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Reliability of sentinel lymph node biopsy in head and neck squamous cell carcinoma

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ABSTRACT

Background: The sentinel lymph node is the hypothetical first lymph node or group of nodes draining a cancer. In case of established cancerous dissemination it is postulated that the sentinel lymph node is the target organs primarily reached by metastasizing cancer cells from the tumor. Thus, sentinel lymph nodes can be totally void of cancer, due to the fact that they were detected prior to dissemination. Sentinel node biopsy is considered to be the gold standard investigation tool for the detection of lymph node metastases in head and neck squamous cell carcinoma.
Methods: Sentinel node mapping uses one or all of the following three :(1) radioisotope scan imaging (2) injection of blue dye (3) use of a handheld isotope tracer probe for localization, it has been shown that the combination of all three techniques increases the accuracy and the yield of sentinel lymph node identification.
Results: Sentinel lymph node biopsy should be recommended only in patients with previously untreated early stage (T1/2) oral cavity and oropharynx cancer with clinical N0 stage. Sentinel node radio localization in head and neck squamous cell carcinoma may potentially reduce the time, cost, and morbidity of regional lymph node management.
Conclusions: Sentinel node biopsy is a reliable means of staging the clinically N0 neck for patients with cT1/T2 head and neck squamous cell carcinoma. It can be used as the sole staging tool for the majority of patients.

Keywords: Sentinel node, Sentinel lymph node biopsy, Squamous cell carcinoma

INTRODUCTION

Anatomically and histologically, the head and neck region is one of the most complex parts of the human body. This complexity serves as the foundation for the development of a myriad of neoplastic processes with diverse behaviours and outcomes. The combination of anatomic and functional intricacies and the neoplastic spectrum necessitates a basic understanding of cancer biology, in addition to a working knowledge of all therapeutic options for delivering optimal care to patients with head and neck neoplasms.

Moreover, in addition to exercising exceptional surgical skills, the head and neck surgeon must appreciate and optimize the anatomic and physiologic impact of treatment. The vast majority of head and neck neoplasms arise from the mucosa of the upper aero- digestive tract, including the oral cavity, pharynx, larynx, nasal cavity, and sinuses, but neoplasms also can originate from the salivary glands, thyroid and parathyroid glands, soft tissue, bone, and skin.[1] The most common malignant neoplasms of the head and neck are squamous cell carcinoma and papillary thyroid cancer. Salivary gland cancers and sarcomas of the soft tissue and bone are relatively infrequent.

Surgery has been the mainstay of therapy for neoplasms in the head and neck for more than a century. With the introduction of ionizing radiation in the latter half of the

20th century, radiotherapy became an important modality used either independently or in combination with surgery. Although initially chemotherapy was used primarily with palliative intent, it is now used as part of curative treatment approaches when combined with radiation, producing significant responses in patients with squamous cell carcinomas of the head and neck. Similarly, biological or targeted agents also are evolving to become part of standard therapy. Accordingly, understanding and implementing multidisciplinary management strategies are cornerstones for achieving optimal therapeutic outcomes. Head and neck cancer is highly curable if detected early, usually with some form of surgery, but radiation therapy may also play an important role, while chemotherapy is often ineffective.

Mucosal squamous cell carcinoma of the head and neck often metastasises regionally via lymphatic routes in the early course of the disease, while distant spread is usually encountered in patients with advanced disease. For optimal treatment planning, a thorough assessment of the metastatic status of the tumour is required. Current imaging methods do not allow the recognition of all patients with metastatic disease. Therefore, elective treatment of the cervical lymph nodes is usually given to patient in whom the risk of subclinical metastasis estimated to exceed 15-20%. Sentinel lymph node biopsy was one as a means of diagnosing patients with subclinical cervical metastasis.[2]

The sentinel lymph node is the hypothetical first lymph node or group of nodes draining a cancer. In case of established cancerous dissemination it is postulated that the sentinel lymph node is the target organs primarily reached by metastasizing cancer cells from the tumor[3]. Thus, sentinel lymph nodes can be totally void of cancer, due to the fact that they were detected prior to dissemination. Sentinel node biopsy is considered the "gold standard" investigation tool for the detection of lymph node metastases.[3]

METHODS

Sentinel node mapping

Sentinel node mapping uses one or all of the following three techniques:

1. Radioisotope scan imaging
2. Injection of blue dye
3. Use of a handheld isotope tracer probe for localization

It has been shown that the combination of all three techniques increases the accuracy and the yield of sentinel lymph node Identification. A preoperative technetium scan is obtained first, which requires injection of a radioactive technetium 99m-labeled sulphur colloid. In general, O.O5 mCi of the isotope is injected in four quadrants around the primary lesion, and a gamma probe is used to obtain visual images at 3 minutes and 15 minutes and a delayed image at 1 hour. Usually the first lymph node identified by the technetium scan is considered the sentinel lymph node.

In some patients more than one sentinel lymph node is identified.[4] Immediately prior to the surgical procedure, isosulfan blue dye 1% (Lymphazurin) is injected similarly in four quadrants around the primary tumor. No more than 0.5 ml of the dye is injected in the sub dermal plane around the tumor. The operative procedure then is carried out with 30 minutes of the injection.

A handheld gamma probe is used before placing the incision to localize the lymph node seen on the preoperative scan. The background activity is averaged from measurements in four quadrants of the neck, and any node that has in vivo 10-second count more than three times that of the background is considered "hot." Correlation is made with the preoperative scan, and this area is marked with a marking pen on the skin. An incision is placed directly overlying the localized sentinel lymph node, and by careful alternate blunt and sharp dissection, the "blue node" is localized. The handheld probe is again used to measure the count of highest radiotracer activity.

If the blue node corresponds to the area of highest radiotracer activity, then the lymph node is excised and sent for pathological analysis. After excision of the lymph node, the surgical bed is tested with the handheld probe to show that the radiotracer activity is now reduced to that observed in the adjacent background area, confirming that the true "sentinel lymph node" has been excised and sent for pathological analysis.

If the residual radioactivity in the basin is more than 10% of the ex vivo count of the hottest node in the basin, further exploration to find more sentinel nodes is warranted. Similarly, after the node is excised, the radiotracer activity is measured with a handheld probe from the lymph node ex vivo to demonstrate that the lymph node itself has a count at least 10 times of an adjacent non-sentinel node.

This Step ensures that the excised lymph node is indeed a true sentinel lymph node because of the special processing required by sub serial sectioning of lymph node to identify occult metastasis, some investigators prefer not to send the lymph node for frozen section and wait for "rush paraffin sections"' within 24 hours to get a more detailed analysis of the sentinel lymph node. Further surgical management of regional lymph nodes then depends on the pathological analysis of the excised sentinel lymph node.

Sentinel lymph node biopsy should be recommended only in patients with previously untreated early stage ($T_{1/2}$) oral cavity and oropharynx cancer with clinical N_0 stage.[5] This procedure is technique sensitive. The isolated

Sentinel lymph node should be subjected to serial step sectioning at 150 µm and by haematoxylin and eosin staining and immunohistochemistry.

RESULTS

Sentinel node biopsy is a reliable means of staging the clinically N_0 neck for patients with cT_1/T_2 head and neck squamous cell carcinoma. It can be used as the sole staging tool for the majority of patients. The sentinel node biopsy procedure has shown high sensitivity rates in pilot studies for oral and oropharyngeal squamous cell cancer across the globe and is reliable and reproducible. This article provides a firm evidence base for forthcoming trials on the role of sentinel node biopsy in head and neck cancer. Sentinel node biopsy can be used safely and with technical success for accessible head and neck squamous cell carcinomas. It offers the potential for more anatomically accurate surgery based on each patient's unique lymphatic drainage pattern. However, selective neck dissection remains the standard approach for most oral cancers, particularly for larger T_2, T_3, and T_4 lesions. Sentinel lymph node biopsy can be advocated as a reasonable alternative to selective neck dissection for very early oral cancers[6]. Unlike melanoma, in which the presence of lymphatic metastasis portends an extremely poor prognosis, squamous cell carcinoma with early lymphatic metastases remains curable. Thus, there is much more to lose by understating patients or missing involved lymph nodes. Accurate localization of the sentinel lymph node using radiolabelled sulphur-colloid is feasible in patients with squamous cell carcinoma of the head and neck region. Sentinel lymph node biopsy should be recommended only in patients with previously untreated early stage ($T_{1/2}$) oral cavity and oropharynx cancer with clinical N_0 stage. Sentinel node radio localization in head and neck squamous cell carcinoma may potentially reduce the time, cost, and morbidity of regional lymph node management; more experience with technique is required before its role can be determined.

DISCUSSION

Most carcinomas result from complex interplay between intrinsic and environmental factors. Environmental carcinogenic signals that promote the development of most human cancers remain ill-denned. In contrast, correlative studies have shown that alcohol and tobacco exposure are key causative factors for carcinomas of the mucosa of the upper aero digestive tract. Head and neck cancers are typically tobacco-related cancers, with initial risk for the development of cancer and subsequent risk for additional primary cancers directly attributable to the duration and intensity of tobacco use. Moreover, persons who both smoke and consume alcohol regularly have a multiplicative increase in risk that is up to 10 to 20 times higher than that of non-smokers and non-drinkers, as reflected by a geometric rise in the incidence with increasing use of tobacco and increasing consumption of alcohol.[7] Accumulating evidence suggests that human papilloma virus is associated with the development of oropharyngeal carcinomas. Genetic predisposition to the development of head and neck cancers in patients with Fanconi anaemia is thought to be related to human papilloma virus infection. Similarly, immune-compromised patients with human immunodeficiency virus infection and patients undergoing chronic immunosuppressive treatment after organ transplantation have an increased risk for the development of head and neck cancers. Several other factors also are known to play a role in the pathogenesis of tumors in the head and neck region. For example, exposure to ionizing radiation increases the risk for the development of primary malignant tumors of the thyroid gland and salivary glands as well as for cancers of the skin, soft tissues, and bone. Similarly, Epstein-Barr virus infection is thought to promote the development of nasopharyngeal cancer.

Head and neck cancers form the fifth most common cancer type and cause for cancer-related deaths worldwide. Significant geographic variation exists in the incidence of squamous cell carcinomas of the head and neck. The highest incidence carcinomas of the oral cavity and oropharynx is reported in Southeast Asia, where chewing tobacco with betel quid ("paan") An extremely high incidence of the development of differentiated carcinoma of the thyroid gland in children has been reported in Belarus and the Ukraine following the Chernobyl accident in 1986. Although initially the adult population in these areas did not show an increase in thyroid cancer, it is becoming apparent that the adult population exposed to the Chernobyl accident is now manifesting a delayed appearance of thyroid cancer. In addition to this phenomenon, during the course of the past decade a rising incidence of differentiated carcinoma of the thyroid gland has been reported worldwide, but this finding is attributed to the early diagnosis of clinically occult tumors due to increasing awareness and frequent utilization of routine sonography of the neck and other imaging studies.

Elective neck treatment refers to treatment of the cervical lymph nodes performed as a precaution, because cervical nodal metastases cannot be excluded. Elective neck treatment usually means elective neck dissection in conjunction with the resection of the primary tumour, though Radiotherapy can also be used, if the primary tumour is treated by Radiotherapy. The morbidity related to unilateral elective neck dissection is usually considered reasonable. The appropriate treatment regimen of clinically N_0 neck in patients with head and neck squamous cell carcinoma has been a subject of much debate[8]. It is a commonly accepted principle to treat the neck electively when the risk of occult metastasis is estimated to exceed 15-20%; otherwise the neck is left under close follow-up and treated therapeutically, if metastases have developed at follow-up. This approach results in considerable over-treatment and on the other hand, occult cervical metastases of some patients are initially left untreated.

History of sentinel node

The basic concept of sentinel node originated from halsted theory which emerged in 19th century. This concept states that tumor cells metastasise to the various parts of the body through lymphatic system before haematogenous spread. The concept of the SLN was first described in 1960 by Gould; he successfully used frozen section analysis of a lymph node in a certain location near the caudal end of the parotid gland to guide in the decision making whether to perform a neck dissection or not in patients with parotid malignancies. In 1977 Cabanas described the use of preoperative lymph angiograms to identify inguinal lymph nodes at greatest risk for metastatic growth in patients with penile carcinoma. In 1992 Morton first described method of intraoperative localization of the Sentinel lymph nodes using blue dye in patients with early stage melanoma[9]. In this preliminary study, Sentinel lymph node biopsy detected the patients with occult metastases with high accuracy.

In 1994, van der Veen et al. introduced the intra-operative use of handheld gamma probe, which is currently the most important method for SLN identification. Since then, validation studies have demonstrated that Sentinel lymph node status accurately reflects the status of the whole lymphatic basin in breast cancer and melanoma.[9] Sentinel lymph node biopsy has become a standard of care in treatment of these tumours sparing the Sentinel lymph node -negative patients the morbidity of more comprehensive lymphadenectomies.

In recent years, the concept of Sentinel lymph node biopsy has been applied to many other malignant tumours, such as oesophageal, gastric, colorectal, and lung. It seems probable that Sentinel lymph node biopsy will have an increasing role in the surgical treatment of malignant tumours in the future. It was not until 1996 that Alex and Krag related its use in the evaluation of the neck in oral and oropharyngeal cancer. The enthusiasm aroused by this concept in N_0 staged patients is due to the prognostic importance of lymph node status and to the high detection rate of metastases or even micro metastases in melanoma and breast cancer. SN biopsy is considered the "gold standard" investigation tool for the detection of lymph node metastases. Lymphoscintigraphic detection of the sentinel nodes has 2 major drawbacks; first, there is no consensus on radiotracer injection technique, which makes comparisons between clinical series difficult, second, regions of increased uptake are not precisely localized. Multimodal registration of scinti-graphic and computed tomography images provides information on localization in an original way[4]. Although image registration is used in numerous clinical situations, it has never been applied to the anatomic identification of sentinel nodes in the head and neck.

Efficacy of sentinel lymph nodes in head neck squamous cell carcinoma

There is increasing literature documenting the efficacy of sentinel lymph node evaluation in patients clinically staged as N_0 necks with diagnostic accuracy of 90% and with few reported false negatives. Elective treatment of cN_O necks by surgery or irradiation is controversial, with some authorities advocating a conservative (watch and wait) approach and other authorities advocating treatment.

Overall risk of occult metastases or neck recurrence in cN0 neck ranges from 10% to 30%, prompting arguments for and against elective treatment. The majority of patients with cN0 necks probably do not harbour occult metastases, but patients with undetected and untreated metastases will with experience high failure rates with increased morbidity and mortality; for this reason, sentinel lymph node procedure is gaining more support in the treatment of cNO neck.

The prognosis of oral squamous cell carcinoma depends of the control of neck metastasis as well as the local cure. For decades, the radical neck dissection has been the classical treatment for cervical metastasis of the oral cancer; but it occasionally results in functional and aesthetic complications. Although cervical lymph node metastasis can be detected by palpation and various imaging procedures such as CT, MRI, Ultrasonic, or Positron Emission Tomography, the accuracy is no more than about 80%.

Sentinel node biopsy is emerging as an alternative technique for staging the neck and although still in infancy, several case series have been reported and the technique seems to have been an accurate means of determining nodal status.[5]

The success of SLNB rests upon the belief that metastases will travel first from the primary tumor site to the sentinel lymph node, and only subsequently move on to the remaining regional lymph nodes. Therefore, if the sentinel lymph node can be identified and then selectively biopsied, the decision to subsequently perform a complete lymphadenectomy would be based on the documented existence of proven metastasis in the SLN, rather than on the less certain statistical probability of nodal metastases based on primary tumor factors.[10] when the sentinel lymph node biopsy is negative for metastasis, lymph node dissection is not necessary [as has been accepted for malignancies like breast cancer and cutaneous melanomas]; thus sparing the patient of the unnecessary morbidity, and, functional and aesthetic complications.

There are various advantages to the sentinel node procedure. First and foremost, it decreases lymph node dissections where unnecessary, thereby reducing the risk of lymphedema, a common complication of this

procedure. Increased attention on the node(s) identified to most likely contain metastasis is also more likely to detect micro-metastasis and result in staging and treatment changes. The main uses are in breast cancer and malignant melanoma surgery, although it has been used in other tumor types (colon cancer) with a degree of success.[11]

However, the technique is not without drawbacks, particularly when used for melanoma patients. This technique only has therapeutic value in patients with positive nodes. Failure to detect cancer cells in the sentinel node can lead to a false negative result - there may still be cancerous cells in the lymph node basin. In addition, there is no compelling evidence that patients who have a full lymph node dissection as a result of a positive sentinel lymph node result have improved survival compared to those who do not have a full dissection until later in their disease, when the lymph nodes can be felt by a physician. Such patients may be having an unnecessary full dissection, with the attendant risk of lymphedema.

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