Original Article

Pre-operative contrast enhanced computer tomographic evaluation of cervical nodal metastatic disease in oral squamous cell carcinoma

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Abstract

AIMS: This prospective study was undertaken to evaluate the contrast enhanced computed tomography (CECT) criteria in detecting cervical lymph node metastasis in 50 patients with an oral squamous cell carcinoma (OSQCC). **MATERIALS AND METHODS:** A total of 50 patients with OSQCC who underwent clinical assessment, routine CECT scanning of cervical lymph node and radical neck dissection were analyzed. Radiologic criteria for diagnosing nodal metastasis in this imaging study were: A nodal size of 1 cm, the presence of central lucency despite the size of the lymph node and grouping of lymph nodes. These criteria were based on modified American Joint Committee on Cancer Radiological Nodal Staging Guidelines. **STATISTICAL ANALYSIS:** Chi-square test/Fisher Exact test has been used to find the significant association of findings. Diagnostic statistics viz.: Sensitivity, specificity, positive predictive value (PPV), negative predictive value, and diagnostic accuracy were obtained. The results were considered significant when *P* value was less than 0.05. **RESULTS:** On using a nodal size of 1 cm and the presence of central nodal necrosis (CNN) as radiological criteria for nodal metastasis CT scanning staged 23 of the 27 histopathologically positive necks, providing accuracy of 88%, sensitivity of 92%, and specificity of 84% in detection of nodal metastasis. A significant relationship between the incidence of CNN, different nodal densities, and primary tumor differentiation was observed. **CONCLUSIONS:** The nodal size cut-off of 1-1.5 cm had a maximal sensitivity of 90.91% and PPV of 86.96%. Furthermore, observation of nodal densities in the absence of frank CNN on the CT scan may be necessary especially in low grade primary tumor. CT assessment of cervical node metastasis was found acceptable, although adjuncts like ultrasound guided fine needle aspiration may further increase efficacy of CT scan in nodes lesser than 1 cm in size.

Key Words: Central nodal necrosis, cervical lymph node metastasis, contrast enhanced computed tomography, oral squamous cell carcinoma

Introduction

Oral cancer constitutes 5.5% of all malignancies globally and holds the 8th position in the cancer incidence ranking world-wide, with epidemiologic variations between different regions (it is 3rd most common malignancy in South Central Asia). In India, oral cancer constitutes 20-50% of all cancers with oral squamous cell carcinoma (OSQCC) representing more than 90% of all head and neck cancers.[1] One of the most important factors that affects favorable treatment outcome is the presence of metastatic cervical lymphadenopathy. The rate of cervical node metastasis in OSQCC is a firm statement of the aggressive nature of the primary tumor and is an important prognosticator,[2-4] which reduces the 5 year survival rate to nearly one half of that seen in early staged patients. A single malignant node in the ipsilateral neck reduces the expected survival rate by 50%. Patients with bilateral metastatic adenopathy have 25% of the expected survival rate of those patients without any cervical lymph node metastasis.[3-7]

The presence of metastatic lymph nodes along with the number of nodal metastasis, the level in the neck, size of the nodes and the presence of extranodal spread have been shown to be significant determinants for distant metastases.[2,8-13] Thus, accurate identification and characterization of lymph nodes by imaging has important therapeutic and prognostic significance in patients with the newly diagnosed cancers. The presence of nodal metastases may limit the therapeutic options and indicate a worse prognosis in patients. Thus, it becomes crucial to have this information before commencing therapy.[2,14]

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Although, computed tomography (CT) is routinely used in staging of OSQCC and pre-operative assessment of cervical node metastasis, there is a controversy about the accepted criteria for diagnosis of smaller diameter nodal disease.[15-21] The objective of the present study was to analyze the size criteria, presence of central nodal necrosis (CNN), and other factors like grouping of nodes in contrast enhanced computed tomography (CECT) diagnosis of cervical lymph node metastasis in 50 patients who underwent radical neck dissections for the treatment of OSQCC. The results were compared with the post-operative histopathological studies to determine the relevance and limitations of CT examination.

Materials and Methods

In this prospective study, 50 patients with OSCC who underwent routine CECT) scanning for the primary tumor as well as cervical lymph nodes and radical neck dissection at our institute were selected, for this study. None of the patients had previously undergone a neck dissection on the affected side or received pre-operative radiation therapy or chemotherapy.

All patients were examined with CECT no more than 1 month before surgery. CT scans were performed with Spiral CT scan machine - SIEMENS - Somatom plus 4 and a conventional scanner SIEMENS - Somatom AR, which were intermittently used for the evaluation. 50-60 ml of IV contrast, Urograffin 300 mg% was used considering the patients weight on infusion of a rapid bolus dose for imaging on the spiral scanner; and 80-90 ml of contrast was utilized for usage in conventional scanner in divided doses. Axial CT was performed with 4 mm contiguous scans from the mastoid process to the hyoid bone and 4 or 8 mm scans from the hyoid bone to the clavicle. All the scans were evaluated independently disregarding clinical information on tumor site and lymph node involvement.

The following features were recorded for the nodes identified on CT: Location, greatest diameter, presence of necrosis, and invasion into the carotid artery or internal jugular vein. CT criteria used to assess nodal metastasis were[17]

1. A discreet mass more than 1cm in diameter, not enhancing to the extent as expected of vessels, in the lymph node bearing regions of the neck. For a mass in the jugulo-digastric and submandibular region, the mass had to be more than 1.5 cm; or
2. strong nodal enhancement, cystic change, calcification, and heterogeneous enhancement (Central necrosis of suspected nodal mass regardless of size); or
3. grouping of three or more nodes, each of 8-15 mm diameters, which are contiguous.

On surgical removal, the anatomical nodal levels of the nodes were carefully recorded at the time of excision and were matched to those on imaging studies based on location and size.

Statistical method

The Chi-square test was used for comparisons of qualitative values and to evaluate the diagnostic performance of CECT findings individually, to obtain diagnostic statistics viz.: Sensitivity, Specificity, positive predictive value (PPV), negative predictive value, and Diagnostic accuracy. Fisher Exact test was used to find the significant association of findings. The results were considered significant when *P* value was less than 0.05. The statistical software namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1, and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate tables.

Results

A total of 50 cases were studied of which 44 underwent unilateral and six underwent bilateral neck dissections and a total of 290 lymph nodes were excised and were matched with CT scans. Pathological examination determined that 70 nodes in 25 of 50 patients were metastatic.

Distribution of the primary tumor site and incidence of nodal metastasis

Distribution of patients by primary site of malignancy showed the highest incidence in the lower Buccal sulcus (20%) followed closely by Buccal mucosa (18%). 14% of patients had primary tumor of the hard palate with 12% having primary tumor of the upper Buccal sulcus. 10% of the patients had primary tumor of the tongue and maxillary alveolus each. Retromolar trigone was involved as the primary tumor site in 8% of cases. The soft palate and floor of the mouth were involved in 4% of patients each [Table 1].

Incidence of metastasis was very high in the floor of the mouth (100%), followed by the upper Buccal sulcus (66%). Maxillary alveolus and the tongue showed a 60% metastatic rate each. This was followed by lower Buccal sulcus retromolar trigone and soft palate, which showed incidence of 50% each. Hard palate and Buccal mucosa showed a metastatic rate of 42% and 22.2% respectively [Table 1].

Incidence of metastasis by the site of lymph nodes

Thus, the incidence of metastasis for patients with OSQCC in this study [Table 2] was 50%. The submandibular lymph nodes showed the highest incidence of histologically proven metastasis (57.1%) followed-by upper jugular lymph nodes (55.5%) and least incidence of metastasis was seen with submental lymph nodes (12.5%).

CT evaluation of lymph node metastasis

CT evaluation of the 50 patients in our study was positive for nodal metastasis in 27 (54%) patients out of which 23 (85%) were histopathologically proved metastatic. CT evaluation was negative in 23 (46%) patients of which only 2 (8.6%) patients were shown to have histopathological evidence of nodal metastasis. The sensitivity, specificity, and overall accuracy of CT evaluation were 92%, 84%, and 88% respectively [Tables 2 and 3].

Nodal size and grouping

Evaluation of lymph nodes by CT scan for nodal size was carried out with distribution of 50 patients, into 4 groups of <1.0 cm, 1.0-1.5 cm, 1.5-3 cm and >3 cm in size. When the lymph nodes measuring 1.0-1.5 cm in size was taken into consideration, the sensitivity, specificity, and overall accuracy were 90.9%, 70%, and 84.38%. When a size of 1.5-3 cm and >3 cm was used as criteria the sensitivity, specificity, and overall accuracy were 80%, 100%, and 88.24% respectively in each [Table 4]. CT was not entirely effective in detecting nodes less than 1.0 cm with a very low sensitivity of 71.43%. This indicated that as the size increased the efficiency of CT scan to detect lymph node metastasis also increased.

CNN

Of the 70 metastatic lymph nodes, 57 showed a hypodensity at their center, with rim enhancement, which was indicative of CNN. Of the 13 remaining metastatic lymph nodes, 9 revealed heterodensity and 4 were homogenous density on the CT scan. 213 of 220 lymph nodes that were benign showed homogenous density and 7 of them showed heterodensity on the CT scan. All the nodes that had shown CNN on the CT scan irrespective of nodal size were proved are metastatic [Table 5].

Extranodal spread

In this study 48.1% of nodes which were positive on CT showed signs of internal jugular vein (IJV) and carotid indentation, 14.8% showed luminal narrowing, 7.4% had luminal obliteration and 22.2% of the nodes were separated from the vital structures.

Of the 50 patients, (25) 50% were found to have histopathologically proven lymph node metastasis as shown in Table 2. The incidence of lymph node metastasis by tumor grading was studied in 50 patients and is shown in Table 6. Cervical lymph node metastasis was found in 4 of 26 patients (15.3%) with Grade I, 14 of 15 patients (93.3%) with Grade II and 7 of 9 patients (77.8%) with Grade III SQCC. Thus, well differentiated carcinoma had the lowest incidence of metastasis.

Differentiation and incidence of CNN

When the degree of differentiation of the primary tumor was compared with incidence of nodal necrosis it revealed that 50 of the 57 metastatic nodes with CNN were associated with well differentiated primary

Table 1: Distribution of patients by primary site of malignancy and metastasis

Primary site	Total (*n*=50)		Metastasis	
	Number	%	Number	%
Lower GBS	10	20.0	5	50.0
Buccal mucosa	9	18.0	2	22.2
Hard palate	7	14.0	3	42.8
Upper GBS	6	12.0	4	66.6
Maxillary alveolus	5	10.0	3	60.0
Tongue	5	10.0	3	60.0
Retromolar trigone	4	8.0	2	50.0
Floor of mouth	2	4.0	2	100.0
Soft palate	2	4.0	1	50.0

GBS=Gingivobuccal sulcus

Table 2: Comparison between CT lymph node examination and histopathological findings

Nodal metastasis	Node status on CT exam (50 patients)	Lymph node metastasis (50 patients)	CT Findings coincident with HPR Findings
Positive	27	25	23
Negative	23	25	2
Total	50	50	25

HPR=Histopathology; CT=Computer tomography

Table 3: Comparison of presence of nodes by clinical, CT and metastasis-an evaluation (number of patients)

Nodes	Sen.	Sp.	PPV	NPV	Accuracy	*P* value
Clinical versus CT (GS)	40.7	69.5	61.4	50.0	54.0	0.4492
Clinical versus metastasis (GS)	36.0	64.0	50.0	50.0	50.0	0.999
CT versus metastasis (GS)	92.0	84.0	85.1	91.3	88.0	<0.001**

**Statistically significant *P*<0.05; GS=Gold standard; Sen.=Sensitivity; Sp.=Specificity; PPV=Positive predictive value; NPV=Negative predictive value; Accuracy=Diagnostic accuracy; CT=Computer tomography

Table 4: Comparison of CT nodal size with metastasis-an evaluation (number of nodal levels)

CT nodal size (cm)	Sen.	Sp.	PPV	NPV	Accuracy	*P* value
0-1.0	71.43	17.95	13.51	77.78	26.09	0.514
1.0-1.5	90.91	70.00	86.96	77.78	84.38	<0.001**
1.5-3.0	80.00	100.00	100.00	77.78	88.24	<0.001**
>3.0	80.00	100.00	100.00	77.78	88.24	<0.001**

**Statistically significant *P*<0.05; GS=Gold standard; Sen.=Sensitivity; Sp.=Specificity; PPV=Positive predictive value; NPV=Negative predictive value; Accuracy=Diagnostic accuracy; CT=Computer tomography

tumor and remaining 7 were associated with moderately or undifferentiated SQCC. Of the 13 metastatic nodes without CNN (hetero or homogenous appearance) 3 were associated with the well differentiated SQCC and remaining 10 were associated with moderately or ill differentiated tumor. The results were proved to be significant as per Fisher's exact test.

Discussion

The oral cavity and other associated with the structures have a rich lymphatic drainage. Of the approximately 800 lymph nodes in the body, about 300 of them are located in the neck.[10] Lymphatic metastasis is the most important mechanism in the spread of SQCC of the oral cavity and the most common cause of treatment failure in oral carcinoma. Regional control of nodal metastasis in the neck is an important factor in predicting the course and outcome of treatment in patients with OSQCC.[2,3] In the present study, the rate of nodal metastasis is 50%.

This study was undertaken to evaluate the efficacy of CT in the identification of cervical nodal metastasis and its correlation with primary tumor staging in patients with SQCC of the oral cavity by means of a prospective analysis of CT examination of cervical nodes and later comparison with the histopathologic findings, in 50 patients.

Previous studies establishing the reliability of pre-operative CT scanning used variations of few generally accepted anatomic criteria to stage nodal disease.[15-21] The present study used criteria, which include nodal size, central necrosis, pericapsular extension, nodal location, and nodal grouping.

Table 5: Characteristics of density within the lymph nodes on CT scans

CT findings	Number of lymph nodes with metastatic tumor	Number of lymph nodes without metastatic tumor
Homogenous	4	213
Heterogeneous	9	7
CNN	57	0
Total	70	220

CNN=Central nodal necrosis; CT= Computer tomography

Table 6: Primary tumor grading and histopathological findings

HPR grading of tumor (Grade)	Number of patients (*n*=50)	%	Metastasis (*n*=25)	%
I	26	52.0	4	15.3
II	15	30.0	14	93.3
III	9	18.0	7	77.8

HPR=Histopathology

By using the criterion of size greater than 1.0 cm to indicate a positive node, 8.6% necks with nodal disease were missed on ideal CT scanning and interpretation. Friedman *et al*. stated that lymph nodes become positive at non detectable size as almost a billion cells are required to produce a mass of 1 cm^3.[15,16] The present study showed that many positive nodes, which were in fact less than 1.5 cm in size were also detected as they occurred together with the multiple other nodes larger than 1.5 cm. Thus, these nodes were not entirely missed by CT evaluation. Previous studies have shown that the primary lymphatic drainage will be the 1st node involved and that node will continue to grow to a maximum size and metastasis to secondary lymphatic sites may involve multiple areas with slower growth in each node.[5,15-21] In this study, presence of multiple nodes ipsilaterally or contralaterally, which showed up on the CT scans as nodes larger than 1.5-3 cm and >3 cm in size were unanimously proved metastatic (100%). However, for OSQCC staging, it is generally more important to have higher sensitivity. CT was not entirely effective in detecting nodes less than 1.0 cm (short-axis cut-off on axial images), with a very low sensitivity of 71.43%. Thus, this could result in a high false-negative rate.[22,23]

CECT [Figure 1] is considered to be the best modality for identification of CNN. Central necrosis is shown on CT as a central area of low attenuation with surrounding irregular wall. Som reported that the presence of a thin enhancing rim around a necrotic area indicates malignancy with rim enhancement reflecting the dilatation of blood vessels in the lymph node capsule. CNN occurs when neoplastic infiltration of the medullary portion of lymph nodes outstrips the blood supply.[20,24,25] Our results confirm previous findings that heterogeneous or rim enhancement is consistent with cervical node metastasis (100%). The results also showed that 9 out of 70 histopathologically positive nodes were heterodense [Figures 2 and 3] and 213 out of 220 lymph nodes that were benign were of homogenous density on CT scan. This outcome validated an earlier study by Morimoto *et al*. demonstrating the change in density of the nodes from homogenous to heterogeneous before advancing to CNN. Thus, observation of density of the lymph nodes in relation to the primary tumor especially of moderately differentiated and undifferentiated primary tumor sites will aid in diagnosing metastatic nodes.[24-27]

The invasion of vital structures or extra nodal spread occurs once the capsular barrier is breached causing obscuration of the margins of the lymph node. Prognostically and therapeutically this is relevant as resection then becomes uncertain. In this respect,

invasion of common or internal carotid is probably most important, specifically, when extracapsular tumor appears to encase or surround the carotid artery; many surgeons elect not to operate.[2,3,19,26] Nearly 48.1% of nodes, which were positive on CT showed signs of extracapsular spread. All the nodes, which showed extracapsular spread on CT scan, were proved metastatic on histopathological examination [Figure 4].

On assessment, the degree of differentiation of the tumor has been found to be correlated with the nodal metastasis.[10] The present study showed a higher incidence of neck involvement in poorly differentiated rather than in well differentiated carcinomas (93.3% and 77.8% respectively in Grade II and Grade III SQCC). This finding indicates that patients exhibiting a high histologic grade of malignancy are more likely to show neck metastasis at the 1st visit.[9] However, there were a few patients who had moderately differentiated (1 case) and undifferentiated (1 case) OSQCC in whom the CT scans were negative for metastasis (heterogeneous or homogenous appearance). In our study, we found a significant relationship between the incidence of CNN of metastatic nodes and extent of differentiation of SQCC in the nodes, wherein the degree of differentiation of the nodes was similar to that of the primary site in most cases. However, in certain cases of moderately differentiated and undifferentiated OSQCC, CNN was not detected on CT as was found in a study by Morimoto *et al*. They proposed that CNN was not able to form in lymph nodes with maximal diameter of less than 25 mm due to a time lag between the tumor filling the lymph nodes and the detection of CNN on the CT scan.[25,28]

Conclusion

Predictive value of CT in detecting cervical lymph node metastases at 85% is acceptable; however, lymph nodes that are less than 1 cm in size still pose a challenge of misdiagnosis, especially when occurring in lower grade primary tumor.[20,25,27,28] In such instances they need to be assessed based on nodal density changes on CT scans. We would suggest that further evaluation of suspected cervical lymph node metastases be performed using adjunctive imaging methods like Doppler ultrasonography (US), which in a recent study carried out by Ashraf *et al*. showed specificity of 97%[29] and US guided fine needle aspiration biopsy which according to a study by Liao *et al*. had 100% specificity.[30-32] CNN which is a consistent criterion for metastasis on CT scans needs to be assessed for incidence in relation to other predictive factors. Furthermore, a larger sample size needs to be assessed to well describe the characteristics of CNN through advanced software in CT scans as well as a detailed histological study.

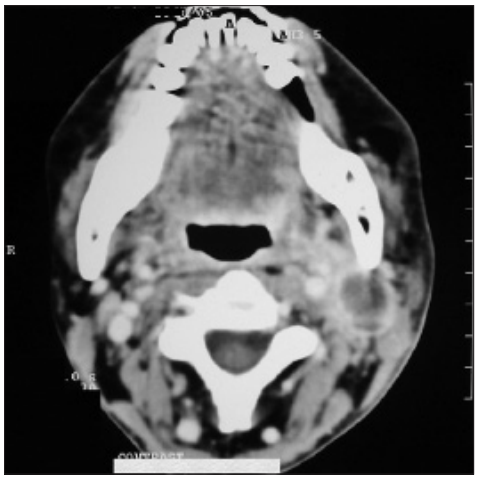

Figure 1: Lymph node (>1.5 cm) showing central nodal necrosis in left level II b, abutting the ramus of mandible and left carotid space structures

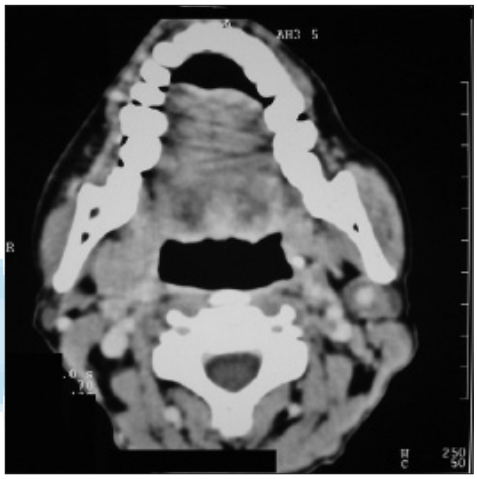

Figure 2: Nodal involvement (>1.5 cm) in left level II b, with a central calcific density abutting the ramus of mandible and left carotid space structures

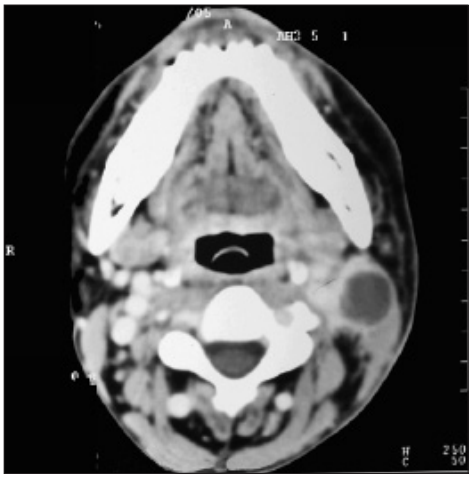

Figure 3: Round hypodense necrotic node seen on the left Level II b, adherent to the sternocleidomastoid muscle

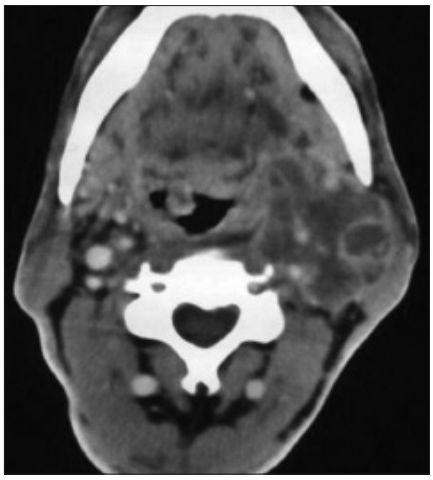

Figure 4: Nodal involvement (>3 cm) with extracapsular spread in left IB/II, causing left IJV obliteration and encasement of the left carotid artery

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