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PROGNOSIS AND MULTIVARIANT ANALYSIS OF N2c NODAL DISEASE IN ORAL CAVITY SQUAMOUS CELL CARCINOMA: A 10 YEAR STUDY IN TERTIARY CANCER CENTRE IN SOUTH INDIA.

Oncology

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ABSTRACT

CONTEXT: Surgery plays a pivotal role in the management of advanced oral cancers. The incidence of contralateral nodal disease in oral cavity squamous cell carcinoma is quite predictable in relation with certain variables, helping us in addressing this nodal disease. The mortality associated with N2c disease is relatively high, hence optimising the treatment of N2c disease can have impact in the survival in certain subset of patients.

AIM: The aim is to identify the clinico-pathological factors associated with N2c nodal disease and mortality associated with the disease.

MATERIALS AND METHODS: A retrospective audit of 484 oral Squamous Cell Carcinoma (SCC) patients treated at Royapettah cancer centre, Chennai from 2007-2017. All cases with N2c disease (39 patients) at presentation /relapsed at opposite node were analysed. The parameters analysed were anatomical subset in oral cavity, age(</>50 yr), gender, tobacco habits, midline crossing tumors, skin/bone involvement of primary tumor, ipsilateral nodal characteristics.

RESULTS: Mortality with N2c disease was nearly 72.5% in our series. Among the oral cancers tongue buccal mucosa and floor of mouth subsets cancer were significantly associated with N2c disease whereas alveolus, palate were not significant. Midline crossing tumors were the single most independent factor significantly associated with N2c disease. T3 and above tumors were also significantly associated. Ipsilateral node parameters like pathological positivity and multiplicity were significant in determining the N2c disease, (size of 3-6cm were 19/39, multiple nodal positivity (≥4 nodes) 4/39, pathological nodal positivity was 9/39). In our audit we found 26:13 M:F ratio. Almost all (~100%) of them had tobacco abuse history.

CONCLUSION: N2c nodal disease is associated with mortality rate nearly equal to distant metastases in our study. By identifying the parameters associated with development of N2c disease and initiating appropriate treatment early we can achieve better survival in certain subset of patients.

KEYWORDS

Squamous Cell Carcinoma - **SCC**, Contralateral Neck node metastases – CLMM, Royapettah Scoring System - RSS Midline Crossing Tumour – MLCT, Ipsilateral Nodal Parameters - IPL, Metastases in Bilateral or Contralateral Lymph nodes none larger than 6cm in greatest dimension & ECE(-), CLNR – Contra Lateral Nodal Relapse.

1. INTRODUCTION:

South India is a region of increased oral cavity cancer worldwide. In this part of the region presentation with advanced stage oral cavity cancer is quite common, so as the presentation with contralateral nodal metastases (4% to 20%). As surgery constitutes definitive treatment amongst the multimodality treatment, treatment of certain subsets oral cavity squamous cell carcinoma (SCC) presenting with N2c by surgery may also be useful. The survival and morbidity of patients by diagnosing these neck node metastases would be better if predictive factors of causing them are identified earlier and subjected to elective contralateral neck dissection. Numerous studies have been made earlier but absence of strong predictive value of factors rendered them not useful in Indian scenario.

Current surgical and radiotherapeutic guidelines for treatment of contralateral neck lack the benefits of large studies that examine the factors predictive of contralateral lymph node metastasis and survival[1].

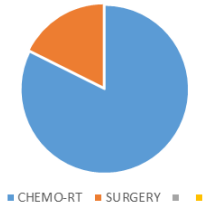
2. MATERIALS AND METHODS

A retrospective audit of oral SCC patients treated at Royapettah cancer centre, Chennai from 2007-2017. All cases with N2c disease (39 patients) at presentation /relapsed at opposite node were analysed. The parameters analysed were anatomical subset in oral cavity, age(</>50 yr, tobacco habits, ECOG performance score, midline crossing tumors, skin/bone involvement of primary tumor,T3 and above, ipsilateral nodal numbers, disease positivity, nodal size. Data collected from 2007-2017 head and neck cancer patients. The 484 oral cavity squamous cell carcinoma patients records were selected. All (39) N2c patients at presentation/relapsed were analysed for clinical-pathological factors. Mean age at diagnosis was 50.5 years (21:18 for > 50 yrvs< 50 yr)Male: female ratio was 26 : 13. Thirty nine (39) patients with N2c (33:6 for primary vs delayed presentation). ECOG Performance ratio at presentation was I:II:III was 29:9:1. Anatomical site wise distribution was tongue: buccal mucosa: floor of mouth : alveolus : palate were 19:10:5:3:2. Midline tumours were 15/39. Ipsilateral node size: Ipsilateral nodal pathological positivity : Ipsilateral number more than 4 positive nodes were 19:9:4 . Treatment wise distribution was Chemo-RT : Surgery= 33: 6.

2.1 Eligibility.

Only oral cavity SCC were included in study. Squamous cell carcinoma histological subtypes were only included, adenocarcinomas and minor salivary gland tumours were excluded. The age at the diagnosis was included. ECOG performance at the stage of diagnosing was included. Oropharyngeal tumors with extension into the oral cavity were excluded. By definition midline tumours were those within 1cm of either side median raphe/midline. Tumors arising from lateral side and extending onto the midline area are classified as non-midline tumours & hence excluded. AJCC 7th edition was used to stage the disease. N2c definition used in AJCC 7th edition was used as a standard. Clinical and imaging /FNAC documentation of N2c was made as essential for documentation purposes.

FIGURE NO. N2C MANAGEMENT



2.2 Patient Characteristics

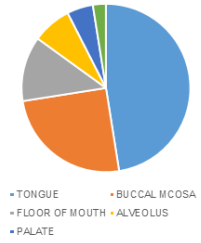
484 Oral Cavity SCC-Distribution

Parameters	N0 (86)	N1 (286)	N2a/b (43)	N2c (39)	N3 (18)	M1 (11)
Tongue (126)	22	51	25	19	5	1

Fom (33)	5	11	7	5	3	2
Buccal mucosa (242)	23	183	18	10	4	4
Alveolus (67)	23	39	0	3	1	1
Palate(16)	13		0	2	0	0
Overall survival (months)	86.7	48.6	34.5	11	6.3	2.8
3 year Mortality	6.9%	13.2%	14%	72.5%	77.7%	90.9%
5 year survival	87.4%	74%	41%	10%	0	0

2.3 Disease Details

ANATOMICAL SITE DISTRIBUTION IN N2C



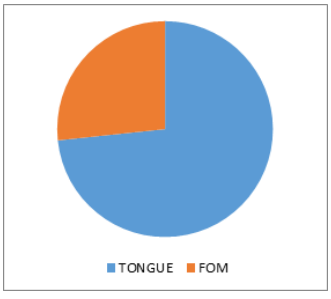
39 N2C Distribution

Primary	T1	T2	T3	T4a	
Tongue (19)	MLCT	0	2	4	5
	Non MLCT	0	5	3	0
Floor of Mouth (5)	MLCT	0	0	2	2
	Non MLCT	0	0	0	0
Buccal Mucosa (10)	0	0	4	6	
Alveolus (3)	0	0	2	1	
Palate (2)	0	0	1	1	

2.4 Description

Factors	Odds Ratio	95% CI	P- Value	Signifi cant
Tongue	2.85	1.48---5.50	0.002	YES
Buccal mucosa	0.305	0.1345 – 0.638	0.002	YES
Floor of Mouth	2.12	0.77 – 5.84	0.145	NO
Mid line crossing	147.7	18.29 – 1192.2	<0.001	YES
T3 & above	2.21	1.08 – 4.56	0.031	YES
IPL N Size 3-6cm	0.76	0.35 – 1.64	0.480	NO
IPL > 4 positivity	152.5	22.1-1243.5	0.002	YES
IPL N p +ve	6.35	2.25 – 17.98	<0.001	YES
Lymphovascular invasion/Grade I	94.0 0.004	11.2 – 786.7 0.001—0.033	<0.001 <0.001	YES YES
Bone / Skin involvement	9.21	3.29 – 25.75	<0.001	YES
MALE VS FEMALE	1.03	0.52 – 2.02	0.941	NO
Age	99.67	1.67-22.02	1.2	NO
PS	123.67	22.32-86.57	2.3	NO
Tobacco Habit	99.98	1.03-99.99	<0.001	YES

MIDLINE CROSSING TUMOURS

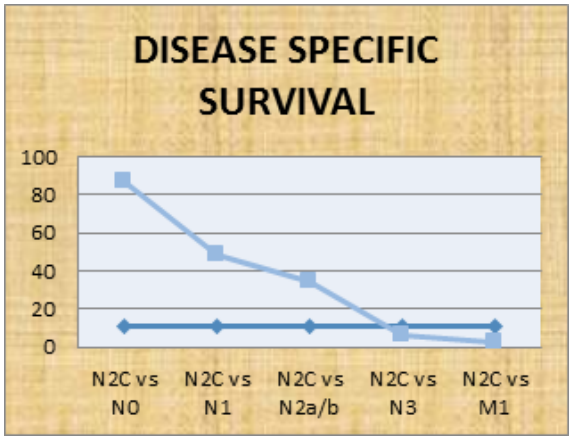


2.5 RESULTS:

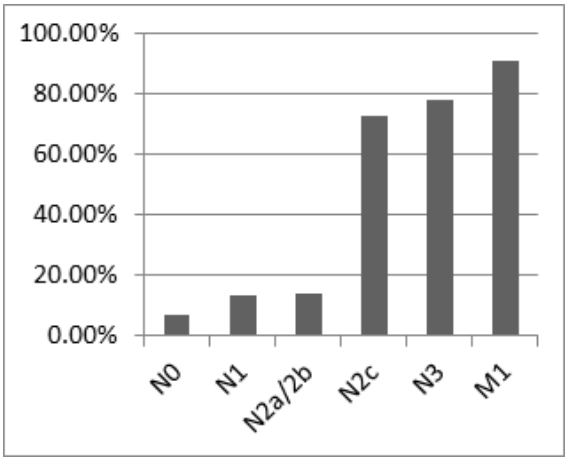
Mortality with N2c disease was nearly 72.5% nearly equivalent and comparable to N3 and M1 disease. The only difference was that of N2c patients died after 6 months of diagnosis while most of N3 and M1 disease patients died within 6 months. There was a significant difference in mortality between N2c and N0, N2c with N1 and N2a/b disease implying nodal parameter in determining prognosis at every stage of disease. Our contention was that it would be better if N2c is subcategorised with N3 as it more resembles with the later than N2 category. The most significant prognostic factors are the size of the positive node and the number of positive nodes.[11]. 3Amongst the N2c tongue subset were significantly associated with N2c disease by virtue of their anatomical site whereas buccal mucosa was significant and FOM, alveolus and palate were not significant. Midline crossing tumors were the single most independent factor significantly associated with N2c disease. T3 and above tumors were also significantly associated. Ipsilateral node parameters were all significant in determining the N2c disease particularly multiple node positivity and pathologically positive nodes, (size 3-6cm were 19/39, pathological nodal positivity was 9/39). In our audit we found 26:13 M:F ratio. Almost all of them had tobacco abuse history.

While controlling for other clinicopathological factors in a Cox proportional hazards model, tumours that cross the mid-line had statistically significant decreased survival with a hazard ratio of 147.7. Other factors that conferred decreased survival were positive ipsilateral or contralateral nodes, T3 and above, grade of the tumours, bone/skin involvement, lymphovascular invasion.

2.6 Observation and Analysis



MORTALITY RATES



DISCUSSION:

The prognosis of N2c nodal disease was comparable to the N3 disease in our study. Further on comparison of N2c with N0, N1 and N2a/b there was significance differences in survival as shown in the diagram[1]. Any nodal disease at presentation decreased survival compared to patients with no nodal disease. Also when a single ipsilateral node was detected, mean survival was greater than when contralateral node(s) were detected[1]. The difference between one ipsilateral node and

multiple ipsilateral node were not statistically significant. But the difference between multiple ipsilateral node and contralateral node(s) were statistically significant. Hence N2c nodal disease may be the last stop station for preventing loco regional disease from becoming metastatic one. Intervening at this juncture may be helpful in not only preventing mortality but also increasing the mean survival rates.

Contralateral nodal metastasis in the absence of ipsilateral nodal metastasisis very rare and frozen section of ipsilateral neck dissection specimen can be an important pointer for addressing contralateral neck[2].

According to Habib et al, patients with lateralized oral SCC undergoing treatment of the primary tumour and ipsilateral neck have a low rate of isolated contralateral neck failure. Although poorly differentiated primaries and ipsilateral nodal metastases were predictors of contralateral recurrence, the risk remains relatively xomodest in this subset of patients suggesting close observation may be more appropriate than elective treatment. The study of Habib et al support current recommendations for observation may be more appropriate than elective treatment[3].

The study by Lim and Lee et al showed that ipsilateral elective neck management is indicated for stage I and II SCC of the oral tongue. On the other hand, their series suggests that contralateral occult lymph node metastasis was unlikely in early-stage oral tongue SCC, and that there was no survival benefit for patients who underwent elective neck dissection in place of observation. Thus, it may not harmful to observe the contralateral N0 neck in the treatment of early oral tongue cancer[8] although this study has its own limitations.

Oral and oropharyngeal carcinomas with ipsilateral positive lymph nodes and tumor extension cross the midline are at higher risk of contralateral lymph node involvement. Prediction of contralateral metastases may be useful in planning more aggressive therapies in patients with head and neck SCC with poor prognostic criteria[5].

In the study by González-García R1 and Gil-Díez Usandizaga JL, delay in diagnosis twelve or more months is associated with increased CLNR. Clinical and pathologic factors predictive for CLNR are TNM tumor staging IV, histopathologic poor-differentiation of the primary tumor, surgical margins less than 1 cm around the primary tumor and perineural tumor involvement. Presence of ipsilateral neck metastasis at the time of diagnosis is associated with an augmented incidence of CLNR in SCC of the oral cavity[6].

Researchers have suggested that patients with primary tumor of the floor of the mouth, which is known to have a rich and bilateral lymphatic drainage pattern exhibit a higher risk of contralateral metastases than those with tongue tumors or those invading the retromolar trigone[12]. Patients with tumors arising in the base of tongue and floor of the mouth have a high frequency of CLNM than those tumors that involve the retromolar trigone area and mobile tongue[12].

Contralateral and ipsilateral neck relapses are similar in occurrence. Pathologic positive nodal status is associated with a higher incidence of contralateral neck relapse. Aggressive and Aggressive and comprehensive adjuvant radiotheraphy to the neck plus close surveillance in the first 2 years postoperatively might curtail the frequency and mortality due to contralateral neck failure[9].

The contralateral side of the neck is a common and potentially preventable site of recurrence in tumors of the oral cavity. The multivariate model obtained discriminates patients with low and high risk (more than 20%) of contralateral metastasis. The application of this mathematical model can be useful for the indication of contralateral neck dissections, because not all tumors crossing midline are associated to a high risk (stages I and II tumors not involving the floor of the mouth) and not all tumors not crossing midline are at low risk (stages III and IV tumors involving the floor of the mouth)[10].

CLNM in oral SCC involved complex mechanism and anatomic structures of the cervical region, while numerous biological and molecular factors may be considered. However, the exact mechanism that takes place in contralateral metastases is not yet clear. Some authors recognize that contralateral metastases of head and neck carcinomas can occur in different ways: firstly, by crossing afferent lymph vessels; and second by tumor spreading over the midline to reach efferent collateral lymphatic vessels while ipsilateral lymph nodes are extensively involved, where there is not a real midline barrier in certain anatomic areas. The incidence of CLNM differs considerably among institutions from 0.9% to 36%[12]. The researchers demonstrated that approximately 25% of all clinically occult metastases are too small to be detected using any of the available imaging techniques[12].

Lymphatic metastasis from the tongue can follow different patterns depending on the location of the primary tumor. It has been shown by Feind and others that more anterior tumors are at a higher risk for contralateral neck involvement. In their study there was an increased rate in patients with dorsal tongue tumors compared to ventral tongue tumors. The explanation for this may be similar to that of the anterior tongue effect in that metastases must travel longer through the tongue, and longer through the lymphatics, giving rise to more chance of crossover[1].

Contralateral lymph node metastasis can only occur if the tumor involves or crosses the midline either clinically or sub-clinically or if the tumor comes close enough to the midline for small lymphatic structures that themselves cross the midline in the tongue are utilized. Lymphatic capillaries and collecting trunks that cross the midline exist and are utilized more frequently the more centrally located the primary lesion. Vascular and perineural infiltration are two sub-clinical factors that may provide an anatomically rational explanation for increased contralateral neck involvement. The propensity for vascular and neural structures to aid in spread across the midline can be expected to rise the closer the tumor is to the midline however[1].

Kurita et al reported that the incidence of CLNM was higher in patients with multi-node involvement (50%) than in those with single node involvement (26.1%). The level of ipsilateral node metastasis was also correlated with CLNM. Level IV/V lymph node metastasis was an independent risk factors for the five-year rates of CLNM. Interestingly, a few authors have reported that CLNM never occurred in patients without ipsilateral lymph node metastasis, but only simultaneously with and after ipsilateral neck node metastasis, which suggests CLNM is unlikely if ipsilateral node metastasis has not occurred. A possible explanation is that the performance of elective neck dissection together with primary tumor resection may predispose patients to aberrant migration of in-transit carcinomatous cells to the opposite side of the neck. Therefore, the management of contralateral N0 neck in early SCC of oral cavity also may need to considered in order to prevent later cervical metastasis, according to these findings[12].

PROPOSAL OF SCORING SYSTEM

Parameters	0	1	2
Subsite		Floor of Mouth	Tongue/Buccal Mucosa
T – Stage	T1	T2/T3	T4a
Midline Tumour Crossing		Yes	
Grade	I/II	III	
Lymphovascular Invasion	Absent	Present	
Node Size	< 3cm	3-6cm	
Pathological Positivity		Yes	
Number of Nodes	Single	Multiple < 4 Nodes	Multiple Nodes ≥ 4

In our study Tongue, Buccal mucosa, Mid line crossing, T3 & above, IPL > 4 positivity, IPL N p +ve, Lymphovascular invasion/Grade I, Bone involvement were found to be statistically significant for contralateral nodal metastasis and hence contribute to the decreased the survival and mortality. In our study floor of mouth and N size of 3-6 cm were not statistically significant probably due to less numbers.

Numerous retrospective studies have supported the role of elective neck dissection in contralateral N0 oral cavity SCC when patients present a high risk for later CLNM. Elective neck dissection of the contralateral neck in OSCC can safely be performed as neck dissection of regions I, II, III, and IV. As a limited procedure, the neck dissection has few complications or long-lasting side effects, and offers the advantage of an accurate classification and the status of contralateral lymph nodes, which is closely linked to adjuvant treatments. Therefore, neck dissections not only a therapeutic procedure, but also a

diagnostic one, and an elective contralateral neck treatment is generally recommended for initial treatment in certain patients with oral cavity SCC. It has been reported that isolated unilateral cervical dissection is predictive for CLNM, accounting for only 1.8% of the patients that primarily underwent bilateral neck dissection developed CLNM, in comparison with 7.4% of those patients undergoing unilateral neck dissection. Several independent authorities suggest one should carefully consider performing elective contralateral neck dissection (cN0) for oral squamous cell carcinoma patients in some certain situations, as follows:

I. tumors arising in the base of tongue and the floor of the mouth;
II. tumors crossing the midline;
III. advanced staging (cT3-4);
IV. multiple ipsilateral nodes involvement12.

We hence put forth the Royapettah scoring system aggregating all the statistically significant factors contributing to the N2c nodal disease. The positive predictive value of >5 among the total score of 14 leads to the 82% among the study group. This indicates the development of contralateral node(s) in the patients who harbor these factors. Hence performing elective contralateral supra omohyoid neck dissection among the subset of patients who are at the high risk of developing N2c (T2 No (Tongue), any T with multiple node positivity and any T with midline crossing, tumours >T3 in our study) may lead to increased survival rates and prospective studies are under way.

CONCLUSION :

N2c nodal disease is associated with mortality nearly equal to distant metastases in our study. Special attention must be paid to the contralateral neck for patients with T2 or T3 tumors that cross the midline and for all T4 tumors. By identifying the parameters associated with development of N2c disease and initiating treatment early we can achieve survival in these subset of patients.

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