



ORIGINAL RESEARCH PAPER

Pathology

ULTRASOUND GUIDED FINE NEEDLE ASPIRATION CYTOLOGY IN EVALUATION OF CERVICAL LYMPHNODE METASTASIS IN ORAL SQUAMOUS CELL CARCINOMA

KEY WORDS: Fnac, Cytology, Oral Cancer, Ultrasound Guided, Squamous Cell Carcinoma, Lymphnode Metastasis.

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ABSTRACT

INTRODUCTION: Oral cancer is the most frequent malignancy of head and neck region. The presence of metastatic lymph nodes greatly affects the outcome. The 5-year survival for a patient is halved if a single ipsilateral neck node is involved, and is reduced by three-quarters if bilateral nodes are present.⁵

One of the most important problems in selecting patients for elective neck dissection is lack of confirmatory diagnostic tests to classify a patient as neck positive or negative. The biggest challenge of FNAC is getting representative sample which can be minimized by ultrasound guidance.⁷ Role of ultrasound guided FNAC in staging of cervical lymph node status in Oral Squamous Cell carcinoma not yet a standard preoperative evaluation.⁸

MATERIALS AND METHODS : All biopsy proven oral squamous cell carcinoma patients with palpable lymph nodes who had undergone neck dissection during the period of January 2016 to June 2017 were included. Cervical lymph node with ultrasonographic features such as round shape, absence of echogenic hilum, sharp nodal borders, presence of intranodal necrosis and peripheral vascularity suggestive of metastatic cervical lymph nodes were aspirated. Smears were stained with H&E, PAP and Giemsa stain. The FNAC diagnosis was correlated with the histopathological findings.

Results: Most of the cases belonged to the age group of 40 to 70 years with a male to female ratio of 1:2.1. The common site of carcinoma of oral cavity was Buccal mucosa (70%). Most of the cases presented clinically at a late stage ie. TNM Stage IV (65.8%). There was significant correlation between cytology and HPE findings. (p value <0.001). Sensitivity of USG guided FNAC was 93.55%, specificity was 100%, positive predictive value was 100%, negative predictive value was 95.12% and diagnostic accuracy was 97.14%. False negative results on USG guided FNAC seen in 2 cases (6.5%).

Conclusion: High diagnostic accuracy of FNAC combined with advantage of ultrasound guidance helps in accurate diagnosis of cervical lymphnode metastasis in oral cancers. Ultrasound guided FNAC should be recommended in the preoperative assessment of cervical lymphnode metastasis in Oral squamous cell carcinoma.

INTRODUCTION

Oral cancer is the most frequent malignancy of head and neck region. Cancer of oral cavity are the sixth most common cancers globally.¹ It is a major problem and is regarded as one of the top three types of cancer in India.² Around 20 per 100000 Indian population are affected by oral cancer.³ Oral cancer is the most common cancer in our geographic area, Kolar.⁴ 90-95% of oral cancer is squamous cell carcinoma.²

The presence of metastatic lymph nodes greatly affects the outcome.³ The 5-year survival for a patient is halved if a single ipsilateral neck node is involved, and is reduced by three-quarters if bilateral nodes are present.⁴ So the ratio of metastasis to lymph nodes reflects the aggressiveness of tumor and is important for assessing prognosis as well as to decide upon how extensive treatment the patient has to undergo.

One of the most important problems in selecting patients for elective neck dissection is lack of confirmatory diagnostic tests to classify a patient as neck positive or negative. Assessment of lymph node by clinical examination for nodal metastasis has low sensitivity and specificity.

The biggest challenge of fine needle aspiration cytology (FNAC) is aspiration from the representative node which can be achieved by ultrasound guidance.⁵ Role of ultrasound guided FNAC in staging of cervical lymph node status in Oral Squamous Cell carcinoma not yet a standard practice.

In this study we evaluated the role of Ultrasound guided FNAC (USG FNAC) in preoperative assessment of cervical lymph node metastasis in oral squamous cell carcinoma by comparing with histopathological diagnosis.

MATERIAL AND METHODS

SOURCE OF DATA:

All cases of oral squamous cell carcinoma with palpable cervical lymph node presenting to the department of ENT and Head and Neck Surgery RL Jalappa hospital and research center and who were planned for neck dissection during the period of Jan 2016 to August 2017 were included in the study. Patients who had undergone preoperative radiotherapy /neoadjuvant chemotherapy/with recurrent or second primary cancers were excluded.

USG was done using Siemens Acuson X 300 using a linear high-resolution transducer and cervical lymph node were scanned for ultra sonographic features suggestive of metastasis such as round shape, absence of echogenic hilum, irregular nodal borders, presence of intranodal necrosis, increased vascularity and clustering of lymphnodes.⁶ The cervical lymphnode showing one or more above features was selected for aspiration. In cases where there is no definite USG evidence of metastasis largest lymphnode was selected for FNAC. Minimum of three slides was prepared from the aspirated material. One slide was air dried and stained with giemsa and other two slides were fixed in alcohol and stained with hematoxylin and eosin and PAP stain. The FNAC diagnosis was correlated with the histopathological findings. Clinical and histopathological features were correlated with status of cervical lymphnode.

STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data. Continuous data was represented as mean and standard

deviation. **p value** (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS:

The present study includes 70 USG guided FNAC of cervical lymph nodes from squamous cell carcinoma of oral cavity.

Mean age of subjects was 52.94 ± 12.02 years. Most of our cases belonged to the age group of 40 to 70 years (74.3%). Female predominance was seen with Male to female ratio of 1:2.1. Most common complaint was ulcer in the mouth seen in 75.70% cases. Betel quid chewing was the most common predisposing factor leading to oral cancer (98.6% cases). The common site of carcinoma was Buccal mucosa (71.4%) followed by lower alveolus (11.3%). Tongue carcinoma was seen in 10% of cases.

Most of our cases showed Ulcerocystic tumor which constituted up to 70.0% followed by ulcerative (21.4%). The least common tumor appearance was flat type constituting 2.9%. In most of our oral cancer cases tumor size was >2 to 4cm comprising of 55.7%. Most common level of lymph node to be involved was Level I in 65 cases followed by level II in 53 cases. In our study majority of the cases had lymph node size upto 3cm (94.2%). Most of our cases were in clinical TNM Stage IV (65.8%) followed by Stage III (34.2%).

On ultrasound 45.7% cases showed round nodes, 42.9% cases showed absence of hilum, 37.10% showed increased vascularity and 25.7% cases showed necrosis. Cystic changes were seen in 15.7% of cases and irregular borders were seen in 11.4%. With ultrasound guidance the most common level to be aspirated was level I comprising of 65.8% cases followed by Level II comprising of 33.2% cases.

On cervical lymph node aspiration 29 cases (41.4%) showed positivity for malignant squamous cells (Fig.1) while 41 cases (58.6%) were negative for metastasis.

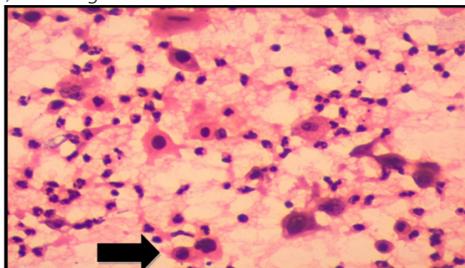


Figure 1: Microphotograph showing squamous cell carcinoma deposit in lymph node on cytology smear. 40X H&E stain.

Among the metastatic cases dyskeratosis was seen in 51.7% cases, necrosis was seen in 31% cases, acute suppurative inflammation was seen in 20.6% cases and cystic change was seen in 13.8% cases. None of the metastatic cases showed granuloma on cytology.

Lymph nodes retrieved from neck dissection specimen were subjected to detailed microscopic examination. Total no. of lymph nodes retrieved were 1460. The average no. of lymph nodes examined were 21 per case. 31 cases (44.3%) showed cervical lymph node metastasis on histopathology. 39 cases (55.7%) were negative for tumor deposit in lymph node. There was no statistical correlation found between tumor site, tumor size, level of lymph node, differentiation of tumor with cervical lymph node metastasis. Statistical correlation found between size of lymph node and cervical lymph node metastasis (p = 0.021). Chances of lymph node metastasis were higher if size of lymph node is >30mm.

Out of 31 metastatic cases on HPE, 29 (93.5%) were positive in cytology and 2 (6.5%) were negative. Remaining 39 cases were negative for metastasis both on HPE and cytology. There was significant correlation between cytology and HPE findings. (p value <0.001)

Table 1: Correlation between Cytology and Histopathological diagnosis

		HPE			
		Positive		Negative	
		Count	%	Count	%
Cytology	Positive	29	93.5%	0	0.0%
	Negative	2	6.5%	39	100.0%

X² = 62.29, df = 1, p < 0.001*

Sensitivity of USG guided FNAC was 93.55%, specificity was 100%, positive predictive value was 100%, negative predictive value was 95.12% and diagnostic accuracy was 97.14%.

2 cases (6.5%) showed false negative results on USG guided FNAC. This is due to aspiration from nonrepresentative node.

Discussion:

Cervical lymph node status is an important predictor for survival of patients with oral squamous cell carcinoma. The presence of metastatic lymph nodes greatly affects the outcome (5-year survival). Various methods are used to evaluate lymph node metastasis which includes palpation, Ultrasonography (USG), FNAC (Fine Needle Aspiration Cytology), USG guided FNAC, CT (Computed Tomography) and MRI (Magnetic Resonance Imaging).

Clinical palpation is the routine method and lymph nodes are assessed for location, number, size, shape, consistency, and fixation but the accuracy, sensitivity and specificity of palpation is in the range of 60-70% and diagnostic accuracy in the range of 60% to 80% for palpation.^{7,8,9}

CT and MRI has the advantage of less inter-observer variation and these are relatively standardized techniques but there is risk of exposure to ionizing radiation.^{10,11} CT and MRI uses size, shape criteria and calcification to detect malignant nodes but USG can detect echogenic pattern, peripheral vascularity which is important to differentiate malignant nodes from benign nodes. But still all these criteria are not specific and many a times show false positivity. In the literature USG shows a sensitivity ranging 78% to 97%, specificity ranging from 71% to 83% and diagnostic accuracy ranging from 67% to 95%.^{12,13} Limitations of USG is that it is highly operator dependent and nodes adjacent to mandible and subcentimetric nodes are likely to be missed. FNAC is a highly specific test to identify metastatic deposits in lymph nodes but biggest challenge is nonrepresentative sample which can be improved by USG. USG guided FNAC has not yet routine preoperative evaluation in evaluation of method in Oral Squamous Cell carcinoma.

Most of our cases belonged to the age group of 40 to 70 years (74.3%) but highest incidence was seen in 6th decade. Our study correlated with similar studies done in North India where highest incidence was seen in the 6th decade.¹⁴

In our study male to female ratio was found as 1:2.1. This is in contrast to most other studies in India where a male preponderance is seen.^{14,15} Increasing trend of oral cancer is seen among women in many rural areas of South India because of betel quid chewing habits as they believe that tobacco has magical and medicinal properties. The most common predisposing factor was betel quid chewing seen in 98.6% cases which is in agreement with a similar study where 91.1% cases had a habit of betel quid chewing.¹⁶

In our study the most common site of carcinoma was buccal mucosa (71.4%) followed by lower alveolus (11.3%). Anterior 2/3rd tongue carcinoma was seen in 10% of cases. This is in agreement to various other studies.^{17,18} The high incidence of buccal mucosa malignancy is due to the fact that betel quid is directly compressed against it and there is direct access to carcinogens.

Most of our cases presented at a late stage on clinical examination. Most were in Stage IV (65.8%) followed by Stage III (34.2%). Cause of presenting at advanced stages may be due to

lack of awareness ,poverty, lack of screening programmes and resorting to home remedies until they have severe symptoms.

Multiple criteria have been suggested to improve the accuracy of ultrasonography in diagnosing metastatic adenopathy. In view of absence of gold standard ultrasound criteria for metastatic lymph node ,combination of ultrasound features were considered for selection of lymph node for FNAC .Nodes which showed round shape, absence of hilum, contour irregularity ,presence of necrosis were selected for FNAC.

In our study on cervical lymph node aspiration 29 cases(41.4%) showed positivity for metastatic squamous cells while 41 cases(58.6%) were negative for metastatic squamous cells.

Smears with large amounts of inflammatory cell infiltration and abscess formation should be carefully searched for metastatic squamous cells. Inflammatory infiltrate can obscure the metastatic squamous cells. The presence of keratinous debris and foreign body giant cell formation indicates the possibility of keratinising squamous cell carcinoma in such cases. In a study by Ross H diagnostic dilemma's were described in a series of 12 patients with metastatic squamous cell carcinoma in regional lymph nodes associated with abscess formation.¹⁸ The aspiration from metastatic nodes with cystic change is often hypocellular .The aspirate should be centrifuged and the centrifuged deposit should be very carefully examined for any malignant squamous cells .In a study done in Ireland out of 42 cases 5 false negative cases were found, all of which were cystic nodal metastasis in neck.¹⁹ USG guided FNAC from the solid area of the lymph node swelling can also be helpful.

Granulomatous reaction especially in a country like ours where tuberculosis is rampant is a very common finding in lymph nodes.In a study it was found that granulomatous response along with necrosis and inflammation as a cause for false negative diagnosis in metastatic SCC.²⁰

In our study on histopathological study of neck dissection specimen out of 70 cases ,31 cases (44.3%) showed cervical lymph node metastasis. 39 cases (55.7%)were negative for tumor deposit in lymph node. In our study there was no statistical correlation found between tumor site and cervical lymph node metastasis(p = 0.101). In a study by Alkaiji and his colleagues it was found that tumor site is a predictor of lymph node metastasis and tumor involving anterior 2/3rd of tongue showed higher number of cases of lymph node metastasis in comparison to other sites.²¹ Tongue, because of its structure and function and complex lymphatic drainage is prone for early local and regional spread of cancer. However in our study only 7 cases of anterior 2/3rd tongue carcinoma were included as the prevalence of tongue carcinoma is less as compared to buccal mucosa in our geographic area.Out of the 7 cases 6 cases showed metastasis to lymphnode.

In our study there was no statistical correlation found between tumor size and cervical lymph node metastasis(p =0.377). In a study in Iraq it was found that tumor size is a predictor of lymph node metastasis (P=0.004).²² In another study it was found that lymph node metastasis was more common in tumors with size >4cm.²³

In our study there was a statistical correlation found between size of lymph node and cervical lymph node metastasis (p = 0.021). In our study it was found that chances of lymph node metastasis are higher if size of lymph node is >30mm. In a study in Turkey the highest rates of metastasis and extracapsular spread were seen in lymph nodes measuring 31 to 60 mm.²³ In a multicentric study positive rates of metastasis was observed in 86.5%, 93.3% and 100%, respectively, were observed in lymph nodes with a size of 1–2 cm, 2–3cm and lymph nodes of more than 3 cm.²⁴

In a earlier study from our institute a significant correlation was found between grades of differentiation and cervical LN metastasis and high occurrence of metastasis was seen in moderate-and poorly-differentiated SCC (55%).²⁵ In a study in Japan a significant correlation was found between a poorly

differentiated carcinoma and the presence of occult nodal metastases in the neck dissection specimen.²⁶

In our study there was significant correlation between cytology and HPE findings. (p value <0.001) in 68 out of 70 cases.

Table 1: Showing comparison of diagnostic value of USG guided FNAC in present study with other studies

Statistical parameters:	Present study	Azam SM et al ²⁷ 2014	Dabirmoghaddam P. ²⁸ 2014	Rottey S ²⁹ 2014	Geeta NT ³⁰ 2010
Sensitivity (%)	93.55%	92.31 %	87.5%	86.7 %	67 %
Specificity (%)	100%	90.91 %	100%	87.5 %	100%
Positive predictive value (%)	100%	96.00 %	100%	81.3 %	100%
Negative predictive value (%)	95.12%	83.33%	95%	91.3 %	67%
Accuracy (%)	97.14%	91.89%	96%	87.2 %	80%

In our study 6.5% showed false negative results on USG guided FNAC. Rescreening of cytology smears in these 2 cases showed no evidence of metastasis. In one false negative case out of 34 lymph nodes retrieved only one lymph node showed metastatic deposit on HPE and in the second false negative case out of 26 lymph nodes retrieved only one lymph node showed metastatic deposit on HPE. The reason for false negativity was due to aspiration from non metastatic node. USG guided aspiration from multiple lymph nodes may improve the sensitivity.In a study in Lucknow 4.7% of the cases were found false negative on USG guided FNAC.³¹ In a study in Iran false negative results on USG guided FNAC was found to be 3.77% .²⁹This false negative results could be due to small metastasis missed by the needle, a single tumor cell overlooked by the pathologist or aspiration of a non metastatic lymph node . In addition, lymph nodes near the mandible are difficult to visualize or aspirate due to the shadow of the mandible . Cystic change in metastatic lymph nodes is an important cause of false negative errors.In a study by it was found that most of the micrometastasis are found in lymph nodes with a size less than 10 mm diameter.³² The size of these lymph nodes is within the resolution of ultrasound; however, placement of the needle into the lesion during FNAC is problematic.

Various challenges are experienced in cytological diagnosis of lymph node metastasis. The benign inclusions of salivary gland, squamous epithelium, and thyroid are most common to occur in lymph nodes of the head-neck area and can lead to diagnostic challenge.²⁹Thyroid gland inclusions can be found within lymph nodes in 1–5 % from neck dissections and salivary gland ducts or acini are found in cervical lymph nodes in ~10 % of adults and are detected in patients undergoing head and neck surgery.Even skin contaminant can lead to diagnostic challenge.

Regional lymphadenopathy in a known carcinoma patient is not always due to metastatic tumour, and not every nodule represents a lymph node. Lymph nodes are enlarged in infections, immune disorders, lymphoma. Especially when the primary tumour is ulcerated, as seen in advanced squamous carcinoma, enlargement of the regional nodes may signify a response to inflammation rather than metastasis. In our study more than half(55.7%)of patients didn't show metastatic deposit in cervical lymphnodes in a known patient with oral carcinoma. All these lymph nodes were reactive suggesting inflammatory/ infectious etiology for regional lymphadenopathy. Many patients with oral cancer have been found to have low immunity making them prone to get infected by various viruses ,bacteria and fungal infection. Poor orodental hygiene also leads to reactive adenopathy.In another study similar results were found and metastasis in the cervical nodes was detected only in 43% of the cases among 90 neck dissection cases on histopathology and remaining 57% cases showed reactive nodes.³³ In a study in Japan 21 out of 38 cases (55.3%) were reactive on histopathology.³⁴ In another study in Iran in 53 neck

dissection specimens metastases was seen only in 16 cases(30.1%) and remaining 69.9% were reactive on histopathology.²⁷

CONCLUSION

Accurate preoperative diagnosis of cervical metastasis is important to reduce the unnecessary morbidity or mortality due to neck dissection .

High diagnostic accuracy of FNAC combined with advantage of ultrasound guidance helps in accurate diagnosis of cervical lymph node metastasis in oral cancers. Ultrasound guided FNAC should be recommended in the preoperative assessment of cervical lymph node metastasis in Oral squamous cell carcinoma.

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