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ORIGINAL ARTICLE

Sentinel node localisation using pre-operative lymphoscintigraphy and intraoperative gamma probe in early oral cavity cancer

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Abstract

Objectives: To assess the diagnostic value of sentinel lymph node localisation using pre-operative lymphoscintigraphy and intra-operative gamma probe radio localisation in Pakistani patients suffering from early stage squamous cell carcinoma of the oral cavity.

Methods: The prospective case series was conducted between September 2007 and April 2010 at the Aga Khan University Hospital, Karachi. It comprised patients with T1and T2 oral cavity cancer with clinically and radiologically negative neck. Pre-operative lymphoscintigraphy was performed one day before surgery and intra-operative gamma probe was used to detect sentinel node. Final histo-pathological evaluation was taken as the gold standard.

Results: The study comprised 42 patients: 32(76%) males and 10(24%) females. The primary tumour site was buccal mucosa in 25 (60%) patients, and tongue in 17 (40%). Sentinel lymph node was detected in 38 (90%) patients.

On final histopathological identification, 7 (17%) patients had cancer in the neck nodes. In all patients with metastasis, sentinel lymph node technique correctly identified the involved neck level. None of the patients revealed metastasis in non-sentinel lymph nodes.

Conclusion: Evidence suggested the use of sentinel node biopsy in patients with head and neck squamous cell carcinoma.

Keywords: Sentinel lymph node, Lymphoscintigraphy, Squamous cell carcinoma, Oral cavity. (JPMA 63: 976; 2013)

Introduction

Squamous cell carcinoma (SCC) is the most common malignancy affecting the head and neck region. It typically metastasizes into the regional cervical lymph nodes before spreading to distant organs. The involvement of lymph nodes by malignant cells is strongly related to a poor prognosis, as the presence of lymph node metastasis has shown to decrease survival by 50%.[1] The determination of nodal status in the neck is, therefore, important and vital for proper patient management. The current pre-operative clinical methods, including radiographic techniques like ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), although helpful, are not confirmatory and often misdiagnose the presence or absence of cervical nodal metastasis in many patients.[2]

These techniques generally disregard nodes smaller than 10mm as suspicious. However, even smaller nodes can harbour micro-metastatic disease.[3] To avoid missing nodal metastasis and its associated poor prognosis, elective neck dissection (END) is advocated for the management of clinically node-negative (cN0)neck. This approach has significantly improved regional recurrence-free survival and has lowered the incidence of distant metastases.[4] However, only in 30% clinically-negative necks metastases is found after END,[5] and 15% of clinically-positive necks are in fact, tumour-negative.[6] END, therefore, may be considered an overtreatment in almost 70% of patients.

In order to avoid associated morbidities and cost of END, a technique that precisely recognises disease in the CNO neck is required. Much interest has arisen in the technique of sentinel lymph node (SLN) mapping for SCC of head and neck throughout the world. Lymphoscintigraphy (LSG) is performed to identify the first echelon node draining the lymph fluid from the tumour region and find out if there is tumour deposit in the node.

The goal of the current study was to assess the diagnostic value of SLN localisation method, using pre-operative LSG and intra-operative gamma probe radio localisation in patients suffering from early stage SCC of oral cavity. To

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the best of our knowledge, this is the first such study from Pakistan.

Patients and Methods

The prospective case series spanned a period between September 2007 and April 2010, and comprised 42 SLN mapping procedures at the Aga Khan University Hospital, Karachi. Institutional ethical committee approval and informed consent from the patients were obtained prior to the SLN procedure in all cases. A multi-disciplinary team was formed which included head and neck surgeons, nuclear physicians, histopathologists and research staff. Further, University Research Council grant was also obtained to decrease the financial burden of the consenting patients.

The inclusion criterion was a clinically and radiologically negative neck, as defined by physical examination and radiological imaging by CT scans. All patients previously treated by surgery or radiation were excluded from the study. All the cases related to T1 or T2 tumours of the oral cavity in cN0 patients and were managed pre-operative LSG, intra-operative use of gamma probe, and pathological evaluation, with a follow-up of at least 2 years.

All the patients were admitted one day before surgery and pre-operative LSG was performed on the day of the admission. Following acquisition of the LSG image, lymphoscintigraphic technique during surgery a gamma probe was used and a unilateral or bilateral neck dissection was performed.

Primary tumour site was anaesthetised with topical 10% Xylocaine. Besides, 37 MBq (Mega Becquerel) of Tc-99m Nano colloid (NanoColl, diameter <80 nm) was given in four quadrants of primary lesion by the nuclear physician. LSG images (anterior and both lateral) were obtained at 15min, 1 hour and 18 hours after injection. Visualized SLN were marked over the skin by an indelible ink using a radioactive point source under gamma camera. The thickness of overlying tissue >5 mm may affect the detection rate, hence intra-operative detection was also performed by placing the probe directly on the lymph nodes.

The combination of dye-like Isosulfan blue dye and nuclear imaging improves the sensitivity, and detection rate, but this was not done in our study due to non-availability of the dye in the country.

All cases involved intra-operative use of a gamma probe detector. In oral cavity malignancy often the primary tumour is very close giving a shine through effect with a positive background, making it difficult to identify the SLN, the primary tumour was first resected in all cases and then hand-held gamma probe was used to detect activity in cervical lymph nodes.

Sentinel nodes were labeled according to their anatomical neck level and their radioactivity. All lymph nodes accumulating activity were initially termed sentinel nodes. A node was labeled as true sentinel node after final histological results. After the removal of the sentinel node, all patients underwent unilateral or bilateral neck dissection, as dictated by the location of the primary tumour.

Full pathological protocol was adapted by a senior pathologist for histopathological exam Sentinel nodes and neck dissection specimens were fixed in 10% neutral buffered formalin and were bisected through their longest axis after fixation. All nodes were evaluated by a haematoxylin-eosin (H&E)-stained multiple sections. Results of the histological examination of the neck dissection specimens and SLNs were compared.

After surgery, all patients were followed up in the clinic every month for the 1st year and at 2 months thereafter. Patients were up-staged according to final histopathology of sentinel and non-sentinel neck nodes. Minimum follow-up was for a period of 24 months.

Results

Of the 42 patients, 32(76%) were male and 10(24%) were female. The mean age of all the patients was 52 ±7.5 years with a range of 31-75 years. The primary tumour site was buccal mucosa in 25(60%) patients and tongue in 17(40%) patients. Tumour was confined to one side in 39(93%) patients, whereas in 3(7%) patients with tongue carcinoma it was crossing the midline. Clinically, 22(52%) patients had T1 and 20(48%) patients had T2stage. The drainage of radio colloid was identified in at least one SLN in 38(90%) patients. A SLN could not be detected in 4(10%) patients.

On final histopathological identification, 7(17%) patients had cancer in the neck nodes: 3(42.85%) had T1 and 4 (57.14%) hadT2 primary tumours. Metastasis was found at level I in 2(28.57%) patients; level II in 2(28.57%); and level III in 3(42.85%) patients. Overall, 7(17%) patients SLN technique correctly identified the involved neck level. None of the patients revealed metastasis in non-sentinel lymph nodes.

In all the 4(9.5%) patients where a SLN was not detected, no metastasis was found on final histopathological examination (Table).

Table: Stage and level of the nodes.

Serial No	T stage	Lymph node level positive by gamma probe (Sentinel node)	Lymph node level positive on final histology
1	1	I	-
2	2	II	II
3	2	II	-
4	1	II	-
5	1	III	-
6	2	I	-
7	1	I	-
8	2	II	II
9	1	-	-
10	2	I	-
11	2	II	-
12	1	II	-
13	2	III	-
14	2	II	-
15	1	-	-
16	1	I	-
17	1	I	I
18	2	III	-
19	1	I	-
20	1	I	-
21	2	I	-
22	1	II	-
23	2	II	-
24	1	I	-
25	2	I	-
26	1	-	-
27	2	III	III
28	2	I	-
29	1	III	-
30	1	I	-
31	2	I	-
32	1	II	-
33	2	I	-
34	2	I	-
35	2	I	-
36	1	II	-
37	1	I	I
38	2	III	III
39	1	II	-
40	2	-	-
41	1	III	III
42	1	I	-

Discussion

The prognosis of head and neck cancer patients depends on final staging. The primary disease, regional and distant metastases, has a powerful influence in reducing overall survival rates.[7] Oral cancers are locally invasive and surgery can be curative if clear margins are achieved.[8] Oral cancers spread through lymphatic pathways to the cervical lymph nodes. The presence of cancer metastasis in neck nodes is the single most important bad prognostic factor, decreasing overall 5-years survival from 82% to 53%.[7]

Traditionally, for the management of clinically and radiologically negative neck, two options are available; observation or elective neck dissection (END). The incidence of regional metastases reported in literature around 30% and the presence of regional disease is the cause of the death of one in every two patients.[9]

The END is the gold standard in patients with higher than 20% risk of occult disease.[3] But traditionally neck dissection was associated with removal of relevant normal structures of neck with significant post-operative morbidity having impact, on the quality of life (QOL). Modifications of neck dissection like Selective Neck Dissection preserving non-lymphopathic structures for the management of the N0 neck was introduced to decrease the morbidity of more traditional modified radical neck dissections.[10]

Morbidity associated with selective neck dissection is definitely less than radical dissection, but there are still quality effects, especially when bilateral dissection is performed. Recent QOL studies have favoured sentinel node biopsy over END.[10]

In search of less invasive procedures, SLN has demonstrated usefulness in other types of cancer like breast and melanoma.[11,12] This has led to SLN biopsy becoming a popular technique for determining whether metastases is present in the first echelon of draining lymph nodes and has allowed these patients to avoid procedural morbidity while undergoing END for their malignancies.[13]

Our result of SLN identification is comparable to other studies reported in literature. The identification was 90%, which is very similar to other comparable series.[14-16] The identification of SLN is far superior and quick in comparison with cervical neck dissections. Identification of SLN and attempt to assess the occult disease with fine needle aspiration cytology, though thought to have the least morbidity, was not successful as it does not detect occult metastatic disease as the sample of the SLN is too small.[17,18]

In four of our patients, no sentinel node was detected. One study 20 reported that this might be due to wrong injection technique, injecting too deep into the tissue or not close enough to the mucosa.[19] Other reasons may be that in-transit metastases blocked the drainage of the radio colloid into the sentinel node.

In 7 patients with occult metastases, H&E staining was sufficient to detect the metastases. Some studies have

recommended serial sectioning of the SLNs at intervals of 1-mm and immunohistochemical staining for keratin with pancytokeratin to reveal occult micro metastases.[16,20,21]

A limitation of our study is that it relied on final histology and not on the frozen section to detect the involvement of a node. This is because the main aim of our study was to find the accuracy of LSG. A separate study is needed to assess the sensitivity and specificity of frozen section for sentinel node detection.

The approximate cost for each patient without frozen section was Rs.6000. Surgeons intending to use this modality should keep cost-effectiveness in their mind

A study has suggested that serial sectioning, immunohistochemistry, and molecular methods may help to identify smaller metastatic deposits. H&E staining with serial sectioning identifies one cancer cell among 10,000 normal cells. Immunohistochemistry identifies one tumor cell amongst 100,000 normal cells. Reverse transcriptase-polymerase chain reaction (RT-PCR) is the most sensitive of them all.

Conclusion

The study provides further weight to the argument in favour of sentinel node biopsy in patients with head and neck SCC, but it should be considered as an investigational tool pending validation by larger randomised clinical trials.

References

1. Alvi A, Johnson JT. Extracapsular spread in the clinically negative neck (N0): implications and outcome. Otolaryngol Head Neck Surg 1996; 114: 65-70.
2. Ferlito A, Rinaldo A, Devaney KO, MacLennan K, Myers JN, Petruzzelli GJ, et al. Prognostic significance of microscopic and macroscopic extracapsular spread from metastatic tumor in the cervical lymph nodes. Oral Oncol 2002; 38: 747-51.
3. Don DM, Anzai Y, Lufkin RB, Fu YS, Calcaterra TC. Evaluation of cervical lymph node metastases in squamous cell carcinoma of the head and neck. Laryngoscope 1995; 105: 669-74.
4. Duwuri U, Simental AA Jr, D'Angelo G, Johnson JT, Ferris RL, Gooding W, et al. Elective neck dissection and survival in patients with squamous cell carcinoma of the oral cavity and oropharynx. Laryngoscope 2004; 114: 2228-34.
5. McGuirt WF Jr, Johnson JT, Myers EN, Rothfield R, Wagner R. Floor of mouth carcinoma. The management of the clinically negative neck. Arch Otolaryngol Head Neck Surg 1995; 121: 278-82.
6. Greenberg JS, El Naggar AK, Mo V, Roberts D, Myers JN. Disparity in pathologic and clinical lymph node staging in oral tongue carcinoma. Implication for therapeutic decision making. Cancer 2003; 98: 508-15.
7. Stoeckli SJ, Alkureishi LWT, Ross GL. Sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. Eur Arch Otorhinolaryngol 2009; 266: 787-93.
8. Oliver RJ, Clarkson JE, Conway DI, Glenny A, Macluskey M, Pavitt S, et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database Syst Rev 2007; CD006205.
9. Kowalski LP, Magrin J, Waksman G, Santo GF, Lopes ME, de Paula RP, et al. Supraomohyoid neck dissection in the treatment of head and neck tumors. Survival results in 212 cases. Arch Otolaryngol Head Neck Surg 1993; 119: 958-63.
10. Schiefke F, Akdemir M, Weber A, Akdemir D, Singer S, Frerich B. Function, postoperative morbidity, and quality of life after cervical sentinel node biopsy and after selective neck dissection. Head Neck 2009; 31: 503-12.
11. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005; 23: 7703-20.
12. Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg 2005; 242: 302-11.
13. Jeong HS, Baek CH, Son YI, Cho DY, Chung MK, Min JY, et al. Sentinel lymph node radiolocalization with 99mTc filtered tin colloid in clinically node-negative squamous cell carcinomas of the oral cavity. J Korean Med Sci 2006; 21: 865-70.
14. Coughlin A, Resto VA. Oral cavity squamous cell carcinoma and the clinically N0 neck: the past, present, and future of sentinel lymph node biopsy. Curr Oncol Rep 2010; 12: 129-35.
15. Ross GL, Soutar DS, Gordon MacDonald D, Shoaib T, Camilleri I, Roberton AG, et al. Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial. Ann Surg Oncol 2004; 11: 690-6.
16. Werner JA, Dünne AA, Folz BJ, Moll R, Behr T. Value of sentinel lymphadenectomy in head and neck cancer. Ann Surg Oncol 2004; 11(Suppl 3): 267S-70S.
17. Colnot DR, Nieuwenhuis EJ, van den Brekel MW, Pijpers R, Brakenhoff RH, Snow GB, et al. Head and neck squamous cell carcinoma: US-guided fine-needle aspiration of sentinel lymph nodes for improved staging - initial experience. Radiology 2001; 218: 289-93.
18. Nieuwenhuis EJ, Castelijns JA, Pijpers R, van den Brekel MW, Brakenhoff RH, van der Waal I, et al. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node? Head Neck 2002; 24: 282-9.
19. Civantos FJ, Gomez C, Duque C, Pedroso F, Goodwin WJ, Weed DT, et al. Sentinel node biopsy in oral cavity cancer: correlation with PET scan and immunohistochemistry. Head Neck 2003; 25: 1-9.
20. Werner JA, Dünne AA, Ramaswamy A, Folz BJ, Lippert BM, Moll R, et al. Sentinel node detection in N0 cancer of the pharynx and larynx. Br J Cancer 2002; 87: 711-5.
21. Kuriakose MA, Trivedi NP. Sentinel node biopsy in head and neck squamous cell carcinoma. Curr Opin Otolaryngol Head Neck Surg 2009; 17: 100-10.