

# Analysis of the Relationship between Grade of Histopathological Malignancy and Cervical Lymph Node Metastasis in Squamous Cell Carcinoma in the Head and Neck Region - A Prospective Study



Dr. Rajay A. D. Kamath



Dr. C. Bhaskar Rao

*Dept of Craniomaxillofacial reconstructive surgery*

## Background:

We present the results of a prospective study on the relationship between the grade of histopathological malignancy and cervical lymph node metastasis in 30 patients with primary intra-oral squamous cell carcinoma treated from June 2004 to May 2006, at the SDM Dental College & Hospital, Dharwad, Karnataka, India.

## Method:

High-resolution ultrasonography, employing a **Philips ENVISOR-B series (7.5 – 12.5 MHz linear transducer/probe)**, was performed to assess the 3-D radiological extent of the tumor. The ultrasonographic (**IMAGING- BASED NODAL CLASSIFICATION**) diagnostic criteria were used to assess levels of cervical metastasis (metastatic nodal criteria), apart from the primary lesion. The microscopic grading of the tumor was expressed in terms of **BRODERS System of Histopathological Grading**. The dissected lymph nodes were studied employing a high-resolution **LEICA Research Microscope**. The results of the two analyses were studied and correlated.

## Results:

Males were more affected in comparison to females, and the site predominately affected was the buccal mucosa, followed by the tongue, retro molar trigone of the mandible, floor of the mouth, the alveolus, the maxillary tuberosity and the palate. The predominant site of cervical metastatic involvement were levels I and II, and to a variable extent level III. There was an inverse relationship between the degree of tumor differentiation and the tendency or rate of cervical metastasis, as observed in our study. It was also noted that there was a tendency toward primary tumor over-staging as well cervical

metastasis misprediction, clinically and radiologically. There was a lack of distant metastasis from the primary, in all the 30 cases included in the study, as supported by normal CXR and ultrasonography of the liver and suprarenal glands.

## Conclusion:

To conclude, there exists a positive correlation between the degree of histopathological malignancy and cervical metastasis in head and neck SCC. The tendency toward tumor over-staging and cervical metastasis misprediction clinically and radiologically can be overcome; whether the type of neck dissection performed is warranted or not and the probable prognosis can also be determined, by and large; all these strongly supports the fact that histopathology still serves universally as the **gold standard!!**

## Introduction

The single most important factor affecting prognosis for patients with SCC of the upper aero-digestive tract is the stage of the disease at the time of initial diagnosis and treatment. Patients presenting with localized primaries without regional (cervical) node dissemination enjoy an excellent prognosis. On the other hand, once dissemination takes place, the 5-year survival probability, regardless of treatment rendered, reduces to nearly 50% of that seen in early staged patients<sup>1</sup>. Metastasis to regional lymph nodes from upper aero-digestive tract primaries occurs in a predictable and sequential fashion. Thus, all regional node groups are usually not at risk of metastases initially from any primary site, in the absence of grossly palpable metastatic nodes. On the other hand, when clinically palpable nodes are present at the time of initial diagnosis, comprehensive regional



clearance of all nodes at risk is warranted<sup>1</sup>.

Landmark studies have confirmed that select (regional) node groups are initially at risk for each primary in the head and neck. However, the therapeutic regimen including radical neck dissection has been selected mainly based on the stage of clinical progression in most cases. Therefore, metastasis may occur even in early cases and it is often difficult to suppress nodal metastasis because of its sufficient prediction with rather unfavorable therapeutic results<sup>2</sup>. Despite advances in surgery and radiation therapy, tumor control and survival remain disappointing, and hence a multidisciplinary approach is often been advocated. Understanding the sequential patterns of neck metastasis, therefore, generally facilitates surgical management of regional nodes in the clinically negative neck where they are at risk of harboring micro-metastasis<sup>1</sup>.

The presence of clinically involved cervical nodes appears a major determinant of patient outcome since a significant relationship exists between the degree of histological malignancy and cervical metastasis in head & neck cancer<sup>2</sup>. Hence, the degree of histological malignancy could serve as a predictor for cervical metastasis<sup>2</sup>. We attempt to correlate the degree of histological malignancy with the clinical and radiological assessment (ultrasonography) of cervical metastasis, which would play an adjunctive role in deciding treatment (surgical) options and eventually aid evaluation of post-operative prognosis in head and neck SCC.

#### **Materials and Method:**

A prospective analysis of 48 patients with SCC of the head & neck was conducted from June 2004 to May 2006. Of these, 30 predominantly had the tumor primarily affecting the oral cavity and were included in the study. Of the remaining 18, 11 were excluded from the study, either owing to a positive history of recurrence at the same site or at a site different from that of the primary. Cases with premalignant lesions or conditions affecting the oral cavity were also excluded from the study.

The sample under study was in the age range of 25 yrs to 65 yrs [mean (F) = 49.9; SD=10.398; age range 30-60 yrs; mean (M) =50.9; SD=9.3773; age range=25-65 yrs] with

a male to female preponderance (22 males & 8 females), irrespective of associated medical problems. The cases were initially examined clinically to inspect for the site of the primary, and the lymph nodes of the neck were palpated to check for nodal involvement by the primary tumor. Following clinical staging of the malignancy, incisional biopsies of the lesions were performed to confirm the provisional diagnosis of carcinoma of the involved site.

High-resolution ultrasonography, employing a **Philips ENVISOR-B series (7.5 – 12.5 MHz linear transducer/probe)**, was performed to assess the 3-D extent of the tumor in terms of its involvement with bone or associated soft-tissue planes deeper to the mucosa of the oral cavity. Neck node status assessment was carried out and expressed in terms of the levels involved by the primary, based on universal anatomic (diagnostic) imaging criteria. The following ultrasonographic (**IMAGING- BASED NODAL CLASSIFICATION**) criteria were used to assess levels of cervical node metastasis, including metastatic nodal criteria:

1. *Short-axis diameter > 8mm.*
2. *Presence or absence of a diffusely hypo echoic texture with or without hilar artery loss (Loss of Echogenic Hilum) in the lymph node.*
3. *Presence or absence of extracapsular extension of the metastatic process/ tumor cells (expressed in terms of irregular or lobulated margins of the lymph node).*
4. *Flow pattern – Low-resistance Flow Pattern.*
5. *“Rounded” sign of the lymph node, indicative of tumor metastasis.*

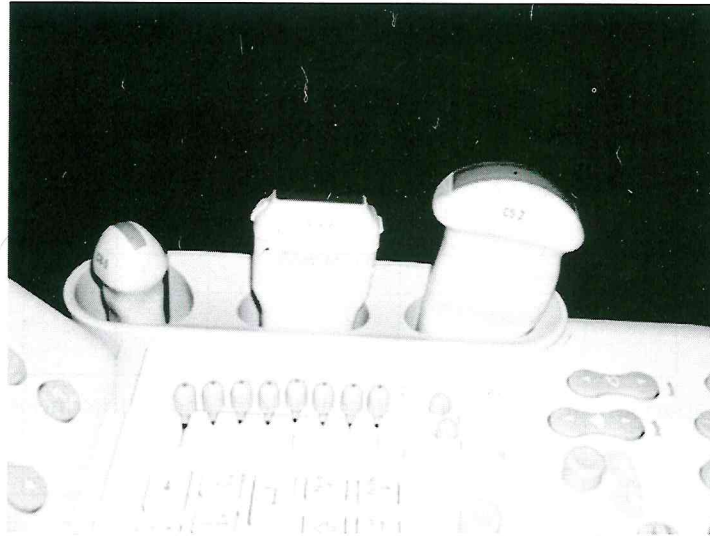
The microscopic grading of the tumor was expressed in terms of **BRODERS System of Histo- pathological Grading**. The criteria taken were:

- 1) *Degree of cellular differentiation (Cellular Dysplasia).*
- 2) *Degree of Keratinization (Keratin Pearl Formation).*
- 3) *Nuclear and Cellular Pleomorphism. Well differentiated, moderately*

*differentiated & poorly differentiated.*

*4) Presence or absence of metastatic tumor cells in the lymphoid tissue of the lymph nodes, dissected from the resected specimen.*

*No scoring system was applied in this study.*



**7.5 -12 MHz transducers used in the ultrasonographic examination of the primary lesion and the cervical node levels.**

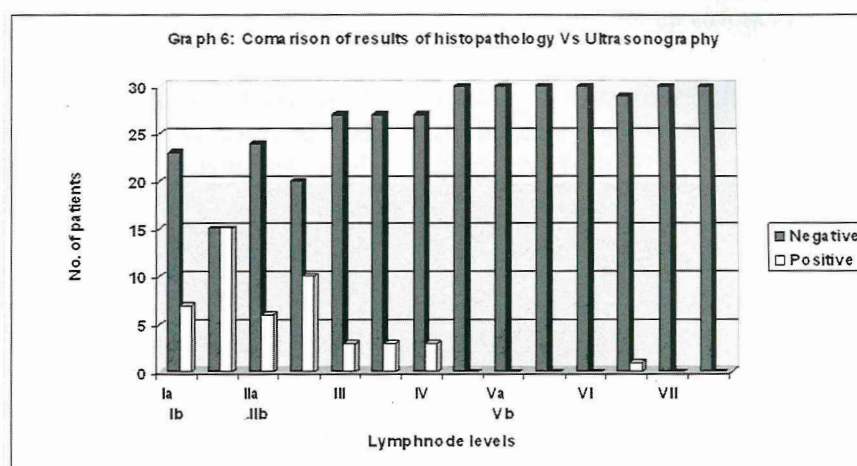


**The ultrasonographic evaluation of cervical nodes being performed to detect metastasis, using universal ultrasonographic (IMAGING-BASED NODAL CLASSIFICATION) criteria.**



## Results

The results of the analysis are expressed in terms of tables and graphs as follows:



Comparison of results of Histo-pathology and Ultrasonography

	Group	Negative	Positive	Totals	Chi-square	p-value	Signi.
Ia Ib	H	23	7	30	4.5933	0.0321	S
	U	15	15	30			
IIa IIb	H	24	6	30	1.3636	0.2429	NS
	U	20	10	30			
III	H	27	3	30	0.1852	0.6670	NS
	U	27	3	30			
IV	H	27	3	30	1.4035	0.2362	NS
	U	30	0	30			
Va Vb	H	30	0	30	0.0000	-	-
	U	30	0	30			
VI	H	30	0	30	1.0169	0.3133	NS
	U	29	1	30			
VII	H	30	0	30	0.0000	-	-
	U	30	0	30			

Comparative histopathologic and ultrasonographic analysis revealed a significant correlation i.e. 7 lymph nodes in level I were true positive, as against a false positive result of 15, obtained by ultrasonography ( $\chi^2 = 4.5933$ ;  $p=0.0321$ ). This indicates a high tendency toward tumor over-staging, including cervical metastasis misprediction.

Site	T1N1 M0	T1N2 M0	T2N0 M0	T2N1 M0	T2N2 M0	T3N1 M0	T3N2 M0	T4N2 M0	Total
1	2	0	0	3	0	0	1	0	6
2	2	0	1	3	5	4	3	0	18
3	0	1	0	1	0	0	0	0	2
4	0	1	0	1	1	0	0	1	4
Total	4	2	1	8	6	4	4	1	30

Correlating tumor site with that of staging, it was found that the T1 and T2 incidence of metastasis was 20% and 50%, while in T3 and T4 cases, was 26.67% and 3.34%.

#### Tumor differentiation versus Lymphatic invasion, Extra-capsular spread and Tumor margins

Tumor Differentiation	Lymphatic invasion	%	Extra-capsular spread	%	Tumor margins	%
Epithelial dysplasia -mild	0	0.00	0	0.00	0	0.00
Epithelial dysplasia -mild to moderate	0	0.00	0	0.00	1	100.00
Epithelial dysplasia-moderate	0	0.00	0	0.00	0	0.00
SCC early-invasion	0	0.00	0	0.00	4	100.00
SCC moderately -differentiated	6	60.00	1	10.00	10	100.00
SCC well-differentiated	2	15.38	0	0.00	13	100.00
<b>Total</b>	<b>8</b>	<b>26.67</b>	<b>1</b>	<b>3.33</b>	<b>28</b>	<b>93.33</b>

7 lymph  
graphy ( $\chi^2 =$   
metastasis



## Discussion

The metastasis rate as reported previously ranges from 35.3% to 60% in patients with SCC<sup>2</sup>. In SCC, metastasis to local as well regional lymph nodes occurs irrespective of the T status of the primary tumor. However, even in light of effective therapeutic regimens, a possible predicting factor for cervical metastasis has not been established<sup>2</sup>.

Cervical metastasis was examined clinically and histopathologically in our patients with males being more affected than females; site predominately affected was the buccal mucosa, followed by the tongue, retro molar trigone, and floor of mouth, alveolus, maxillary tuberosity and palate. The mean rate of cervical metastasis was found to be 56.67% in level I (B) and in level II, 43.33% which is not statistically significant compared to other studies ( $p=0.331$ ). Clinically, the predominant lymph node groups involved were levels I and II; the middle and lower internal jugular groups however required ultrasonographic evaluation. This finding is in agreement with the anatomical running pattern that the lymph flow in the cervical region enters predominantly into the submandibular nodes and then descends from the superior internal jugular nodes<sup>2</sup>. In addition, according to the primary site, the metastasis rate is reported to be 37-55% in the tongue, 11-50% in the mandibular alveolus, and 24-75% in the buccal mucosa<sup>2</sup>. We documented a metastasis rate of 20% in the tongue, 60% in the buccal mucosa, 6.67% in the retro molar trigone and 13.34% in the maxillary tuberosity and alveolus.

Metastasis at the proximal level is predominant when metastasis involves a single group, while metastasis involving regional (multiple) groups is frequent clinically<sup>2</sup>. This correlates well with the results of our study. In one case, however, it was observed that metastasis involved the anterior compartment group of nodes (level VI), as indicated by ultrasonography, apart from clinical involvement of level IB and II. Though the cervical metastasis rate was as high as about 60% in T3 and T4 cases, as compared to about 30% in T1 and T2 cases, no significant difference was noted between them, suggesting misprediction of cervical metastasis by means of T classification alone<sup>2</sup>. Correlating tumor site with

that of staging, it was found that the T1 and T2 incidence of metastasis was 20% and 50%, while in T3 and T4 cases, was 26.67% and 3.34%, which do not correlate well with other studies. Comparative histopathologic and ultrasonographic analysis revealed a significant correlation i.e. 7 lymph nodes in level I were true positive, as against a false positive result of 15, obtained by ultrasonography ( $\chi^2 = 4.5933$ ;  $p=0.0321$ ). This indicates a high tendency toward tumor over-staging, including cervical metastasis misprediction.

Extracapsular tumor spread is considered to be one of the most important factors in head and neck SCC<sup>6</sup>. Extracapsular was evident in only 3.33% of our cases while in 96.6% there was lack of evidence. **Debra et al** reported a linear relationship between extracapsular spread and nodal size i.e. the incidence of extracapsular spread increases with increase in nodal diameter. Most important is the finding that extra capsular spread occurred in a notable percentage of smaller lymph nodes, and being malignant, can occur in conjunction with other multiple nodes of the same size or larger. Additionally, spherical rather than flat or ovoid lymph nodes are believed to have a greater incidence of malignancy<sup>6</sup>.

Tumor invasion pattern is variable. **Frierson and Cooper** described a higher index of metastasis in cases with a diffuse architectural pattern or a completely disorganized or haphazard growth without a well-defined deep border than in cases with a uniform, pushing deep border<sup>5</sup>. The predominant pattern of invasion we observed was that of the infiltrating type, and to a variable extent, the pushing or verrucous type. Perineural invasion has been described in several reports as an independent factor for predicting lymph node metastases in tumors located in the oral cavity and the lower lip. However, the relation between perineural spread and rate of metastasis in some cases has not been shown<sup>5</sup>. We had no evidence of perineural invasion.

**Michiel M.W. et al** estimated the accuracy of seven different radiologic criteria of 2,719 lymph nodes in 71 neck dissection specimens from 55 patients, in assessing cervical metastasis. Nodes with a minimal axial diameter of 11mm or more in the subdigastic region & 10mm or more in other node-bearing regions are



considered metastatic. All lymph nodes showing irregular enhancement and surrounded by a rim of enhanced tumor or lymph node tissue is also considered metastatic<sup>4</sup>. It was evident here, that the number of positive lymph nodes detected ultrasonographically in level I were 15 while that in level II and III were 10 and 3 respectively. In all, the lymph node diameter was > 8mm (ranging from 9mm to 12mm) with a "rounded" sign of metastasis, together with irregular, lobulated margins and a diffuse echoic texture. All nodes revealed central necrosis with loss of echogenic hilus and a low-resistance flow pattern. In other levels, there was lack of evidence of metastasis.

Of considerable importance, is the grade of tumor differentiation in relation to neck metastases? Nevertheless, several authors have found no statistical correlation. T-category has not been associated, in some studies, with the rate of metastases or only T1 in comparison with superior categories, but most studies have reported a high correlation between T-category and cervical lymph node metastasis<sup>5</sup>. It was also observed in our series, that by and large, an inverse relationship exists between the grade of tumor differentiation and the tendency toward metastatic nodal involvement.

**Jatin Shah** analyzed 1081 patients undergoing 1119 RNDs for primary SCC of the upper aero digestive tract. Levels I, II and III were at greatest risk for nodal metastases from oral primary tumors and levels II, III and IV were at greatest risk for nodal metastases from oropharyngeal, hypo pharyngeal and laryngeal carcinomas<sup>3</sup>. Similarly, in our study, nodal metastases from oral SCC was predominantly confined to levels I, II and III of the neck, and hence, we recommend supraomohyoid or the modified radical type of clearance, in cases of skip metastases. The factors affecting prognosis are the level of lymph node involvement and the presence or absence of soft tissue spread after penetration of the lymph node capsule. As the carcinoma spreads to lower neck nodes, there seems to be a corresponding reduction in five year survival, at least in those with involvement of the lower neck<sup>3</sup>.

## Conclusion

To conclude, there exists a positive correlation between the degree of histopathological

malignancy and cervical node metastasis in head and neck SCC. Histopathological diagnosis, in terms of tumor-grading, still remains to be the **confirmatory diagnostic tool** to reach a conclusive diagnosis, apart from ultrasonography serving as a supplemental diagnostic aid in radiologically assessing neck metastasis and the primary tumor per se. by and large, the tendency toward tumor over-staging and cervical metastasis misprediction, clinically as well as radiologically, can be overcome; whether the type of neck dissection performed is warranted or not and the probable prognosis can also be determined; all these strongly support the fact that histopathology still serves universally as the gold standard!

## References

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