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Review

The history of sentinel node biopsy in head and neck cancer: From visualization of lymphatic vessels to sentinel nodes

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SUMMARY

The aim of this report is to describe the history of sentinel node biopsy in head and neck cancer. Sentinel node biopsy is a minimally invasive technique to select patients for treatment of metastatic lymph nodes in the neck. Although this procedure has only recently been accepted for early oral cancer, the first studies on visualization of the cervical lymphatic vessels were reported in the 1960s. In the 1980s mapping of lymphatic drainage from specific head and neck sites was introduced. Sentinel node biopsy was further developed in the 1990s and after validation in this century the procedure is routinely performed in early oral cancer in several head and neck centers. New techniques may improve the accuracy of sentinel node biopsy further, particularly in difficult subsites like the floor of mouth.

Introduction

The sentinel node (SN) procedure is a diagnostic staging procedure that is applied in a variety of tumor types. The procedure aims to determine the tumor status of the SN(s). An SN is defined as a lymph node on a direct drainage pathway from the primary tumor [1]. The concept is based on the premise that lymph flow from the primary tumor travels sequentially to the SN and then on to the other regional lymph nodes. So, the SN is the node most likely to harbor metastases. The histopathologic status of this node should reflect the histopathologic status of the entire nodal basin, and additional treatment of the nodal basin (e.g., surgery) is routinely performed in case of metastatic involvement of the SN. A negative SN, however, would justify a wait and see policy avoiding unnecessary elective neck dissections and the associated shoulder morbidity, hospital stay, costs and loss of barrier for tumor spread in case of recurrence or second primary head and neck tumor.

The routine SN biopsy (SNB) consists of preoperative peritumoral injections of technetium-99m-labeled nanocolloidal albumin (or similar radiopharmaceutical) followed by lymphoscintigraphy using planar and single photon emission tomography/computed tomography (SPECT/CT) imaging. Based on the preoperative lymphoscintigraphy results, the position of the SN is marked on the skin. Peroperatively, a blue dye is administered at the tumor site. This dye will also travel to the SN, staining the afferent lymph vessel and the node. SNB is performed under general anesthesia and intraoperative detection of the SN is guided by a combination of a portable (free hand) gamma ray detection probe (radionuclide detection) and dissection of the blue lymph vessel. Ideally, one or more blue and/or radioactive ('hot') SNs are identified and excised. After surgical removal, the SN is subjected to meticulous histopathological examination using stepped serial sectioning and immunohistochemistry.

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SNB is currently standard in melanoma and breast cancer. The role of the SN in head and neck cancer is evolving and the procedure is now standard in patients with T1-T2cN0 oral squamous cell carcinoma suitable for transoral excision without entering the neck for resection of reconstruction in several head and neck centers in Europe. This report describes the history and the validation of this technique with particular reference to oral cancer.

The human lymphatic system

Herophilus (300 BC) in Alexandria first noticed lymph vessels although he thought they were blood vessels [2]. Thomas Bartholin (1616–1680) from Denmark gave the lymph vessels their name [3]. Virchow, in the nineteenth century, formulated the theory that lymph nodes filter particulate matter from lymph. To determine the barrier function of lymph nodes, several investigators injected particles or tumor cells into certain afferent lymphatics in animal models. Tumor cell emboli were immediately trapped in the subcapsular sinus and do not spread to the next node for some time [4]. Rouvière described the anatomy of the cervical lymphatic system in 1932 [5].

The cervical lymphatic system

Based on information obtained in large groups of patients, Lindberg [6], Byers et al. [7,8] and Shah et al. [9] described the common patterns of lymphatic drainage of head and neck tumor sites. Knowledge of these patterns has allowed the neck dissection to be progressively limited to those nodal levels at highest risk. The SN concept can be considered to be an extension of this philosophy. However, clinical experience from groups of patients may not provide reliable information to direct therapy in an individual patient. Byers et al. [10] found in 16% of 277 patients with squamous cell carcinoma of the oral tongue "skip metastases" that bypassed the expected first nodal basin. Moreover, the neck contains over 100 lymph nodes and there was a need to determine the nodes at risk in individual patients. The sentinel node biopsy fulfills this need.

Lymphatic mapping

Visualization of the lymphatic system in humans using the direct method of lymph vessel cannulization and injection of water-soluble contrast material was first described by Kinmonth in 1952 [11]. This technique was performed in studies of the lymphatic system of the upper and lower extremities. The introduction of oil-contrast material has extended the clinical application of lymphangiography by allowing better visualization of lymph nodes, e.g. in the retroperitoneal space [12].

Visualization of the cervical lymphatics

Lymphangiography of the cervical lymphatic system was developed some years later. In 1960 lymphangiography using water-soluble contrast was reported [13,14], and visualization of cervical lymph nodes with oil-contrast material was reported two years later [15,16]. The original method required cannulization of lymph vessels at three separate sites [16], whereas later cervical lymphangiography used a single retroauricular approach for cannulization of a deep retroauricular lymph vessel and injection of an oil-contrast material was presented in 100 patients by Fisch and Sigel [17]. They demonstrated that separate channels from the injection area exist that by-pass a single node or a group of nodes when cervical metastases block lymphatic flow. The absence of flow to the contralateral side was considered to be important in evaluating the possibilities of metastatic patterns [17]. Fish performed this procedure in 20 patients with laryngeal or pharyngeal carcinoma and found a block to oil-contrast material in all patients. A block in the lymphatic system not necessarily implied the presence of metastatic carcinoma as a reticular or lymphatic hyperplasia of the cervical nodes alone also produced an obstruction in the lymphatic flow. Although cervical lymphangiography alone could not be used to prove the presence of lymph node metastases, it was considered that the absence of a block or of a filling defect in a node might exclude the presence of cancer [18].

Schwab and Winkel [19] performed lymphoscintigraphy after retroauricular subcutaneous injections of ^{198}Au-labeled colloid. Large lymph node metastasis created a defect on the scintigrams, but small lymph node metastases could not be identified by this technique. Similar findings were reported by Zita [20] in 1967. Fernholz [21] reported on 67 of these procedures in cancer patients after injections at several sites, i.e. mastoid, anterior tongue, posterior tongue, buccal mucosa and lower lip. The visualization of the different lymph node regions was best with a deposit in the tongue. Non-palpable lymph node metastases could not be detected by this technique with certainty [21]. Because of more favorable physical characteristics, ^{99m}Tc replaced ^{198}Au as radionuclide for lymphoscintigraphy. Thommesen et al. [22] studied the lymphoscintigraphic pattern in the head and neck region in 45 healthy subjects after submucosal injection of ^{99m}Tc-Sn(II)-sulfide colloid in the oral cavity and found a substantial variation in the number of visualized lymph nodes and in the accumulated radioactivity [22]. In 1987, Hildmann et al. [23] were the first to use ^{99m}Tc-labeled colloid for lymphoscintigraphy in head and neck cancer patients. Twenty-three patients with pharyngeal and laryngeal carcinoma were bilaterally injected in the paramedian mucosa of the nasopharynx or hard palate. The drainage pattern was highly variable and micrometastases could not be detected [23]. Sri-Pathmanathan and Railton [24] conducted a pilot study to assess the role of lymphoscintigraphy in the detection of lymph node metastases in 16 patients with oral squamous cell carcinoma who received ^{99m}Tc-labeled sulphur microcolloid injections over each mastoid. Perfusion or gap defects were considered abnormal. There were no false positive cases but some false negative results were found. These studies provided extensive information on the cervical lymphatic system in general, but appeared not to be of value for the detection of (occult) lymph node metastases.

Peritumoral injections were introduced the 80's and replaced cannulation of the cervical lymphatics to investigate the drainage pattern from the primary tumor. Lymphoscintigraphy after peritumoral injections of ^{99m}Tc-labeled sulphur microcolloid was already used in 1981 to evaluate the status of neck nodes preoperatively in small group of patients with oral squamous cell carcinoma. Differences in imaging intensity between both sides of the neck were used to predict the presence of metastases. This technique correctly predicted the presence of metastases in 2 out of 2 patients with palpable nodes, and the absence of metastases in 3 out of 4 patients with clinically tested negative necks [25]. More than a decade later, Terui et al. [26] reported lymphoscintigraphy 3 h after after peritumoral injections of ^{99m}Tc-labeled rhenium sulphur colloid in 21 head and neck cancer patients, of whom 6 had mucosal carcinoma (i.e. retromolar area). The cervical regions were visible in 86% of the patients on the affected side and in 91% on the healthy side. An average of 4.8 nodes per patient were visualized on the affected side and 5.5 on the healthy side. Klutmann et al. [27] observed lymphatic drainage in 53 of 75 (71%) head and neck squamous cell carcinoma (HNSCC) patients after peritumoral injections of ^{99m}Tc-labeled colloid. Unexpected drainage was found in 17 (23%) of these patients with clinically negative or positive necks. The investigators stated that aberrant lymphatic drainage