TECHNIQUE

SENTINEL LYMPH NODE BIOPSY IN PATIENTS WITH ORAL CANCER

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Abstract

The presence of lymph node metastases is the most important prognosticator in patients with head and neck squamous cell carcinoma. Treatment for node positive disease is well standardized but considerable variations still exist in managing patients with clinically undetectable nodes in the neck. It is in this scenario that sentinel lymph node (SLNB) is investigated, in identifying the presence of occult metastases. This article reviews the evolution, concept, technique and scope of sentinel lymph node biopsy for metastases detection, especially in oral cancers.

Introduction

Early detection and diagnosis are crucial in order to maximize the potential for successful outcomes in the management of cancer patients. This is vital in oral cancer cases as an early diagnosis can lead to adequate treatment and a better prognosis. The effective management of patients with oral cancer requires the accurate staging of the disease, which greatly depends upon the status of the cervical lymph nodes. Many studies have confirmed that with the presence of lymph node metastasis, the five-year survival rates decrease by approximately 50% from the rates in those without nodal metastases.¹² Further, the presence of lymph node metastasis correlates with both recurrence of the primary tumor as well as the development of distant metastases.

Treatment for node positive disease is well standardized but considerable variations still exist in managing patients with clinically negative nodes in the neck. Almost 20% of patients clinically negative nodes in the neck are thought to have occult metastases which is nodal metastatic disease that has not been detected by clinical staging investigations or radiologic examination.³⁴ Identifying subclinical cervical metastases holds the key to managing these subset of cases. Currently available imaging techniques such as ultra sonography, CT, MRI and positron
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Staging of cancers by sentinel lymph node identification and biopsy is based on the concept that metastasis from a primary tumor occurs by predictable orderly spread. The first to receive the metastatic spread will be the first echelon node before filtering to the remainder of the lymphatic basin (figure 1). Therefore, identification and histopathologic examination of the sentinel node can define the disease status of the entire regional lymphatic nodal basin. This technique identifies patients who are more likely to benefit from therapeutic lymph node dissection, which will be thus performed on documented evidence rather than on probability of metastasis.

Evolution of the concept

The sentinel lymph node concept was first postulated by Gould in 1960 while performing parotidectomy. In the year 1977, Morton and colleagues introduced cutaneous lymphoscintigraphy for identifying the regional lymphatic basin of primary drainage at metastatic risk in melanoma cases. Research directed toward the development of a technique to selectively identify the sentinel lymph nodes progressed over the next 15 years and in 1992, Morton et al., published the first report describing the use of blue dye and radiotracer to successfully identify these nodes.

The first report of a patient with neck metastases successfully identified by sentinel lymph node biopsy in head and neck squamous cell carcinoma was from Alex and Krag, in the year 1996. The patient had a primary laryngeal primary tumor. Shortly thereafter, the procedure was introduced for oral cancer by Koch, Pitman and co-workers. They found that the technique was feasible only in selected cases when the radio colloid and isosulfan blue dye technique was used.
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Shoaib and colleagues then combined blue dye and radio-colloid to successfully identify sentinel lymph nodes in 16 of 17 patients with oral and oropharyngeal tumors.\textsuperscript{11}

In 2001, an international conference on SLNB in head and neck cancer was convened by experienced investigators in the field, from 21 cancer centres around the world. The pilot studies of these centres culminated in a European multi-centric trial using a standardized technique to allow meaningful comparisons and in 2002, The American College of Surgeons - Oncology Group initiated a multicenter prospective trial to compare SLNB with elective neck dissection in the staging of patients with oral carcinoma.\textsuperscript{12}

The technique

SLNB involves preoperative lymphoscintigraphy, intraoperative lymphatic mapping using hand held gamma probe or vital blue dye and finally pathologic evaluation of the sentinel lymph node.

Preoperative lymphoscintigraphy

Under topical or local anesthesia, a radiocolloid tracer is injected into the submucosa around the periphery of the primary tumor using a 25-gauge needle, usually at four quadrants (figure-2).

The optimal colloid to which the radioactive tracer is tagged is the one that accumulates in the first lymph nodes with minimal uptake in the surrounding capillaries or at the initial injection site. Filtered Tc 99 m (Technetium) sulfur colloid preparation with a particle size in the range of 15-20 nm in a volume approximately 0.2 to 0.4 ml produce acceptable results. This colloid is readily available, and has an energy peak 140 kev, which is within the operating parameters of most gamma cameras and hand held gamma detectors (figure-3).
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Figure 3. Positioning of the patient under the Gamma camera

The tracer travels quickly to the first echelon sentinel lymph node, where it becomes trapped and filtered through the nodes before reaching the second and third echelon node, which is located at a lower radioactivity level. The transit time in oral lesions are less than 30 minutes. Lymphoscintigraphic imaging serves as a road map for planning the surgical procedure. Dynamic and static scans are captured using gamma cameras after injection of the tracer (figure-4). The areas of focal uptake in the cervical lymphatics corresponding to the sentinel lymph nodes are marked on the patient’s skin (figure-5). This marking facilitates the design of an appropriate incision later.

Figure 4. Dynamic and static scans captured using gamma cameras
Intraoperative lymphatic mapping

The patient is then brought to the operating room for surgery under general anaesthesia. Whenever possible, the primary tumor is excised first to reduce background radioactivity.

The neck is probed transcutaneously using a hand held gamma probe to confirm the location of radioactive lymph nodes that were identified by lymphoscintigraphy (figure-6).

**Figure 5.** Corresponding sentinel lymph nodes marked on the patient’s skin

**Figure 6.** The neck of the patient is being probed transcutaneously using a hand held gamma probe
For guidance to sentinel lymph nodes, a hand-held gamma probe with collimated 14 mm tip can be used. An initial reading serves as background level. A sentinel lymph node is defined as a node with an activity ratio of 3:1 (counts at least three times the background levels). Once the lymph node is identified, it is then removed by sharp dissection or electrocautery. The radioactivity level of all excised nodes is measured with the probe and recorded. A ratio of radioactivity in an excised sentinel node relative to a non sentinel lymph node (ex vivo activity ratio) of 10:1 or higher confirms correct identification of sentinel node. The nodal basin is reprobed for residual radioactivity to verify that all sentinel nodes are removed. The activity of the lymphatic bed drops to background level which ensures the removal of all sentinel lymph nodes. It is important to note that there can be more than one sentinel nodes for a lesion.

A vital blue dye can also be used to identify sentinel lymph nodes. An amount of 0.5 to 1.0 ml is injected into the submucosa around the periphery of the primary tumor before excision. The most investigated dye is isosulfan blue in 1% aqueous solution. When the dye enters a sentinel node, it stains part of the node pale blue, thus clearly distinguishing the sentinel lymph node from the surrounding non sentinel node. Blue dye permits sentinel lymph node identification when radio colloid fails, such as when the sentinel nodes are located in lymphatic basins lying close to the primary tumor. This technique lost popularity due to significant incidence of allergic reactions, including life threatening anaphylaxis. Moreover, it is necessary to expose the entire nodal basin to detect the sentinel nodes as they are identified only through visual examination.

Pathologic evaluation of sentinel lymph node

Intraoperative examination of the sentinel lymph node is very important for patients with nodal metastasis. Patients with nodal metastasis can undergo immediate neck dissection and can be spared a separate operation. The two techniques currently employed for rapid diagnosis are imprint cytology with touch preparations of the sentinel lymph node cut surface (made by gently rolling the freshly obtained biopsy specimen between two slides or by gently pressing the glass slides over the specimen before fixation) and frozen section examination. The main advantage of frozen section is that it offers an opportunity to decide immediately whether to perform a neck dissection during the same time. The disadvantages include frozen tissue artifacts and loss of some tissue.

Examination by imprint cytology is useful during operation because multiple cut surfaces can be examined quickly. Advantages include excellent cytological detail, speed, and preservation of tissue for paraffin section histopathology. Disadvantage includes less cells for examination and a higher chance of indeterminate results (atypical or suspicious cells) compared with frozen section technique.

In the traditional approach to the examination of regional lymph node, a longitudinal section from the middle of each
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node is cut and stained. This represents only a partial procedure as the remainder of the node is left unexamined. Many published reports indicate that single sectioning of lymph nodes underestimates the true metastases status of lymph nodes. On the other hand thorough examination of the entire node calls for extraordinary labour intensive and expensive procedure. Thus to increase the chances of finding small metastasis it is desirable to make serial step sections followed by routine staining with haematoxyline and eosin H&E). Immunohistochemical analysis for cytokeratin staining can also be performed.

The formalin fixed node is bisected through the long axis and further divided into slices of 2.5mm. It is then serially step – sectioned at 150um intervals. Four sections are cut and mounted from each step. The first section is stained with H&E. In the absence of metastases, the second section is stained with an antibody to pancytokeratin, for immunohistochemical analysis. If the cytokeratin staining is positive, the third section is stained with H&E to confirm the presence of viable tumor. The fourth section is retained for any further evaluation. This technique is expected to identify all metastases including micro metastases.19-21

Advantages of SLNB

- Improves the accuracy of tumor staging
- Less invasive procedure
- Avoid unnecessary nodal dissection
- Limited morbidity and mortality

Possible pitfalls

- Unlike small primary tumors, a bulky invasive primary tumor invades adjacent anatomic subsites thus posing difficulty for peritumoral injection.
- Occurrence of skip metastases makes interpretation of lymphatic mapping complicated due to altered lymphatic drainage pattern.
- Proximity of primary tumor to the draining lymphatic basin, as is seen in floor of the mouth tumors.
- Clinically positive nodes are difficult to be identified by sentinel node mapping because of the poor uptake of tracer; instead they redirect the entire lymphatic flow.

Conclusions

Staging with SLNB when there is no involvement of lymph nodes in the neck and an extensive pathological workup will help to decide the treatment and further management of patients with oral cancer and occult metastases. However, the technique of SLNB needs to be validated by doing large scale studies with long term follow up data in order to establish this as a new standard procedure. SLNB needs to be proven yet to be practical for primary tumors at a wider spectrum of sub sites in the oral cavity. The regional control and overall survival rates of patients undergoing SLNB in staging and the management of oral cancer should be equivalent or superior to those achieved with elective neck dissection; then only the potential of this procedure would be known.

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