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REVIEW

Sentinel Lymph Node Biopsy

A new approach in the management of head and neck cancers

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خزعة العقدة الليمفاوية الخافرة

نهج جديد في معالجة سرطان الرأس والعنق

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ABSTRACT: Cervical lymph node metastasis affects the prognosis and overall survival rate of and therapeutic planning for patients with head and neck squamous cell carcinomas (HNSCCs). However, advanced diagnostic modalities still lack accuracy in detecting occult neck metastasis. A sentinel lymph node biopsy is a minimally invasive auxiliary method for assessing the presence of occult metastatic disease in a patient with a clinically negative neck. This technique increases the specificity of neck dissection and thus reduces morbidity among oral cancer patients. The removal of sentinel nodes and dissection of the levels between the primary tumour and the sentinel node or the irradiation of target nodal basins is favoured as a selective treatment approach; this technique has the potential to become the new standard of care for patients with HNSCCs. This article presents an update on clinical applications and novel developments in this field.

Keywords: Head and Neck Cancer; Squamous Cell Carcinomas; Neck Dissection; Sentinel Lymph Node Biopsy; Lymphoscintigraphy.

الملخص: يؤثر انتشار سرطان العقدة الليمفاوية في الرقبة على التشخيص ومعدل البقاء على قيد الحياة والتخطيط العلاجي للمرضى الذين يعانون من سرطان الخلايا الحرشفية في الرأس والعنق. مع ذلك لا تزال طرق التشخيص المتطور تفتقر إلى الدقة في الكشف عن هذا الانتشار السرطاني الخفي. أخذ خزعة من العقدة الليمفاوية الحارسة وسيلة مساعدة لتقييم وجود المرض المنتشر الغير ظاهر سريريا. هذا الأسلوب يسهل تحديد مكان عملية تشريح الرقبة، وبالتالي يقلل من نسبة انتشارالمرض عند مرضى سرطان الفم. يفضل إزالة العقده الحارسة والطبقات بين الورم الرئيسي والعقدة الحارسة أو العلاج الإشعاعي لتجمعات عقدية مستهدفة كنهج للعلاج الانتقائي. يمكن لهذه التقنية أن تصبح معيارا جديدا لتقييم ورعاية المرضى الذين يعانون من سرطان الخلايا الحرشفية في الرأس والرقبة. تقدم هذه المقالة تحديثا على التطبيقات السريرية والتطورات الجديدة في هذا المجال.

الكلمات المفتاحية: سرطان الرأس والعنق؛ سرطان الخلايا الحرشفية؛ تشريح العنق؛ خزعة العقدة الليمفاوية الخافرة؛ تصويرالعقد اللمفاوية الحارسة.

As opposed to primary tumours, metastasis is responsible for the high mortality rate of most cancer patients; moreover, cancer cells primarily invade the regional lymph nodes before spreading to other parts of the body.[1] Genetic instability results in tumour cell heterogeneity, leading to the emergence of metastatic clones and dissemination of the cancer from the primary tumour site.[2] Malignant cells metastasise due to an interaction between the host factors and tumour cells. Genes related to the extracellular matrix, adhesion, motility and protease inhibition constitute a significant part of the metastatic process.[3]

Nodal Metastasis

NODAL METASTATIC CASCADE

The migration and invasion of cancer cells into the lymphatic system is governed by a variety of intricate genotypic, phenotypic and microenvironmental processes. After entering the lymphatic draining channels, the tumour cells metastasise to the regional lymph nodes in the neck and form the metastatic *foci*.[4] Macrometastases refer to lymph nodes that appear suspicious on clinical or radiographical examinations; in contrast, nodal metastases—which are not detectable by imaging methods or physical examination—indicate occult or subclinical metastasis. Hermanek microscopically differentiated occult metastases into macrometastases (metastatic deposits of >2 mm), micrometastases (metastatic deposits of <2 mm) and isolated or small clusters of tumour cells (metastatic deposits of <0.2 mm).[5] Isolated tumour cells (ITCs) can also be defined as a cluster of ≤200 tumour cells visible on one histology slide; these cells can further be categorised into those detectable by light microscopy, immunohistochemistry or molecular methods.[6] Chemoradiation or elective neck dissection (END) should be considered in patients

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with ITCs or those with a high risk of occult micrometastasis.[7]

The microenvironment of the lymph node is initially hostile to cancer cells due to a predominance of immune effector cells and cytokines; immunoresistant clones in the hostile lymph node *milieu* subsequently proliferate, spread and invade the rest of the lymphatic system to establish metastasis.[8] Malignant cells follow an orderly sequence, spreading from one nodal basin to the next as the disease progresses down the neck. In some situations, lymph node groups can be bypassed, which can result in a process known as skip metastasis.[9] However, controversial reports exist as to whether lymphatic tumours spread through new lymphatic vessels (i.e. lymphangiogenesis) or pre-existing peritumoural lymphatic vessels.[10] Different molecular components are also involved in the metastatic cascade, including *prospero homeobox 1*, lymphatic vessel endothelial hyaluronan receptor 1, podoplanin, vascular endothelial growth factor receptor-3, epithelial cadherin, catenins, syndecans, focal adhesion kinase, matrix metalloproteinases-2 and -9, metallothioneins and laminins.[11] These markers have recently been explored as a result of increased research interest in tumour lymphatics.[12]

A SIGNIFICANT PROGNOSTIC FACTOR

Lymph nodes in the head and neck constitute approximately 30% of the 800 lymph nodes in the human body.[13] Neck node metastasis is a major determinant in the prognosis of oral, oropharyngeal and other head and neck cancers; the disease-free survival rate decreases to approximately 50% with the presence of a single cancer-positive lymph node.[14] The extent of lymph node involvement should be considered as an indirect index of the systemic tumour load and is an important aspect of tumour staging; thus, the size, level and presence of a metastatic neck node determines overall survival and treatment planning.[15] In patients with oral cancer, the lymph node levels I to III are most commonly involved.[16] The frequency of skip metastasis to levels IV or V, bypassing the upper nodal levels, is approximately 4–5% in oral cancer, although this can increase to 16% in the tongue.[17] A clinically negative neck indicates a primary tumour of either ≤2 cm or 2–4 cm with no regional lymph node metastasis (N0).[18] The incidence of occult neck metastasis in stage I/II disease for patients with clinically negative necks is 30–34%.[12,19] The traditional approach to treatment has been to proceed with wide-margin radical neck surgery. However, prophylactic END for all patients with carcinomas of the oral cavity and a clinically negative neck results in an overtreatment rate of 65–70%; nevertheless, overall survival may be jeopardised if the carcinoma is not treated.[20]

Predictive factors associated with occult metastasis of the cervical nodes include primary tumour site, size, degree of differentiation, perineural and vascular invasion, inflammatory response and tumour ploidy status.[21] Advanced diagnostic approaches with greater accuracy are required, since these factors alone or along with conventional methods are insufficient to assess neck metastasis.[13] Advanced imaging modalities such as computed tomography, magnetic resonance imaging, ultrasonography, positron emission tomography (PET), lymphoscintigraphy and ultrasound-guided fine-needle aspiration cytology are often used for neck evaluation and screening in patients with oral cancer. Nonetheless, these approaches can fail to detect occult neck metastasis and subcentimetric or microscopic metastatic *foci*.[22]

For patients presenting clinically without regional disease, treatment approaches for oral squamous cell carcinoma (OSCC), and head and neck cancers in general, have been debated.[23] In cases of more advanced oral cancer, clinically evident and diagnostically proven locoregional metastasis give a clear-cut indication for treatment of the neck, based on the treatment approach for the primary tumour.[24] However, the management of patients with stage I/II disease and a N0 neck remains unclear; patients can be treated either with prophylactic END, irradiation or observation with regular follow-ups.[14] A surveillance approach can result in poor survival and increased risk of occult metastasis.[25] However, performing ENDs on all patients with N0 necks would lead to undue surgeries with large incisions, skin flaps and scars, the sacrifice of the spinal accessory nerve and the involvement or sacrifice of the sternocleidomastoid muscle and internal jugular vein, particularly if the surgery is bilateral.[26] Neck dissection could also lead to other *sequelae*, including shoulder and neck dysfunction, pain, contour changes, haemorrhage, nerve injury, lower lip *paresis*, lymphoedema, an increased need for postoperative radiotherapy, poor cosmetic outcomes and greater expenses.[27]

Sentinel Lymph Node Biopsy

A NOVEL APPROACH

Recently, the concept of a sentinel lymph node (SLN) was introduced in head and neck squamous cell carcinomas (HNSCCs) in order to more precisely

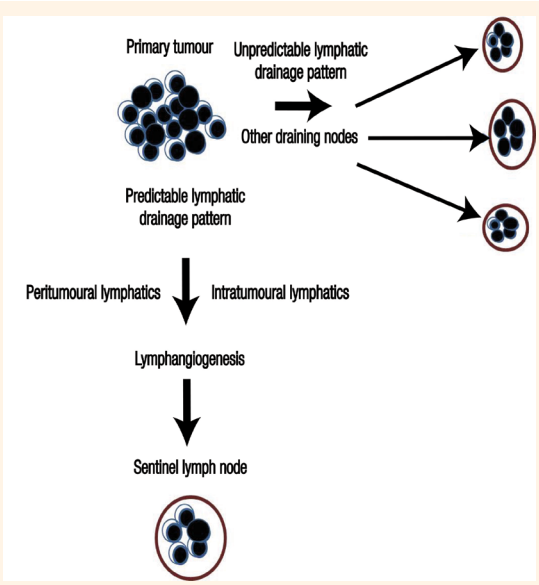

Figure 1: Flowchart depicting the process of primary tumour spread to a sentinel lymph node.

detect and evaluate neck metastasis and unpredictable lymphatic drainage patterns, following its successful application in melanomas and breast cancer.[22,28] Several validation studies involving ENDs have resulted in SLN cancer detection rates of >95%.[12] Following the orderly and sequential drainage in the lymphatic stream from the tumour site, the first node reached is the SLN, which could help predict the nodal stage of metastasis [Figure 1]. In theory, if the SLN is free from cancer cells, then distal node involvement is assumed to be rare.[29] Thus, the lymphatic basin status can be ascertained along with a reduction in poor prognosis and morbidity rates.[28,30]

A SLN biopsy is an ancillary diagnostic method for assessing the presence of occult metastatic disease in a N0 neck. This minimally invasive technique eliminates the need for a neck dissection, which until recently was thought to be the only means of neck staging.[31] A SLN biopsy is a selective procedure based on the identification and evaluation of echelon nodes (i.e. first station or levels I and II) for metastatic spread; hence, the first drainage node or group of nodes, known as the SLN, are chosen for dissection as the location at which a primary tumour first metastasises.[14] In 1996, the first successful SLN biopsy was performed by Alex *et al.* on a patient with a laryngeal supraglottic carcinoma; Koch *et al.* subsequently proved the feasibility of this procedure in 1998 for selected patients with head and neck mucosal lesions.[27] Morton *et al.* found that selective lymphatic dissection performed after a SLN biopsy was therapeutically equivalent to a comprehensive elective lymphatic dissection among patients with skin melanomas.[32]

TREATMENT PROTOCOLS

In recent decades, improved understanding of lymphatic drainage patterns in the head and neck region have simplified the assessment of higher risk nodal levels.[27] There has been a gradual shift towards a more conservative/selective surgical approach for patients with clinically negative necks, progressing from radical neck dissection to modified radical neck dissection and subsequently selective neck dissection.[33] The techniques and methodology for SLN identification in head and neck cancers have been widely debated and are still under investigation [Tables 1 and 2].[5,14,15,22,24,27–31,34–46]

Shoaib *et al.* suggested a protocol involving preoperative lymphoscintigraphy, intraoperative blue dye and gamma probe localisation [Figure 2].[30] This technique is based on observing the route of lymphatic flow via imaging after the injection of a radioactive contrast agent near the primary tumour.[42] The flow and direction of the lymph, comparable to the possibly metastatic flow from the tumour, can be visualised preoperatively by means of lymphoscintigraphy or single-photon emission computed tomography (SPECT). Lymphoscintigraphy reveals SLNs associated with the primary tumour, unexpected lymphatic drainage patterns and lymphatic vessels associated with different lymphatic drainage basins.[14] To enhance the detection rate, blue dye is often used in combination with radioisotopes.[47] During the surgery, a handheld gamma probe is used for radionuclide detection to trace the SLN perioperatively and a gamma camera is used for dynamic monitoring of lymphatic drainage. The site of the radioactive lymph nodes, which are important anatomical landmarks, are marked using a gamma camera and the *ex vivo* radioactivity of the nodes and surgical bed is checked after removing the nodes.[31]

Histopathological evaluation, immunohistochemistry and molecular markers have been suggested for a small number of harvested SLNs to help detect occult metastasis in serial lymph node sections, including molecular techniques such as polymerase chain reaction and immunohistochemistry using cytokeratin markers.[43] These could potentially lead to more accurate nodal staging and the detection of nodal micrometastatic deposits and ITCs.[48] It has been suggested that step serial sectioning at 150 μm intervals with pan-cytokeratin enhances nodal detection by approximately 20% in comparison to the initial routinely stained section.[15] Murer *et al.* reported lower postoperative morbidity rates and better shoulder function following a SLN biopsy in comparison to an END.[49] Hernando *et al.* observed

Table 1: Literature review of studies regarding lymph node identification and the utility of a sentinel lymph node biopsy in the management of head and neck cancers[22,24,28,29,31,34–41]

Author and year of study	N	Lymphatic mapping method	SEN/SPEC	Association	Conclusion
Werner *et al.*[35] (2002)	90	^{99m}Tc nanocolloidal injection during lymph node dissection	SEN: 89%	-	•Serial sectioning may serve to increase the diagnostic reliability of a limited ND •There is a need to remove all radioactive SLNs
Chikamatsu *et al.*[22] (2004)	11	LSG (^{99m}Tc-labelled colloidal rhenium sulphide), gamma probe and gamma camera for radiolocalisation and monitoring	SPEC: 100%*	NPV: 100%	•A ND is not necessary for patients with a N0 neck as determined by a SLN biopsy, even if a physical examination or imaging is positive for lymph node metastasis
Alvarez Amézaga *et al.*[29] (2007)	25	LSG (colloidal human serum albumin), vital dye and gamma probe	SEN: 93.4% SPEC: 100%	OR: 183.71	•Due to its high SEN, a SLN biopsy can be performed even in the initial stages of OSCC
Stefanicka *et al.*[31] (2010)	12	LSG (^{99m}Tc-labelled radiocolloidal human serum albumin), gamma probe and gamma camera for radiolocalisation and monitoring	SEN: 100%	NPV: 100%	•Identification of SLNs in patients with OSCCs is technically feasible and accurate and can predict occult metastasis
Civantos *et al.*[28] (2010)	140	LSG (^{99m}Tc colloidal sulphur) and gamma probe for radiolocalisation	-	NPV: 96%	•A SLN biopsy with step sectioning and immunohistochemistry correctly predicts a pathologically-confirmed N0 neck
Broglie *et al.*[36] (2011)	79	LSG, SPECT and intraoperative use of a handheld gamma probe	-	-	•A SLN biopsy can help to select patients with stage I/II OSCC and occult lymph node disease for an elective ND •The occult metastasis recurrence rate in SLN-negative patients is superior to that of SLN-positive patients
Melkane *et al.*[24] (2012)	53	LSG (^{99m}Tc-labelled colloidal rhenium sulphur) and gamma probe for radiolocalisation	-	NPV: 95.2%	•A SLN biopsy may be an excellent staging method in early oral cancers •Routinely undiagnosed micrometastasis may also be clinically significant
Borbón-Arce *et al.*[37] (2014)	25	LSG (hybrid tracer with ICG dye and a ^{99m}Tc nanocolloid) followed by SPECT two hours later, a portable gamma camera with a NIR fluorescence camera and a handheld gamma ray probe for detection	-	-	•A multimodal approach resulted in the identification of 26% additional SLNs compared to a traditional method
Rigual *et al.*[38] (2013)	38	Preoperative LSG with intraoperative gamma probe localisation	SEN: 71%	NPV: 94%	•Most patients with positive SLN biopsy results also had additional positive nodes on ND •There was a low rate of isolated neck recurrence among patients with negative SLN biopsy results •Patients with negative SLN biopsy results had better overall/disease-specific survival rates
Milenović *et al.*[34] (2014)	30	LSG and ultrasound-guided puncture of the lymph nodes, gamma probe and gamma camera for radiolocalisation	SEN: 93%	-	•A SLN biopsy should be performed in selected cases, as it is sometimes easier to perform a ND in certain localisations
Flach *et al.*[39] (2014)	62	Preoperative LSG, blue dye and intraoperative gamma probe for detection	SEN: 80%	NPV: 88%	•A SLN biopsy reduces occult lymph node metastasis risk in T1/T2 oral cancer (40% versus 8%) •Patients with negative SLNs and no elective ND achieve an excellent rate of occult metastasis recurrence with a SLN biopsy which compares favourably with primary elective ND outcomes
Den Toom *et al.*[40] (2015)	90	Preoperative LSG and intraoperative blue dye and gamma probe for detection	SEN: 93%	NPV: 97%	•A SLN biopsy is a reliable diagnostic staging technique for early-stage N0 oral cancer
Salazar-Fernandez *et al.*[41] (2015)	96	Cervical LSG and SPECT	SEN: 88%	NPV: 94%	•A SLN biopsy is an excellent OSCC staging method •There is a small risk of additional lymph node metastasis with SLN micrometastasis

SEN = sensitivity; SPEC = specificity; ^{99m}Tc = technicium-99m; ND = neck dissection; SLN = sentinel lymph node; LSG = lymphoscintigraphy; NPV = negative predictive value; N0 = without regional lymph node metastasis; OR = odds ratio; OSCC = oral squamous cell cancer; SPECT = single-photon emission computed tomography; ICG = indocyanine green; NIR = near-infrared; T1 = primary tumour of ≤2 cm; T2 = primary tumour of 2–4 cm.

**For all N0 patients.*

Table 2: Indications, contraindications, advantages and disadvantages of a sentinel lymph node biopsy[5,14,15,27–30,42–46]

Indications	Contraindications	Advantages	Disadvantages
•For patients with T1/T2/N0 head and neck tumours •To assess bilateral T1/T2/N0 primary head and neck tumours close to or crossing the midline •To clarify the need for contralateral dissection in tumours with one clinically positive side close to the midline •To ensure accurate radiocolloid application in well accessible primary tumours	•For clinically positive neck nodes, as metastatic involvement interferes with the normal lymph node architecture, leading to anomalous draining patterns •For patients with a history of prior surgeries or treatments that may have altered normal lymphatic drainage patterns •For pregnant or lactating patients, as the extent of the SLN biopsy may need to be modified to minimise the risk of radiation exposure and blue dye injections •For large primary tumours which can directly compress the draining lymphatic vessels	•Allows the accurate detection and staging of SLN metastasis with minimal morbidity as the technique is minimally invasive •Guides decision-making during the management of head and neck tumours •Limits the necessity of performing prophylactic END for all patients •Prevents the unnecessary removal of functional nodes •Allows selective excision of the SLN •Allows adequate assessment of the nodal status of the remaining neck tissue with a subsequent histopathological examination •Helps to identify skip metastasis, micrometastasis and unpredictable lymphatic drainage patterns •Improves the histological evaluation of surgical specimens •Reduces the number of lymph nodes required for a detailed history and physical examination in comparison to an END •Saves time and expense •Shortens the recovery period •For medically fit patients	•May be difficult as the approach is technique-sensitive •The use of blue dye may elicit an allergic response •False-negatives can occur due to uneven radionuclide injection, the obscuring of the SLN by the radioactive signal of the primary tumour and the obstruction of the lymphatic vessels by the gross tumour, resulting in a redirection of lymphatic flow •The accuracy of this technique in identifying true SLNs is inadequate in patients with tumours of the floor of the mouth •In cases of multiple SLNs and SLNs at different levels, the number of SLNs to be removed is still unknown, which may lead to an extensive procedure similar to that of an END •The 'shine through' phenomenon and scatter radiation due to the primary tumour can obscure identification •Variability in head and neck lymphatic drainage may result in collateral channels leading to skip metastasis

T1 = primary tumour of ≤2 cm; T2 = primary tumour of 2–4 cm; N0 = without regional lymph node metastasis; SLN = sentinel lymph node; END = elective neck dissection.

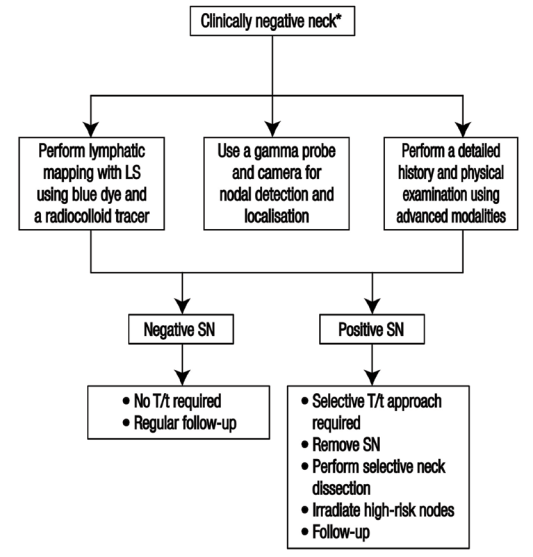

Figure 2: Proposed treatment protocol for a sentinel lymph node biopsy.[30]

**A clinically negative neck indicates a primary tumour of either ≤2 cm or 2–4 cm with no regional lymph node metastasis.[18]*

LSG = lymphoscintigraphy SN = sentinel node; T/t = treatment.

statistically significant increased shoulder function and reduced average scar length among patients receiving a SLN biopsy in comparison to those undergoing END; neck haematomas and orocervical communication were reported only in the END group and SLN biopsies were associated with lower rates of postoperative morbidity.[44]

Alkureishi *et al.* reported that the pathological review of a SLN or neck dissection specimen can affect the staging of a lymph node if it reveals occult or additional positive lymph nodes which might have been missed on a routine physical examination or radiographical evaluation.[43] This alteration in lymph node staging could increase the risk for distant metastasis and change the patient's prognosis and treatment plan.[50,51] In HNSCC cases, a SLN biopsy has been suggested as a valid method to improve the accuracy of pathological staging of lymph nodes and subsequently allow treatments to be tailored.[32] In a meta-analysis, Thompson *et al.* found that a positive SLN biopsy confirmed occult metastasis in 31% of patients; this correlates with a previously reported occult metastatic rate of 33%.[45,52]

Evaluation of a positive lymph node status is critical as it is a major indicator for adjuvant radiation and chemotherapy. The use of a SLN biopsy allows adjuvant or elective chemoradiation to be avoided, as well as the associated morbidities of these treatment options.[53] For example, HNSCC patients receiving chemoradiation are more likely to develop acute mucositis, oral pain, *dysphagia* and xerostomia; in addition, they are more frequently hospitalised.[45,54] Patients with a negative SLN biopsy can therefore

avoid adjuvant therapy, which would lessen patient morbidity; this option can be reserved for a later time in the event of a second primary diagnosis or tumour recurrence.[46] While a SLN biopsy is not yet considered the standard of care for cancers of the oral cavity, many single- and multi-centre studies have successfully demonstrated its feasibility in oral cancers with high detection rates (approximately 95%) and negative predictive values (88–100%), thus substantiating its significance and use in the staging and treatment of early-stage head and neck cancers.[43,55,56]

Advances and Future Developments

A variety of soluble tracers and radiocolloids have been used in lymphoscintigraphy, including technetium-99m (^{99m}Tc)-labelled colloidal human serum albumin, colloidal sulphur, ^{99m}Tc colloidal rhenium sulphide and a dextran-based product modified to allow ^{99}Tc-labelling.[13,21,44,57] Tsuchimochi *et al.* proposed performing a SLN biopsy using multimodality imaging and polyamidoamine-coated silica nanoparticles loaded with ^{99m}Tc and indocyanine green dye.[47] Deeply situated SLNs can be detected more accurately with the use of near-infrared dyes; recently, hybrid tracers combined with radiotracers and fluorescence dyes have resulted in high sensitivity for preoperative SLN mapping.[57] Bluemel *et al.* evaluated the feasibility and potential advantages of freehand SPECT in oral cancer in comparison with conventional intraoperative localisation techniques for a SLN biopsy; they found that one of the most important limitations of a SLN biopsy—the 'shine-through' phenomenon—was overcome by freehand SPECT.[58]

According to Denoth *et al.*, metastatic deposits are not randomly distributed within SLNs but are predominantly found in the central planes, closer to the lymphatic inlet; analysis of the distribution pattern of metastatic spread within SLNs with a virtual microscope resulted in a detection rate of 90% and 80% for micrometastasis and ITCs, respectively.[59] Van Den Berg *et al.* introduced the concept of hybrid tracers containing both radioactive and fluorescent labels which allowed for the direct integration of pre- and intraoperative guidance technologies when used in combination with new surgical imaging modalities and navigation tools in SLN detection.[57] Using ultrasound-guided spectroscopic photoacoustic imaging of molecularly-activated plasmonic nanosensors in an OSCC murine model, Luke *et al.* demonstrated that lymph node metastases as small as 50 µm could be detected *in vivo* at a depth of 1 cm with high sensitivity and specificity; this new approach could potentially be a sensitive alternative to a SLN biopsy.[1]

In various animal studies, attempts to combine several techniques have been reported, including the addition of ^{99m}Tc, iodine-125 or iodine-111 to phthalocyanine tetrasulfonate, dextran and Evans blue, methylene blue or blue Ficoll dyes.[47,60] Tsopelas *et al.* found ^{99m}Tc-Evans blue to be useful in differentiating the initial draining lymph node from higher-tier nodes in linked chains.[61] The clinical applications of a SLN biopsy could be enhanced through on-going developments and innovations. These might include the preoperative use of PET, the biological staging of primary site biopsies, the discovery of more radionuclide-avid lymph nodes or ultrasound-detectable injectable contrast agents as potential second tracers, the application of intraoperative reverse transcriptase polymerase chain reaction analysis of the sentinel node and the use of endoscopic SLN biopsies.[14,26,27,62,63]

Conclusion

A SLN biopsy can prevent the unnecessary removal of functional lymph nodes and limit the extent of neck dissection surgery. However, surgical precision and experience as well as specific technical devices are required for its successful application and implementation in the head and neck region. Although a review of the current literature demonstrated the reliability and worldwide acceptance of this approach, the role of SLN biopsies in HNSCCs is still under investigation. Using the sentinel node concept helps to define the surgical approach to a clinically negative neck and identify skip metastasis and unpredictable lymphatic drainage patterns, resulting in a more favourable prognosis for patients with head and neck cancers.

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