Journal of the Egyptian Nat. Cancer Inst., Vol. 14, No. 3, September: 177-183, 2002

The Value of Sentinel Lymph Node Localization and Biopsy in Squamous Cell Carcinoma of the Oral Cavity

AMR A. ATTIA, M.D.** and WALID OMAR, M.D.*

*The Departments of Surgery**, Nuclear Medicine*, National Cancer Institute, Cairo University.*

ABSTRACT

Purpose: Since the description of the technique of sentinel lymph node biopsy for malignant melanoma in the early 1990s, there has been a wide development of interest in this issue. It is now being investigated for several malignant diseases as carcinoma of the vulva, cervix and penis. In our country, head and neck cancer represents a larger group than most western reports (17% vs. 5%). Oral cavity cancer represents one of the most common malignancies second to skin cancer in this region. Accordingly our objective in this study is to investigate the feasibility and value of sentinel lymph node biopsy in squamous cell carcinoma of the oral cavity. Since neck dissections are being done for this group of patients, it would seem rational to devise this new technique to modulate patient treatment.

Material and Methods: Thirty patients with oral cavity carcinoma (T_1-T_4) N_0 underwent sentinel node biopsy (SNB) at the National Cancer Institute Cairo University, prior to an elective neck dissection (END) for over two years.

Results: Identification of sentinel lymph nodes using isotope injection was successful in 28 of the 30 patients (93.4%) and when using the patent blue dye the SLN was identified in 21 of the 30 cases examined (70%).

Pathological examination of the 28 SLN identified with isotope injection proved negative for micrometastases in 25 cases (89.3%) and positive in 3 cases (10.7%). Pathological examination of the other lymph nodes of the neck after neck dissection found 100% agreement with pathology of SLN. Pathological examination of SLN in the 21 cases identified using the dye found no micrometastases. Also examination of the lymph nodes after neck dissection found no micrometastases.

Conclusion: This preliminary but promising experience with SLN identification in squamous cell carcinoma of the oral cavity may offer the potential to treat only node positive patients with this approach while avoiding the morbidity of treatment of node negative patients.

Key Words: *SNB (sentinel node biopsy) - END (elective neck dissection) - SOND (supra-omohyoid neck dissection).*

INTRODUCTION

Since the description of the technique of sentinel lymph node biopsy for malignant melanoma in the early 1990s, there has been a wide development of interest in this issue. It is now being investigated for several malignant diseases as carcinoma of the vulva, cervix and penis. In our country, head and neck cancer represents a larger group than most western reports (17% vs. 5%) [3]. Oral cavity cancer represents one of the most common malignancies second to the skin cancer in this region.

Since most neck dissections are being done for this group of patients, it would seem rational to devise this new technique to modulate patient treatment after investigating the feasibility and value of sentinel lymph node biopsy, which is the main objective of this study.

At the National Cancer Institute, Cairo University, we have been performing sentinel node biopsy (SNB) in oral cavity squamous cell carcinoma for over two years. We performed the technique prior to an elective neck dissection (END). We will describe the initial results using sentinel node biopsy in conjunction with an END.

PATIENTS AND METHODS

This study was conducted at the National Cancer Institute (NCI), Cairo University, between November 2000 and May 2002. It included thirty patients (22 males, 8 females with different ages) with squamous cell carcinoma of the oral cavity (T_1 9, T_2 10, T_3 6, T_4 5), (N_0). Preoperative evaluation of the patients included clinical examination, routine, laboratory investigations, chest X-ray, ultrasound and C.T of the neck. All patients were injected preoperatively with radiocolloid and intraoperatively with patent blue dye.

Lymphoscintigraphy was performed on the morning of surgery, using technetium 99m (^{99m}TC) prepared with nanocolloid. The tracer (0.5 mCi in 1 mL) was injected around the circumference of the primary tumor. A syringe with a permanently secured needle was used for injection to prevent inadvertent spillage of nanocolloid into the mouth. Activity was estimated at as many points as necessary in an attempt to surround the tumor completely.

Imaging commenced within 2 minutes of injection. Dynamic imaging of 15 minutes duration (30 x 15 frames/sec) in the anteroposterior (AP) projection with the patient lying supine, was followed by static imaging in both A-P, Fig. (1) and lateral projection with the patient setting Fig. (2).

At operation, 0.5-1 ml of patent blue dye was injected peritumoral just before skin preparation (15-30 min prior to surgery) to minimize the risk of disrupting lymphatic channels draining the primary tumor.

A triradiate incision was then made in the neck and the skin flaps were raised. If the sternomastoid muscle was to be preserved, it was separated from its investing fascia and retracted posteriorly to expose the deep cervical chain of lymph nodes.

Measurements of the accumulated radioactivity in the radiolabeled lymph nodes were performed with a handheld γ detector. The point of maximal emission identified the sentinel node. For each patient, the following γ-count measurements were obtained:

1- The hot spot/node in vivo before incision.

2- The hot spot/node ex vivo.

3- The lymphatic bed after hot spot/node removal.

4- The background in the operating room.

Radioactive nodes were excised and a 10 sec count was performed to measure ex-vivo radioactivity within the node. Blue stained lymphatics, if seen, were followed to the first draining lymph node. Elective neck dissection was done (supraomohyoid neck dissection) (S.O.N.D) with resection of the primary tumor according to current accepted treatment standards in the first 10 patients. The sentinel lymph node and lymphadenectomy specimen were submitted separately for histopathological evaluation.

Contrary to what had been done by other authors [2,5] in the literature to reduce emission of radiation from the injection site and to avoid the problem of overlapping of the radioactivity from the primary tumor to the neck, at first resection of the primary tumor according to current accepted treatment standards, was done, then localization of sentinel lymph node was carried out by a hand held γ detector and blue dye.

Data were analyzed according to:

1- Number of patients with identified sentinel lymph nodes.

2- Number of sentinel lymph nodes in each patient.

3- Status of sentinel lymph node.

4- Status of neck dissection.

5- Site of sentinel lymph node.

6- Correlation between staining, isotope uptake, pathological status and imaging studies.

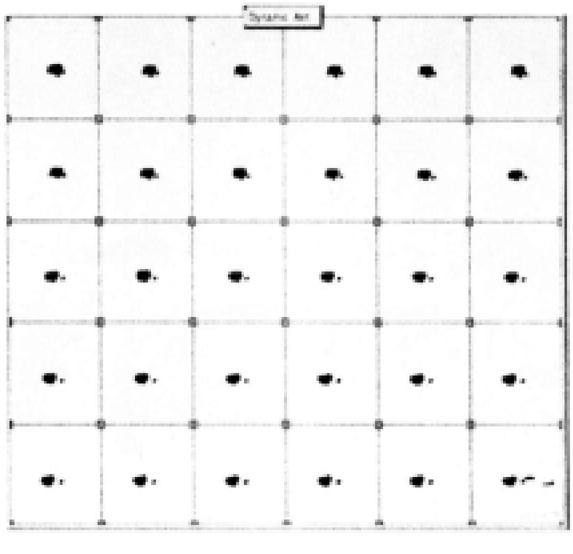

Fig. (1): T_2 lower lip N_0 Sq.c.c. dynamic images of sentinel lymph node scintigraphy.

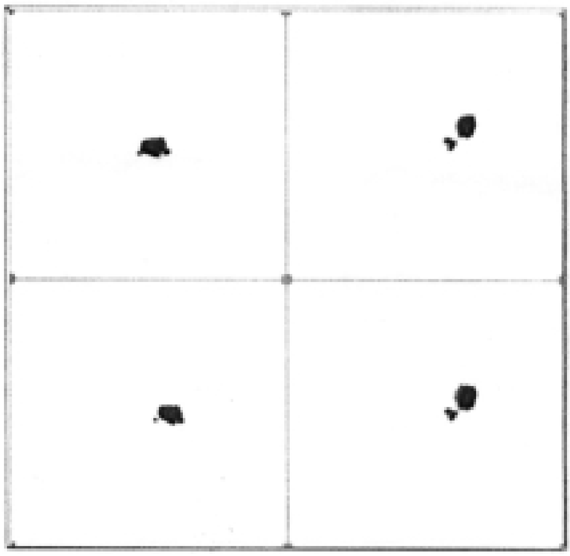

Fig. (2): T_2 lower lip N_0 Sq.c.c. static images of sentinel lymph node scintigraphy.

RESULTS

The study included 30 cases of oral cancer. Two methods were adopted for identification of the sentinel lymph nodes; nanocolloid injection and patent blue dye injection.

The sex distribution was 22 males (73.3%) and 8 females (26.7%). Table (1) shows the site of lesions encountered in the patients.

Table (1): Site of lesion.

	Frequency	%
Tongue	7	23.3
Buccal mucosa	7	23.3
Lower lip	8	26.7
Retromolar	2	6.7
Floor of mouth	2	6.7
Upper alveolar	2	6.7
Lower alveolar	2	6.7
Total	30	100.0

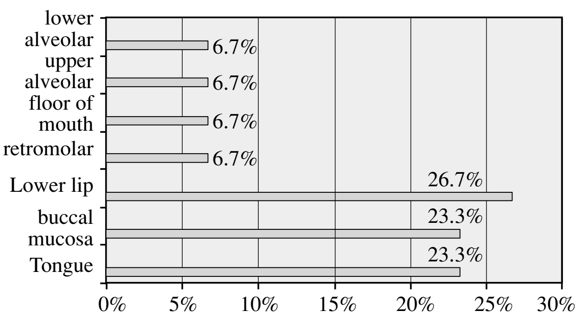

Fig. (3): Site of lesion.

Table (2): T stage of cases.

	Frequency	%
T_1	9	30
T_2	10	33.3
T_3	6	20
T_4	5	16.7
Total	30	100

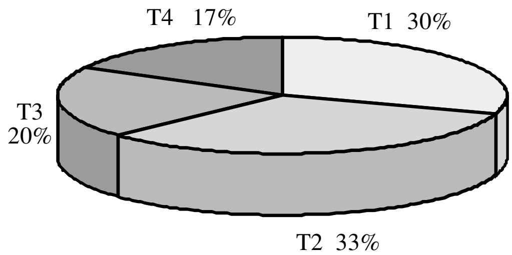

Fig. (4): T stage of the cases.

Isotope injection succeeded in identification of sentinel lymph nodes in 28 of the 30 patients (93.4%). In fact, the remaining two cases were expected to fail. This is due to the unavoidable delay of surgery on these two cases for 2 days after injection of the radioactive isotope ^{99m}Tc which has a relatively short half-life (6 hours). So, no radioactivity was detected with the gamma probe at the time of operation. The sites of SLN detected in the cases are shown in table (3).

Table (3): Site of sentinel lymph node identified.

	Frequency	%
Submental	5	16.7
Submandibular	14	46.7
Level II	7	23.3
Level III	2	6.7
No SLN	2	6.7
Total	30	100

Table (4) shows the distribution of SLN in relation to the site of lesion in the cases as identified by the isotope injection. In tongue cases, SLN are mainly in level II then in level III. All buccal mucosa cases are distributed to submandibular nodes.

Table (4): Distribution of SLN in relation to the site of lesion.

	Submental	Submandibular	Level II	Level III	Total
Tongue			4 (66.7%)	2 (33.3%)	6 (100%)
Buccal mucosa		6 (100%)			6 (100%)
Lower lip	3 (37.5%)	5 (62.5%)			8 (100%)
Retromolar		1 (50%)	1 (50%)		2 (100%)
Floor of mouth	2 (100%)				2 (100%)
Upper alveolar			2 (100%)		2 (100%)
Lower alveolar	2 (100%)				2 (100%)

Pathological examination of the 28 SLN identified proved -ve for micrometastases in 25 cases (89.3%) and positive in 3 cases (10.7%). Pathological examination of the other lymph nodes of the neck after neck dissection found 100% agreement with the pathology of SLN, where all cases with negative SLN had negative results from other nodes and vice versa.

Identification of SLN using patent blue dye gave the results shown in table (5) in relation to the findings of isotope injection. It was evident that the dye identified the SLN in 21 of the 30 cases examined (70%). In relation to the findings of isotope injection, these 21 cases represent 75% of the 28 cases identified. The dye did not identify SLN in the 2 cases that failed on isotope injection.

Pathological examination of SLN in the 21 cases identified using the dye found no micrometastases. Also, examination of the lymph nodes after neck dissection found no micrometastases.

Table (5): Relation between SLN identification using the dye and isotope methods.

Isotope	Blue		Pale		Total
	No.	%	No.	%	
Identified	21	75.0	7	25.0	28
Failed			2	100.0%	2

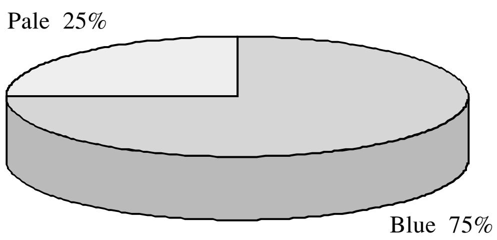

Fig. (5): Results of dye injection among the 28 cases with identified SLN on isotope injection.

DISCUSSION

Cancers, of head and neck represent 5% of all malignant tumors in USA and 17% in Egypt [3]. The incidence of oral cancer in developed countries is less than 5% of oral malignancies and in developing nations is reported to be the third most common malignancy [14].

Intraoral cancer constitutes 25-35% of head and neck cancer. The age of patients at presentation ranges from 50 to 60 years with a male predominance of 3:1 [12].

In oral cavity squamous cell carcinoma, the incidence of occult cervical lymph nodes can be estimated by several prognostic factors (site, size and depth of tumor, perineural lymphatic vascular invasion and host tumor interface) and ranges from 15% to 60%. Management of the N0 neck has been advocated when the risk of micrometastases is approximately 30% [11].

Controversy remains about the best means to determine the nodal status of these patients. Clinical examination and radiologic imaging techniques are relatively inaccurate for staging the neck and nodal status can only be determined accurately following a forma neck dissection.

Identification and staging of subclinical disease depends on the clinical acumen of the examiner, the adequacy of imaging studies, and whether imaging-guided fine needle aspiration cytology is used. This incidence ranges from 12% to over 50% (median 33%) and varies with the site of the primary tumor. Because uniform criteria to identify the presence of subclinical disease have not been established, the gold standard remains the identification of metastatic deposits by careful methodological examination of the surgical specimen obtained at the time of neck dissection. The goal of infallibly identifying "subclinical disease" without surgical intervention remains elusive. It would be preferable to have proof of the existence of cancer to be treated in the individual patient, but the means to obtain such proof nonsurgically do not exist [6].

Treatment modalities include radiation therapy and elective neck dissection. Radiation therapy has several shortcomings [8] First, patients without metastases are treated unnecessarily. Second, once irradiated, patients with new primaries or recurrences cannot be treated by this treatment modality. Third, histological staging of lymph status is not possible and thus these patients are denied this diagnostic parameter. In contrast, elective neck dissection allows complete pathological evaluation and conclusive assessment of the regional lymph node status. When micrometastases are identified, the patient's planned therapy can be modified to reflect the more serious nature of the disease. The principle disadvantage of elective neck dissection is that a significant number of "at-risk" patients do not have micrometastases and thus are unnecessarily subjected to the time and morbidity of lymph node resection [2,4].

Currently, surgical judiciousness guides the extent of regional lymph node resection for all at-risk patients. However, if a precise, minimally invasive method of diagnosing metastatic disease were available, treatment would be based on the actual, not the hypothetical, presence of micrometastases. The surgical emphasis would shift from decreasing the extent of surgical resection to restricting the number of patients who undergo surgery. Only patients with proven metastasis would have treatment and the 55% to 85% of at-risk, but non-affected, patients would avoid the morbidity of presumptive elective treatment.

In a study by Carvalho et al. [5], it was found that nodal recurrence after supraomohyoid neck dissection occurred in 4.5% of 154 patients who had elective supraomohyoid neck dissection for oral and oropharyngeal cancer. In this study, all patients were initially clinically N_0 and nodal recurrence occurred inside the limits of supraomohyiod neck dissection in 57.1% and beyond in 42.9% [5]. Although the overall incidence of nodal recurrence was small we may deduce from the previous study that it may have occurred due to a skip beyond the limits of supraomohyiod neck dissection or failure to identify a node harboring metastasis at the time of dissection and this adds importance to the concept of the sentinel lymph node localization to obviate the small failure of supraomohyiod neck dissection.

The most accurate method currently available for staging N_0 neck is pathologic examination of the neck contents after elective neck dissection. The identification of occult cervical metastases before neck dissection would represent an important advance in the treatment of patients with squamous cell carcinoma, since 60% to 70% of patients with N_0 necks do not harbour occult regional metastases. Preoperative diagnosis of microscopic metastases would derive therapeutic benefit from neck dissection. Therefore, if there were a method to accurately identify occult metastases preoperatively, management of the N_0 neck would be more selective and would reduce the overall morbidity and cost of treatment in cases that are now managed with the policy of elective neck dissection [9].

So, our study was undertaken to formulate a method for sentinel node biopsy in patients with oral cavity squamous cell carcinoma when using a combination of preoperative lymphoscintigraphy, intraoperative identification of radioactive nodes with the gamma probe and lymphatic mapping after injection of blue dye before skin incision.

In our study at National Cancer Institute, 30 patients with squamous cell carcinoma of the oral cavity were submitted for identification of the sentinel lymph node with preoperative lymphoscintigraphy using nanocolloid injection and intraoperative gamma probe identification combined with patent blue dye and 28 sentinel lymph node were identified [28,30].

Twenty-eight sentinel lymph node cases accurately reflected the status of nodal basin i.e. pathological examination of the other lymph nodes of S.O.N.D. found 100% agreement with pathological examination of sentinel lymph node; i.e. 25 sentinel lymph nodes were negative for micrometastases and the rest of S.O.N.D. were negative also, while the other 3 sentinel lymph node were positive for micrometastases, The other two cases failed to identify sentinel lymph node intraoperatively by the gamma probe due to delay in surgery for two days due to cardiac problems. This due to the short half life of nanocolloid (6 hours), so no radioactivity was detected by gamma probe after 2 days.

The dye identified sentinel lymph nodes in 21 of 30 cases, i.e. failure in 9 cases. Two of these cases were pale, but detected by gamma probe and pathological examination was positive (this is called skip phenomenon).

The main problem occurs when the lymphatic bed being surveyed is adjacent to the radionuclide injected primary (i.e., the evaluation of level I nodes that are next to a floor of mouth lesion). Shielding the hand piece from scatter by adding a collimator, changing the angulation of the hand piece, shielding the primary with lead and adjusting the window and threshold parameters of the scintillation counter have all been effective manoeuvers when identifying the sentinel lymph node in this particular situation [2,4].

In our experience, to avoid the problem of the proximity of lymph nodes to the site of injection, to reduce emission of radiation from the injection site and to avoid the problem of overlapping of the radioactivity from the primary tumor to the neck, the primary tumor was resected according to current accepted treatment standards, then localization of sentinel lymph nodes was done by handled γ detector and blue dye.

Alex et al. [2] studied sentinel lymph node radiolocalization in head and neck squamous cell carcinoma using ^{99m}TC sulfur colloid peritumoral injection and γ-probe intraoperative localization in 8 patients (who clinically had N_0 neck). In one patient, 2 of 3 of lymph nodes were identified to contain micrometastases, and in all cases in which sentinel lymph nodes were negative, the pathological examination of supraomohyiod neck dissection specimen was negative for metastases [2].

Mozzillo et al. [10] found 35 sentinel nodes in 37 patients with T_1 & T_2 oral cavity tumor using ^{99m}TC labeled nanocolloids of albumin and patent blue dye intraoperative mapping. Full neck dissection was performed after sentinel lymph node excision. Thirty three of 35 (94%) sentinel nodes accuracy reflected the status of the nodal basin. Intraoperative lymphoscintigraphy with and without intraoperative blue dye mapping was successful in identifying sentinel nodes in squamous cell carcinoma in head and neck.

Shoaib et al. [13] studied 26 patients for sentinel lymph node biopsy in squamous cell carcinoma of the head and neck. They used the dye only method in 13 patients out of which sentinel lymph node could be identified in 5 patients only and all were negative. However, positive lymph nodes existed elsewhere in the neck in 3 out of these patients. When they used radiolocalization using ^{99m}TC sulfur colloid in addition to the dye method, they could identify sentinel lymph nodes in 15 out of 16 neck dissections. Seven of these patients were subsequently found to have cervical lymph node metastases by pathological examination and in each patient at least one sentinel lymph node was identified to contain metastases [13].

Conclusion:

This preliminary, but promising, experience with sentinel node identification in squamous cell carcinoma of the head and neck suggests the applicability of this approach in staging the regional lymphatic basin in these patients as in cutaneous melanoma and breast cancer. This approach offers the potential to treat only node positive individuals, while avoiding the morbidity of treatment of node negative individuals.

REFERENCES

1- Albertini J.J., Cruse C.W., Rapaport D. et al.: Intraoperative radiolymphoscintigraphy improves sentinel lymph node identification for patients with melanoma. Ann Surg., 1996; 223:217-224.

2- Alex J.C., Saski C.T., Karg D.N., et al.: Sentinal lymph node radiolocalization in head and neck squamous cell carcinoma. Laryngoscope, 110:198-203, 2000.

3- Bolkainy M.: Head and Neck Cancer, Topographic Pathology of Cancer, NCI Cairo University, 2000, pp. (7-22).

4- Byers R.M., El- Naggar A.K., Lee Y.Y., Rao B., Foramge B., Terry N.H.A., Sample D., Smith T. and Wolf P.: Can we detect or predict the presence of occult nodal metastases in patients with squamous cell carcinoma of the oral tongue. Head & Neck, 20:1998; (138-141).

5- Carvalho A.L., Luiz P., Kowalski, Borges J.A., Aguiar S. Jr. and Margin J.: Ipsilateral neck cancer recurrence after elective supraomohyoid neck dissection. Arch Otolaryngol head neck Surg., 126: 919-924, 2000.

6- Chow J.M., Levw B.C., Krivit J.S. and Applebaum E.L.: Radiotherapy or Surgery for Subclinical Cervical Node Metastases. Arch Otolaryngol head and neck Surg., 115: 981-984, 1989.

7- Giuliano A.E., Kogan D.M., Guenther J.M., et al.:

Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg., 1994; 220:391-410.

8- Johanson J.L.: Cervical Metastases, in Gluckmam J, Gullane P, Practical Approach to Head and Neck Tumors. New York: Raven Press, 1994, pp. 47-63.

9- Karen T., Pitman, Jomas T., Johnson, Howard. Edington, Eleon Banes, Roges Day, Robil L., Wagner, Eugene N. and Myers L.: Lymphatic mapping with Isosulfan Blue Dye in squamous cell carcinoma of the head and neck. Arch Otolaryngol head neck Surg., 124: 790-793, 1998.

10- Mozzillo N., Ionna F., Lastroia S., et al.: Sentinel lymph node useful in the in patients with T_1 and T_2 oral cavity tumours, In Proceedings and Abstracts, European Journal of Nuclear Medicine, 1st International Congress on Sentinel Node in Diagnosis and the treatment of Cancer, Amsterdam (17-24), 1999.

11- Robbins K.T.: Neck metastasis. In: Gates GA, (ed): Current Therapy in Otolaryngology-Head Neck Surgery, -St. Louis, Mosby, pp. 309-315, 1994.

12- Shah J.P., Zelefsky M.J. and O'Malley B.B.: Squamous cell carcinoma of the oral cavity. In Harrison LB, (ed): Head and neck cancer: a multidisciplinary approach. Philadelphia, Lippincott-Raven, 189-196, 1999.

13- Shoaib T., David S., Souter, Joanne E., Prosser, David J., Dunaway, Henry W., Gray and Graham M.: Sentinel Node Biopsy Methodology in Head and Neck Cancer. Head & Neck., 728-733, 1999.

14- Wotkinson J.C., Goze M.N., Wilson U.A., et al.: National No Neck In Stell and Maran's Head and Neck Surgery, Butterworth- Heinemann, 197-214, 2000.