Chapter 16
Sentinel Node Biopsy for Head and Neck Cancer

Lee Alkureishi and Gary L. Ross

Abstract The presence of cervical lymph node metastases remains one of the most important prognostic factors for various solid tumors of the head and neck, including melanoma, squamous cell carcinoma (SCC), and Merkel cell carcinoma (MCC). In patients with clinically evident neck involvement, the regional lymphatics clearly require directed treatment, and this may involve therapeutic neck dissection or radiotherapy. However, the decision whether or not to electively treat patients with clinically uninvolved cervical lymphatics is usually less clear-cut. On the one hand, elective neck dissection simultaneously allows for accurate pathological neck staging and definitive surgical management of patients found to harbor occult metastatic disease. On the other hand, the majority of patients with clinically negative (cN0) necks do not harbor occult disease and would therefore be overtreated by an elective neck dissection. The significant morbidity associated with neck dissection means that this is a real concern, and efforts to minimize the extent of surgical intervention while maintaining oncologic safety are ongoing.

The radical en bloc cervical lymph node dissections introduced at the start of the twentieth century have largely been surpassed by more focused surgical procedures, including the modified radical neck dissection (MRND) and more recently, selective neck dissection (SND). The operative morbidity of MRND and SND procedures compares favorably with more extensive dissections, though it remains significant. Sentinel lymph node biopsy (SLNB) represents an extension of this principle; by super-selecting the small subset of lymph nodes most likely to harbor disease, the extent of surgical intervention can be further minimized without adversely affecting diagnostic accuracy. The sentinel node concept states that tumor spread occurs in a stepwise progression from the primary tumor to the first-echelon lymph nodes, before progression to the remainder of the lymphatic basin.

These first-echelon lymph nodes, known as the sentinel nodes, can be harvested, examined for the presence of tumor, and used to predict the disease status of the entire basin. In the head and neck region, considerable variability exists in the patterns of lymphatic drainage from each primary tumor site, and the exact location of the sentinel nodes therefore varies between patients. In order to accurately locate the SLNs, a number of techniques may be employed. Preoperatively, radio-labeled tracer is injected in a peritumoral fashion, traveling via the lymphatics to the first-echelon nodes, where it may be detected by gamma camera during lymphoscintigraphy (LSG). A handheld gamma probe is utilized intraoperatively to afford more precise radiolocalization, and some surgeons choose also to inject peritumoral blue dye, easing visual identification of the lymphatics. These comprise the sentinel lymph node biopsy technique, which has been applied to a variety of solid tumors, including breast cancer, malignant melanoma (MM), and penile cancer.

This chapter describes SLNB as it relates to the management of solid tumors in the head and neck region, particularly malignant melanoma, SCC, and MCC. A brief history of the development of the technique and its reported accuracy are presented, and the advantages and disadvantages of this relatively new application are discussed. Finally, this chapter explores the possible roles that SLNB may play in the future management of head and neck cancer.

Keywords Head and neck cancer • Oral cancer • Squamous cell carcinoma • Sentinel node biopsy

Introduction

Head and neck cancers comprise a diverse group of tumors arising from the epidermis, with significant differences in tumor biology, disease characteristics, and prognosis. The three most common types of head and neck cancer are malignant melanoma (MM), arising from melanocytes; squamous cell carcinoma (SCC), arising from keratinocytes;

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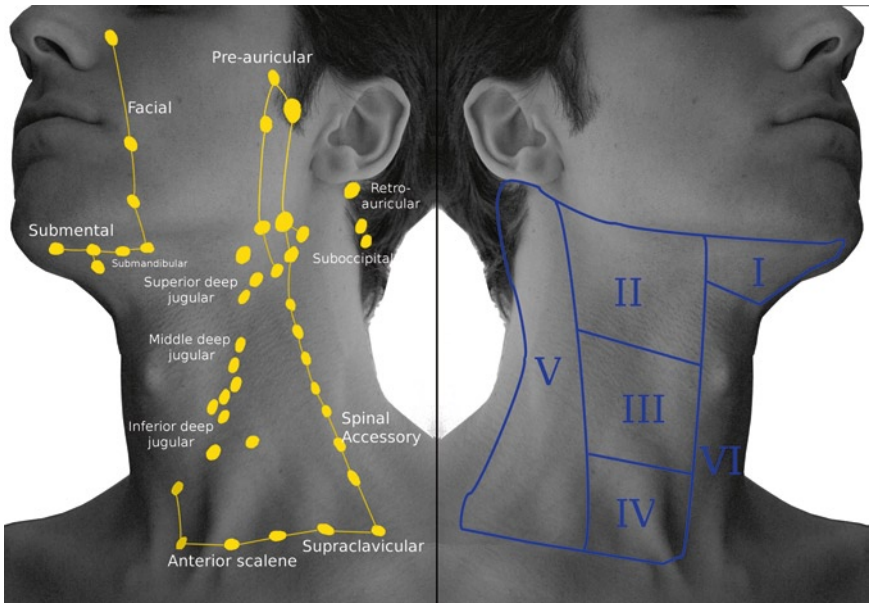

Fig. 16.1 (**a**) Individual lymph node groups in the head and neck, grouped into superficial and deep jugular chains. (**b**) Robbins' Classification of cervical lymph node levels

and Merkel cell carcinoma (MCC), a rare aggressive skin tumor arising from neuroendocrine cells.

Despite their differences in many regards, these cancer types share one important characteristic; their prognosis is heavily dependent on the presence or absence of lymph node metastases. Patients with malignant melanoma and nodal involvement demonstrate less than 50% 5-year survival [1], and similar figures have been reported for patients with SCC [2]. In MCC, the presence of nodal disease has been shown to be the most important prognostic indicator by multivariate analysis [3], with a further study demonstrating a drop from 40 to 13 months median survival with nodal involvement [4].

Virchow [5] was the first to postulate that lymph nodes act as a barrier to particulate matter, and in particular cancer cells. The contention that cancer progression followed a sequential route from the primary site to the regional lymphatics before distant metastasis laid the way for the development of regional surgical treatments for a variety of cancers; first, Halsted radical mastectomy for breast cancer [6]; and in the case of the head and neck, the radical neck dissection (RND) as described by Crile [7].

Anatomy of the Cervical Lymph Node Basin

The lymphatic anatomy of the head and neck is complex, comprising approximately 250–350 lymph nodes and demonstrating great variability in the patterns of lymph flow observed [8]. The cervical lymph nodes may be divided into superficial and deep chains. The superficial chain lies between the skin and the superficial fascia of the face and scalp, following the anatomy of the major veins, and eventually drains into the deep chain. The deep chain lies along the course of the internal jugular vein under the sternocleidomastoid muscle, draining inferiorly from the base of the skull to the brachiocephalic junction, where lymph is returned to the venous system. The most popular system of classification for cervical lymphatic anatomy was developed at the Memorial Sloan-Kettering Cancer Center [9], and forms the basis for describing the various types of neck dissection in current usage [10]. In this system, the cervical lymph nodes are divided into levels I through VI. The anatomy and classification system are illustrated in Fig. 16.1.

Neck Dissection

The introduction of the RND in 1906 [7] represented an important step for both staging and treatment of patients with head and neck cancer. However, the morbidity associated with such an extensive dissection was considerable. Complications included shoulder stiffness, pain, muscle atrophy, facial swelling, and cosmetic defects while the mortality rate following bilateral RND was reported as high as 10% [11]. A number of "modified radical" neck dissections were developed as a means of minimizing associated morbidity, being designated MRND I–III depending on the structures preserved (accessory nerve, sternocleidomastoid and/or internal jugular vein) [12]. Studies demonstrating the oncologic safety of the MRND led to its adoption as the standard of care, and the RND fell out of favor [13].

The goal of reducing morbidity continues to push the development of more conservative surgical management techniques, however, and this is particularly true for patients

with clinically uninvolved necks. Improved understanding of the lymphatic anatomy of the head and neck has facilitated the development of more selective lymphadenectomies, concentrating on the groups of lymph nodes most likely to be involved [14–16]. These selective neck dissections (SNDs) require less extensive dissection, leaving more of the normal lymphatic anatomy intact and have been shown to cause less morbidity when compared with MRND [17]. The various types of neck dissection are outlined in Table 16.1.

Despite these recent advances, neck dissection remains an invasive procedure with appreciable morbidity [18] and, while its use in clinically node-positive patients is well established, elective neck dissection for patients with clinically negative (cN0) necks remains controversial. Traditionally considered the gold standard, END provides tissue for accurate pathologic staging while also treating the neck by removing lymph nodes at risk for involvement [19]. However, the majority of cN0 patients do not in fact harbor occult nodal metastases, and may be unnecessarily subjected to the morbidity associated with the procedure.

As a result, selection of patients who would benefit most from neck dissection becomes increasingly important. Clinical staging of the cervical lymph nodes is unreliable, with poor reported sensitivities for both palpation and clinical imaging, and it is generally accepted that an occult nodal metastasis rate of 20–30% persists despite meticulous clinical staging [20–22]. For SCC, elective neck dissection is currently recommended for patients with a greater than 20% risk of occult nodal metastases based on primary tumor characteristics, such as site and T-stage [23]. The role of END for cN0 head and neck melanoma patients is unclear, with no consistent survival benefit demonstrated [24]. It has been suggested that END may be most beneficial for patients with primary tumors between 1.5 and 3.99 mm in thickness [25].

Table 16.1 Neck dissection classification

1991 Classification	2001 Classification
1. Radical neck dissection	1. Radical neck dissection
2. Modified radical neck dissection	2. Modified radical neck dissection
3. Selective neck dissection	3. Selective neck dissection
a. Supraomohyoid	Each variation is depicted by "SND"
b. Lateral	And the use of parentheses to denote
c. Posterolateral	The levels or sublevels removed
d. Anterior	
4. Extended neck dissection	4. Extended neck dissection

From Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, Som P, Wolf GT. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg. 2002;128(7):751–8. Reprinted with permission.

Sentinel Node Biopsy

Sentinel node biopsy (SNB) represents a means of superselecting the group of lymph nodes most at risk for disease involvement, allowing histopathologic staging of the neck while minimizing the extent of surgical intervention for patients without nodal involvement. The sentinel node concept is based on the assumption that spread from the primary tumor occurs to a single node (or group of nodes) before progressing to the remaining nodal basin and systemic metastasis (Fig. 16.2). Identification of these sentinel nodes allows for selective biopsy and pathologic evaluation of the nodes most likely to represent the disease status of the remaining nodal basin [26]. The results of SNB can then be used to guide further management, with SNB-positive patients going on to receive definitive (therapeutic) neck dissection and/or parotidectomy while SNB-negative patients may be followed clinically. These SNB-negative patients may therefore avoid some of the morbidity associated with neck dissection [27].

The potential advantages of SNB over neck dissection are many-fold, including its minimally invasive nature, a lower per-patient cost compared with comprehensive neck dissection [28, 29], and a drastic reduction in the number of lymph nodes submitted for pathologic evaluation. In turn, this allows a more in-depth search for micrometastatic deposits utilizing techniques, such as step-serial sectioning (SSS) and immunohistochemistry [30, 31]. However, SNB can be a technically challenging technique with a steep learning curve [26, 32] and as such, investigators wishing to begin using the technique for SCC are recommended to do so within the context of SNB-assisted END [33]. As with any biopsy technique, there exists the potential for sampling error and the reported false-negative rate ranges from 0 to 10.5% in most studies for both SCC and melanoma [33–39]. Finally, the usefulness of SNB is currently restricted to cN0 patients, since distortion of the normal lymphatic anatomy by extensive tumor infiltration may lead to unexpected drainage patterns and increase the likelihood of false-negative results [40].

Development of the Sentinel Node Concept

The first description of a "sentinel" lymph node dates back to 1960 with a total parotidectomy reported by Gould et al., during which frozen section examination of a single facial lymph node was used to guide the decision for neck dissection [41]. Subsequently, Cabanas et al. reported direct drainage from the penis to the lymph nodes associated with the superficial epigastric vein in a series of 46 patients with penile SCC and described 90% survival for sentinel node-negative patients [42]. Similarly, Weissbach and Boedefeld suggested a limited retroperitoneal lymph node dissection in

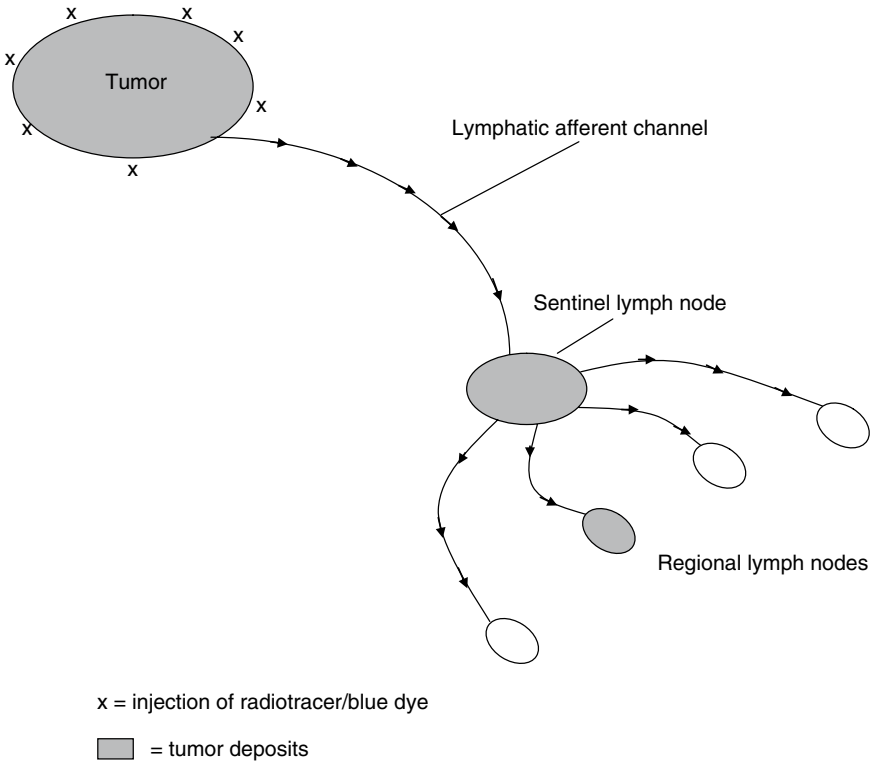

Fig. 16.2 The sentinel node concept

patients with testicular cancer, in order to detect lymphatic involvement while minimizing operative intervention [43]. Holmes et al. introduced the use of colloidal gold injections to demonstrate the actual patterns of lymph drainage for ambiguous areas, such as the midline [44], and followed this in 1992 with the description of intraoperative vital dye injection, providing a means of visually tracing dye-stained lymphatics to the first-echelon nodes [26]. In 1993, Alex and Krag described the intraoperative use of a handheld gamma probe, easing detection of the sentinel nodes and improving identification rates [45]. Since these early studies, SNB has gone on to become increasingly important as a staging tool for patients with early-stage melanoma [46], and work is underway to fully elucidate its utility in SCC management [33, 47]. The role played by SNB in the management of these and other head and neck cancers is described later in this chapter.

Technique of Sentinel Node Biopsy

In general, SNB comprises three parts: preoperative lymphoscintigraphy (LSG), intraoperative identification and harvest, and pathological evaluation of sentinel nodes. These components are described in detail in this section, with reference to the minor differences in protocol for each of the major head and neck cancer types.

Preoperative Lymphoscintigraphy

The lymphatic anatomy of the head and neck is complex and variable, with discordance between predicted and actual lymphatic drainage in up to 67% of patients [8]. Aberrant drainage patterns can lead to inaccurate placement of the initial access incision, and may contribute to the failure of sentinel node identification [15]. The goal of preoperative LSG is to demonstrate the location of sentinel nodes prior to incision. This begins with injection of a radio-labeled colloid solution at the site of the primary tumor. The radiocolloid may then track along the same afferent lymphatics draining the tumor, accumulating in the first-echelon lymph nodes where the resultant radioactivity may be detected by gamma camera. LSG may be carried out up to 24 h before surgery, or on the day of surgery, and this should be coordinated between the nuclear medicine physician and the surgeon.

The technique of radiocolloid injection varies according to the type of cancer being studied. For melanoma and other cutaneous tumors, multiple intradermal injections should be employed to completely encircle the tumor or site of previous excision biopsy. There has been considerable debate regarding the accuracy of LSG, and SNB in general, in cases where wide local excision (WLE) has previously been carried out. While it is strongly preferred that SNB be performed prior to excision, there is some evidence to suggest that previous WLE is not an absolute contraindication [48]. For intraoral lesions, the majority of which are SCC, multiple mucosal/

submucosal injections should be performed around the periphery of the tumor or scar margin, and deeper injections may be employed according to the depth of the lesion [49]. Ideally, the operating surgeon should be present for the injections to ensure consistency with injection of blue dye if used. The volume injected varies according to the location and size of the lesion, and ranges from two to four aliquots. A mouthwash should be employed following intraoral injections, to prevent sumping or swallowing of radiotracer.

The ideal radiotracer should emit only gamma rays, be cleared rapidly from the injection site, have a uniform particle size, and should persist in the lymph nodes until imaging can be performed [50, 51]. A variety of Technetium99m (99Tcm)-labeled colloids are available, including 99Tcm human serum albumin, 99Tcm colloidal albumin, 99Tcm antimony sulfur colloid, and 99Tcm sulfur colloid, although regional licensing issues may restrict the available choices. In Europe and parts of the USA, Albures™ and Nanocoll™ (Nycomed Amersham, Buckinghamshire, UK) are the most commonly available colloidal albumin preparations. The larger particle size of Albures™ (500 nm) limits its use to primary tumor sites with high lymphatic density, such as the anterior tongue or floor of the mouth, while the 50 nm particle size of Nanocoll™ allows its use in other sites [33, 51]. For regions where human albumin-based colloids have not been approved, sulfur colloid preparations are available in both unfiltered (300–340 nm) and filtered (<200 nm) forms [52]. There is little consensus on the optimum activity for injection, which varies from 15 to 120 MBq between studies with higher doses or repeat injections being employed for the 2-day protocol [53–55]. However, it has been suggested that much lower doses (0.37–2.2 MBq) may be used in the setting of head and neck melanoma [56].

Planar lymphoscintigraphic imaging may be static or dynamic, or a combination of the two. The addition of dynamic imaging for melanoma patients improves the detection of "in-transit" nodes, which are reported to occur in 5–8% of the population and should also be considered sentinel nodes [57, 58]. To date, there have been no reports of in transit nodes in patients with SCC. There is currently no evidence favoring either technique in these patients, and the exact timing of static image acquisition varies between centers. Images should be obtained in two planes: anterior and lateral or lateral-oblique. A gamma camera fitted with a low energy, high resolution (LEHR) collimator is used to image the patient, whose silhouette can be delineated by a flood source of ^{57}Co or ^{99m}Tc placed behind the patient or by tracing his/her outline with a ^{57}Co-labeled marker pen. At this point, it may be helpful to mark the skin overlying visualized sentinel nodes with indelible marker pen [33, 49, 51]. However, this practice has not been universally accepted due to concerns that the change in positioning between LSG and surgery may misguide the placement of initial access incision [59].

Recent studies have reported potential improvements in preoperative sentinel node identification through the use of Single Photon Emission Computed Tomography (SPECT/CT) imaging [60, 61]. This hybrid anatomical/functional imaging modality affords better topographical orientation and separation of SLNs from adjacent structures, compared with planar LSG alone. In the melanoma literature, it appears that SPECT/CT can lead to more accurate incision placement and improvements in SLN detection rates [61, 62]. However, these advantages of SPECT/CT imaging have not been consistently demonstrated in the SCC population [63].

Surgical Technique

Within 24 h of LSG, patients may undergo the operative portion of SNB. Although SNB of cervical lymph nodes under local anesthesia has been reported [64], most surgeons prefer to employ general anesthesia for this technique. The patient is prepared and draped as for a standard excision and neck dissection. Preoperative LSG images should be available for reference in the operating suite, in electronic or hard copy form, and these may be used to guide the placement of the initial access incision. If skin markings have been placed in the nuclear medicine suite, underlying radioactivity levels should be verified using a handheld gamma probe prior to making the incision. The orientation of the incision should be such that it may be easily excised in the event of a future neck dissection.

If injection of vital (blue) dye is desired, this may be carried out prior to preparing and draping. Injections should be undertaken by the same operator as the radiotracer injection in order to ensure consistency, and the pattern and depth of injection should mirror that of the radiotracer. The brand of dye used varies according to geographical region, with Patent Blue V Dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) available in Europe and Lymphazurin™ (Tyco Healthcare Group LP, Norwalk, CT, USA) in the USA. The technique of blue dye injection, introduced by Morton et al., provides a means of visually identifying the small lymphatic vessels intraoperatively, allowing them to be traced to the first-echelon nodes [26]. However, the success rate of identification of SLNs by blue dye injection is less than that of radiolocalization by gamma-probe, and the technique has a steeper learning curve [65]. In a study of 55 patients with head and neck melanoma, Wells et al. reported a 67% identification rate by blue-dye mapping and 95% utilizing a combined approach [38].

While most blue dye-stained SLNs are also found to be radioactive or "hot," a small minority of SLNs are "cold," and proponents of blue dye injection report the facilitation of intraoperative identification [33, 49, 66]. The major perceived

disadvantages to blue dye are related to persistent cutaneous staining and masking of true surgical margins; however, rare cases of anaphylactic reactions have also been reported [67]. As a result, the use of blue dye is considered optional, though many authors employ a combined approach.

Guided by the preoperative LSG images, skin markings (if present) and the handheld gamma probe, a small skin incision (2–4 cm) is made and limited skin flaps elevated. Dissection is carried through the superficial fascia, and is guided by the handheld gamma probe. If blue-stained lymphatics are visualized, these may be followed to the draining lymph node(s); if no staining is present (or dye was not used), the dissection may be guided solely by the gamma probe, which is fitted with a 14 mm diameter straight collimated probe. The angle of the probe may be gradually altered while watching or listening for a change in the counts-per-second (cps). In cases where the primary tumor site lies in close proximity to the regional lymph nodes, radioactive "shine-through" from the primary tumor site may mask the true position of the sentinel node. In these patients, the use of malleable lead plates between the injection site and the nodal basin may address this issue [26, 45, 49, 51]. All radioactive and/or blue-stained nodes are clipped and excised, and radioactivity is confirmed ex-vivo. Following excision, the remaining basin is examined with the gamma probe and no further SLNs are considered present when the residual count-rate is less than 10% that of the "hottest" excised SLN [68]. Patients undergoing SNB-assisted END may then proceed to completion neck dissection.

Pathologic Evaluation of Sentinel Nodes

Detection of metastatic disease in sentinel nodes by pathologic examination is intrinsic to the success of the procedure, and offers a number of advantages over traditional elective neck dissection. Principally, the absolute number of lymph nodes examined is far fewer during SNB, allowing the pathologist to perform a more thorough search for micrometastatic deposits.

Metastases, Micrometastases, and Isolated Tumor Cells

Occult metastases may be defined as those found in patients with cN0 necks, and may be subdivided into metastases (greater than 2 mm), micrometastases (≥0.2 mm and ≤2 mm), and isolated tumor cells (ITC; <0.2 mm, single cells or small clusters, with no stromal reaction and no contact with vessel wall) according to the most recent International Union Against Cancer (UICC) classification. The relationship of this classification to the most recent AJCC Tumor-Node-Metastasis (TNM) classification of malignant tumors is illustrated in Table 16.2 [69].

In order to compare results across studies, uniform reporting standards for pathologic staging are critical. When SNB is undertaken, the designation (sn) should be added after the N category. The finding of ITCs does not upstage the cN0 neck, and should be reported as pN0 (i+)(sn) while micrometastatic disease results in upstaging and is reported as pN1 (mi)(sn). For each of the head and neck cancer types, the sequence of pathologic examination is broadly similar, and involves gross examination, bivalving of the lymph node, sectioning at predefined intervals and staining with a variety of histopathologic techniques. However, there are a number of minor differences in protocol according to the type of tumor being studied, and exact sectioning/staining protocols vary between centers. In some cases, additional techniques, such as real-time polymerase chain reaction (RT-PCR), may also be employed; these differences are briefly outlined below [70, 71].

Table 16.2 Comparison of UICC and TNM classifications of micrometastases and isolated tumor cells

Generic TNM coding for sentinel nodes	
pNX (sn)	Sentinel lymph node could not be assessed
pN0 (sn)	No sentinel node metastasis
pN1 (sn)	Sentinel node metastasis
Sentinel nodes with micrometastasis only are identified by (mi)	
pN1 (sn)(mi)	Single ipsilateral node with micrometastasis
pN2 (sn)(mi)	Multiple ipsilateral nodes with micrometastasis
SLNs with ITC are coded separately for morphological and nonmorphological techniques	
pN0 (i–)(sn)	No SLN metastasis histologically, negative morphological findings for ITC
pN0 (i+)(sn)	No SLN metastasis histologically, positive morphological findings for ITC
pN0 (mol–)(sn)	No SLN metastasis histologically, negative nonmorphological findings for ITC
pN0 (mol+)(sn)	No SLN metastasis histologically, positive nonmorphological findings for ITC

From Alkureishi LWT, Alvarez JA, Britten AJ, Gray HW, et al. Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma. Eur J Nucl Med Mol Imaging. 2009;36(11):1915–1936. Reprinted with permission from Springer

Melanoma

The addition of immunohistochemical (IHC) techniques to standard H&E examination has been shown to increase melanoma detection rates by at least 10% [72], and a number of sectioning/staining protocols have been described in an effort to maximize detection rates while minimizing unnecessary workload. Some authors have advocated examination of only the central portion of the lymph node, based on the suggestion by Cochran et al. that the vast majority of micrometastases occur centrally [73], while other suggested protocols have included sectioning of the entire node into 1 mm slices [74], or examination of one half of the SLN using a combination of histology and immunohistochemistry, and the other half using RT-PCR with a variety of probes [75].

RT-PCR detection of occult metastatic deposits is an attractive technique, potentially reducing the cost and labor associated with SLN evaluation. However, disadvantages include its destructive nature, and positivity rates of up to 70% in some studies [76]. False positives may be due to capsular or trabecular nevus cells, nerves, or macrophages. In a recent report by Cook et al., utilizing an extended stepwise study of bivalved nodes with immunohistochemistry, the discrepancy between detection rates using histology/IHC and RT-PCR was found to be only 3–5%. Nevertheless, the exact role of RT-PCR remains to be fully elucidated and the authors therefore recommend the routine use of their extended histology/IHC protocol, which sections deeper into the periphery of the node, until further data become available [70]. This protocol is currently recommended by the EORTC, and is illustrated in Fig. 16.3. Briefly, the sequence involves bivalving the formalin-fixed SLN, embedding in paraffin, and sectioning at 50 μm intervals to a total depth of 250 μm. Several sections are taken at each interval, and are alternately stained with H&E, S100 and/or HMB45 for IHC. Sections found positive by IHC are compared with adjacent H&E-stained sections in order to confirm the presence of viable tumor cells. "Spare" sections were stored for future use or stained with additional investigational antibodies, such as Pan Melanoma Plus (Biocarta). The use of this extended sectioning protocol results in thorough evaluation of the central 700–800 μm of each SLN, and is thought to represent the best balance between sensitivity, cost-effectiveness and pathologist workload [70].

For SCC, there remains considerable debate regarding the optimal method for sectioning SLNs. Current recommendations were formulated during the Second International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer in 2003, and are included in the recent joint guideline published by the European Association of Nuclear Medicine (EANM) and European Sentinel Node Trial (SENT) committee [54, 71].

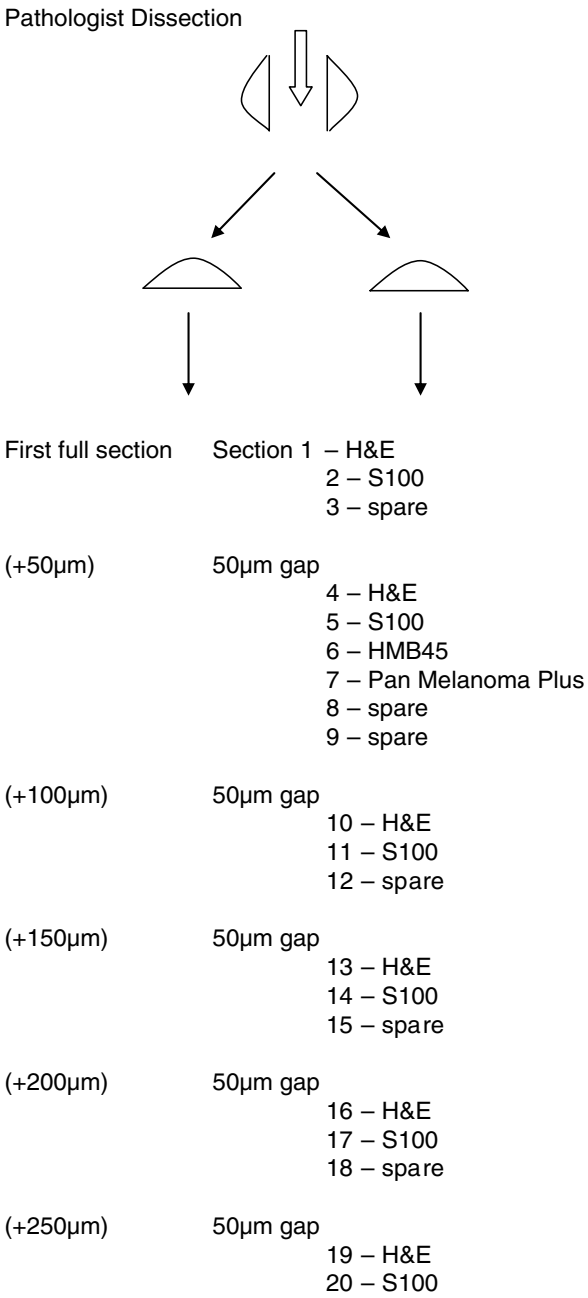

Fig. 16.3 Extended stepwise examination of bivalved SLNs with immunohistochemistry using S100 and HMB45 stains

SLNs less than 2 mm in longest dimension are processed whole while those measuring 2–5 mm should be bivalved and both halves processed en face. Nodes greater than 5 mm are cut into 2 mm slices, and each slice processed en face. A section from each slice is stained with H&E, and positive nodes/slices result in upstaging of the patient. Step-serial sectioning (SSS) at finer intervals of 150 μm (six sections per interval) should be carried out for SLNs found negative after initial sectioning, and these are H&E stained and examined as before. Finally, SLNs that remain negative are

subjected to immunohistochemical (IHC) staining with pancytokeratin antibody (AE1/AE3 or MNF116). The combination of SSS and IHC has previously been shown to detect an additional 10% of occult/micrometastatic deposits compared with H&E alone [33]. If no disease is found following H&E and IHC staining, the lymph node is considered free of tumor. For SLNs with positive IHC staining, the positive section must be compared with the immediately adjacent serial section in order to avoid false-positives due to nonviable tumor cells, artifacts and/or inclusion of other cell types [54].

The use of intraoperative frozen section analysis of SLNs offers the potential advantage of avoiding a second anesthetic for SNB-positive patients, but has traditionally been avoided due to concerns regarding freezing artifacts and loss of tissue. More recently, these views have been challenged by a number of authors who report excellent results using the technique, with only 10–17% of SNB-positive patients requiring a second procedure [35, 77, 78]. However, the technique has not yet gained universal acceptance. Novel techniques, such as imprint cytology [79] and intraoperative real-time genetic evaluation, [80] currently remain under investigation.

Merkel Cell Carcinoma

Pathologic evaluation of the sentinel nodes in MCC is similar to that of melanoma, though no standardized protocol has yet been adopted. The differences lie mainly in the type of step-serial sectioning, which varies from 2–3 mm slices [81] to 1 mm slices with multiple 200 μm sections per slice [82], and the use of anti-CK-20 staining (Dako Corp, Carpentaria, Calif.) in place of S100/HMB-45 for immunohistochemistry. CK-20 is well established as the most sensitive and specific marker currently available for the detection of MCC [83].

The Role of SNB in Current Practice

Melanoma

Following the initial reports of SNB for cutaneous melanoma using blue dye only, technical difficulties and the significant learning curve associated with the procedure led to variable technical success rates ranging from 60 to 80% [46]. Subsequently, the introduction of radio-labeled tracer injection, preoperative LSG and intraoperative gamma-probe guidance led to significant improvements in identification rates to greater than 90%, and the use of both blue dye and radiotracers quickly gained acceptance [36, 59, 84]. Since then, the technique of SNB has been demonstrated to accurately predict the disease status of the remaining nodal basin in a number of landmark studies of cutaneous melanoma (all sites) [48, 85, 86].

The presence of metastases within SLNs has been demonstrated to be the most accurate predictor of outcome in melanoma patients without clinical lymph node involvement [87], and there is now some evidence to suggest that early lymphadenectomy following a positive SNB may confer a small but significant survival benefit over lymphadenectomy for nodal recurrence, albeit based on subgroup analysis (data from all sites) [88, 89].

As a result, SNB is now widely regarded as the gold standard for staging the lymphatic basins of intermediate-thickness melanoma patients without clinical evidence of nodal involvement [46]. The primary indication for lymph node staging in this population is a primary tumor greater than 1 mm in Breslow thickness, though SNB should also be considered for thinner tumors in the presence of high-risk features, such as ulceration, high mitotic rate, or Clark level IV/V [46, 87].

In the head and neck, the prognostic significance of sentinel node status is less clear, with SLN-negative patients demonstrating a 5-year disease-free survival rate of only 55% in one report. In their review of the existing head and neck melanoma literature, the authors noted false-negative rates in excess of 10% in 12 of 21 studies, and suggested that this high false-negative rate may contribute to the poor survival they observed in their series [90]. Similar results were described in the large Sunbelt Melanoma Trial, where false-negative rates were 12% for the head and neck, compared with 2–3% for other sites [37]. However, this view has been challenged by Civantos et al., who contended that surgeons with a subspecialty focus on the head and neck may achieve negative predictive values comparable to the 98.2% for cutaneous malignancies and 92% for oral cancer described in their series of 106 patients with head and neck malignancy [91].

Concluding their review, Tanis et al. stated that there is currently no conclusive survival advantage for either elective lymph node dissection or SNB in patients with intermediate thickness melanoma of the head and neck; however, the benefits of SNB may potentially justify its use in this patient population. These benefits include early prognostic information for patient and physician, reduced tumor load due to earlier lymphadenectomy, and the possibility of a survival advantage based on subgroup analysis [90].

A variety of micromorphometrical parameters of SN tumor deposits have been used in an attempt to determine the likelihood of further disease in the remaining nodal basin, such as tumor penetrative depth from the central plane, location within the node, and size. The potential applications for these measurements would include guidance of the decision to proceed with formal lymphadenectomy and prediction of survival.

For example, the knowledge that only 10–30% of patients with positive SLNs are found to have additional positive "non-SLN" nodes following lymphadenectomy has led some authors to suggest that formal lymphadenectomy may not be required in patients with SLN deposits <0.1 mm in size [92]. However, the promising results reported in some series have not been universally reproduced in other studies, and as a result the prognostic significance of tumor burden in the sentinel nodes has not yet been fully elucidated. In the meantime, it is recommended that all patients with detectable disease in the sentinel nodes be treated as SN-positive and offered formal lymphadenectomy [46, 75].

Future Application of SNB for Melanoma of the Head and Neck

For melanoma, SNB is well established as a staging tool for patients with intermediate thickness primary tumors, and for selected patients in other groups. The main questions now focus on the optimal management of SNB-positive patients, and this is currently unclear. The MSLT-2 trial is a prospective randomized controlled trial, comparing the outcomes of completion lymphadenectomy and observation alone for SNB-positive patients [48] while further upcoming studies aim to randomize SNB-positive patients to receive completion lymphadenectomy or therapeutic irradiation [93], and interferon-alpha alone or interferon-alpha and completion lymphadenectomy [94]. Until the results of these studies become available, the recommended management of all SLN-positive patients is completion lymphadenectomy. In addition, the differences in technical success and false negative rates for SNB in the head and neck compared with other sites suggests that the results of large-scale prospective RCTs reporting all-sites melanoma data may not be immediately applicable to the head and neck population. Therefore, similar prospective trials tailored specifically to this patient group are required before definitive conclusions regarding optimal management can be reached.

Oral/Oropharyngeal Squamous Cell Carcinoma

Validation of the SNB technique for patients with early oral/oropharyngeal SCC has, until recently, involved staging patients with SNB, followed by immediate elective neck dissection [34, 49, 95]. From these studies, it has been demonstrated that SNB may be safely and successfully applied to patients with T1 or T2 disease and cN0 necks [33, 54]. The vast majority of the tumors studied to date are located in the oral cavity or accessible oropharynx and, while some reports do exist of SNB for other locations, such as the hypopharynx and supraglottic larynx [96], the status of the technique should remain "investigational" in these sites until further data becomes available. Furthermore, the use of SNB may be limited in patients with larger tumors which may be difficult to completely surround with tracer injections and which may ultimately require a neck dissection for tumor access or reconstruction purposes [51].

The promising results of these validation studies, demonstrating false negative rates of approximately 5%, have led some centers to over SNB as the sole staging tool for selected patients with early OSCC, with only those patients found SNB-positive going on to receive completion lymphadenectomy [33, 35].

The applications for SNB in early OSCC include staging of the ipsilateral cN0 neck, staging bilateral cN0 necks for tumors with ambiguous drainage (i.e., midline), and staging the contralateral cN0 neck for a midline tumor with an ipsilateral cN+ neck. Other applications, including the use of SNB for patients with recurrent primary tumors or following prior treatment to the neck, remain under investigation.

At the time of writing, there have been two large prospective clinical trials reported, examining SNB in this patient population [33, 35]. The interim results of a European multicenter trial involving patients from six centers were published in 2004, and demonstrated a 93% SN identification rate and 93% sensitivity in 134 patients undergoing SNB-assisted-END or SNB-alone for cT1/2 cN0 OSCC [33]. The 5-year follow-up for this population revealed one further nodal recurrence, giving an overall sensitivity of 91% at 5 years [97]. The identification rate and sensitivity were found to be significantly lower for patients with floor-of-mouth tumors, which the authors attribute to the technically challenging access to these tumors and close proximity to the first echelon lymph nodes. The authors concluded that SNB can safely be used as the sole staging tool for the majority of patients with early OSCC, but advise caution when evaluating floor-of-mouth tumors [33, 97].

Similar outcomes were reported by Stoeckli et al. in the largest single-institution series reported to date [35]. The authors reported a 98% identification rate and 94% negative predictive value in a series of 51 patients undergoing SNB alone for cT1/2, cN0 OSCC. The SENT is a large prospective study, incorporating the data from these two previous studies and several additional European centers. An interim analysis of this dataset, focusing on SLN-positive patients, was reported at 27 months of follow-up [98].

Of 72 patients (86 neck sides) undergoing completion lymphadenectomy for a positive SNB, 42% were found to harbor additional disease in the neck dissection specimen. Fifty-two percent of these additional positive nodes were located in the same neck level as the positive SLN, and only

4% were located out with the two adjacent neck levels. The authors conclude that it may be reasonable to limit therapeutic lymphadenectomies following positive SNB to three levels – one above and one below the positive SLN – potentially further reducing the morbidity associated with treatment of the neck.

Cutaneous SCC of the Head and Neck

For patients with cutaneous SCC, the rate of nodal metastasis is much lower, ranging from 0.3 to 16% [99, 100]. As a result, SNB has not been well studied in this patient group. As part of a larger series of multiple tumor types, Civantos et al. undertook SNB in a series of ten patients with "high-risk" cutaneous SCC, and detected occult nodal disease in only one patient. The authors concluded that further study is required to determine the most appropriate management strategy for these patients [91].

The Future of SNB in Oral/Oropharyngeal SCC

SNB provides the means for accurate and minimally invasive pathologic staging of the cN0 neck in patients with early OSCC. However, the exact role of SNB in the management of this patient group has yet to be fully elucidated and as a result, the technique has not yet gained universal acceptance. It is hoped that the upcoming results of the SENT trial and American College of Surgeons' Oncology Group (ACOSOG) Z0360 validation study [101] will provide the foundations for randomized phase III studies comparing SNB-alone with elective neck dissection, which currently remains the gold standard in most centers [101].

Merkel Cell Carcinoma

MCC is a rare, highly aggressive neuroendocrine tumor arising from the Merkel mechanoreceptor of the skin. It is associated with an overall 5-year survival of 30–64%, with a high incidence of local recurrence, regional lymph node involvement, and distant metastasis [102, 103].

In part due to the rarity of this tumor, there is no consensus on the current standard of care for management. Excision of the primary tumor may require wide margins for elective local control [104], or the addition of adjuvant radiotherapy if smaller margins are used [105]. In some series, radiotherapy alone has been shown to achieve similar local control rates to primary excision [106]. Elective treatment of the lymph nodes should be strongly considered due to reported nodal recurrence rates of up to 76% of stage I MCC patients in some series [107]. Prophylactic lymph node dissection appears to improve regional control, but does not lead to improved survival [108]. As a result, there is some disagreement regarding the utility of prophylactic node dissection in this population [82, 109].

Similarly, the utility of SNB in patients with early stage MCC is a topic of considerable debate. Advocates of the technique contend that SNB can help identify patients with occult nodal disease, demonstrate aberrant drainage patterns, and may prevent unnecessary neck dissection, parotidectomy and/or irradiation [81, 82]. In an exhaustive review of the existing literature, Mehrany et al. considered 60 patients undergoing SNB for MCC, and reported that SNB-positive patients were 18.9 times more likely to have nodal recurrence compared with SNB-negative patients after a median follow-up of 7 months [110]. Schmalbach et al. subsequently described a series of ten patients, eight of whom were found SNB-negative. After median follow-up of 34 months, nodal recurrence was observed in only one patient (12%), leading the authors to conclude that SNB is a safe and reliable technique for staging MCC [81].

However, these findings are at odd with a subsequent report by Warner et al., who found that SLN status is not an accurate predictor of locoregional recurrence in a series of 17 patients with MCC and a median follow-up of 16 months. The authors instead advocate the use of local and regional radiotherapy as a means of obtaining elective infield disease control [111]. Similarly, in a series of 23 patients undergoing SNB after previous excision of MCC, a nodal recurrence rate of 33% was noted in the SNB-negative group, leading the authors to question the prognostic value of SNB for MCC [112].

A smaller series of ten patients was recently reported by Schnayder et al., with six patients found SNB-negative. Of these, one patient developed nodal recurrence during the follow-up period (median 24 months). The authors concluded that, in this patient population with very high rates of occult micrometastatic lymph node involvement, the true utility of SNB may be ensuring that all at-risk nodes are adequately addressed, even in cases of "aberrant" drainage, e.g., to intraparotid lymph nodes or the contralateral lymphatic basin. Furthermore, SNB may allow for accurate staging in patients who are reluctant to undergo formal lymphadenectomy [82].

As with melanoma and SCC, the true prognostic significance of submicroscopic lymph node metastases, which are reported to occur in up to 100% of MCC patients, remains unclear [113]. Further study will be required to clarify the exact role of SNB in this population.

In the USA, the National Comprehensive Cancer Network (NCCN) currently recommends SNB for all patients presenting with previously untreated, localized stage I disease (NCCN Clinical Practice Guidelines in Oncology, v.1.2004).

Complications of Sentinel Node Biopsy

The steep learning curve, technical difficulty and minimally invasive approach of SNB may potentially lead to a higher risk of complications compared with formal lymphadenectomy; principally, damage to the facial or spinal accessory nerve. In addition, the requirement for a completion lymphadenectomy in SLN-positive patients represents a second procedure in an inflamed, recently operated surgical field, theoretically contributing to the risk of iatrogenic injury [91]. However, in experienced hands the incidence of complications following SNB is reported to be as low as 1% [37, 114].

For SLNs located in the region of the parotid gland, some authors advocate careful dissection and enucleation of the sentinel nodes. However, high rates of facial nerve paresis in selected studies have led some authors to recommend superficial parotidectomy over biopsy alone [37, 115].

Summary

SNB represents a useful tool for staging the cN0 lymphatic basins in patients with selected head and neck malignancies. For patients with melanoma, SNB is widely accepted as the gold standard staging tool for patients with intermediate thickness tumors, and may also be useful for patients in other groups. However, questions remain with regards to the optimal management of SNB-positive patients and the prognostic significance of very small tumor deposits. For the management of patients with early OSCC, SNB has not yet gained universal acceptance as a sole staging tool, and the results of ongoing large prospective trials are awaited in order to better understand its true role. Finally, the prognostic value of SNB for MCC has been questioned, and its utility may ultimately be limited to improvements in staging. Sentinel node biopsy has improved staging and has led to a more appropriate selection of oncological therapies. It is essential that sentinel node biopsy be performed in oncological centers by validated teams of surgeons, pathologists and nuclear medicine physician's with rapid access to oncologists and clinical trials on site.

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