cancer and Gynecologic Oncology Group, have reported false negative rates ranging from 5.9% to 7.7%, but decreasing to 2.0% in tumor sizes below 4 cm [65-67].

Conclusion

Today, accurate staging of lymph node basins is essential to the appropriate care of the cancer patient, offering prognostic and predictive values that can direct medical management. Historically, extensive dissection of all draining lymph nodes was performed to adequately stage nodal disease, resulting in significant morbidity without additional survival benefit. In recent decades, SLNB has

emerged as a practice-changing technology that decreases surgical morbidity while providing adequate cancer staging. While these benefits have been most pronounced in early stage cancers, as technology and practice progress further, the role of SLNB in oncologic care will likely continue to expand.

List of Abbreviations

cALND	Complete axillary lymph node dissection
CLND	Complete lymph node dissection
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy

Conflict of interests

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