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RADIOLOGIC-PATHOLOGIC CORRELATION OF EXTRANODAL EXTENSION IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY

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ABSTRACT **Background:** The purpose of this study was to assess the accuracy of preoperative CT imaging for predicting pathologic nodal ECE (pECE). **AIM:** To estimate the accuracy of the presence of radiologic extranodal extension (rENE) in reference to pathologic extranodal extension (pENE) in patients with oral cavity squamous cell carcinoma (OSCC) **MATERIALS AND METHODS:** This is a prospective study in GSVM Medical College, LLR & Associated Hospitals, Kanpur (UP). The records of 50 consecutive patients with oral cavity cancer (OCC) who underwent preoperative CT imaging before initial surgical resection and neck dissection between 2020 and 2021 were reviewed. Specimens with pECE had the extent of ECE graded on a scale from 1 to 4. **RESULTS:** Radiographic ECE was documented in 6 patients (12%), and pECE was observed in 11 (22%). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 45.4%, 97.4%, 83.6%, and 86.3%, respectively. The sensitivity of radio- graphic ECE increased from 40% for grade 1 to 2 ECE, to 50% for grade 3, and 50% for grade 4. Radiographic ECE criteria of adjacent structure invasion was a better predictor than irregular borders/fat stranding for pECE. **CONCLUSION:** Radiographic ECE has poor sensitivity, but excellent specificity for pECE in patients who undergo initial surgical resection. PPV and NPV are reasonable for clinical decision making. The performance of preoperative CT imaging increased as pECE grade increased.

KEYWORDS :

INTRODUCTION

Lymph node extracapsular extension, also termed extranodal extension or extracapsular spread (ECS) from lymph nodes, is defined as metastatic cancer extending through the nodal capsule into the peri-nodal adipose tissue and is a hallmark of aggressive phenotype for multiple cancers Patients treated with initial surgical resection and neck dissection are typically risk stratified for adjuvant therapy using validated pathologic risk factors[1] Patients with involved surgical margins and/or nodal extracapsular extension (ECE) are at increased risk for loco-regional recurrence and death, and trimo- dality therapy consisting of adjuvant concurrent CRT is indicated[2]. Patients with locally advanced disease who undergo initial surgical resection may be able to receive a lower dose of adjuvant RT and avoid concurrent chemotherapy if no high-risk pathologic risk factors are present[1]

A continuing theme in oncologic therapy is that as the number of treatment modalities increase, the risk of both acute and late toxicity also increases. TORS for oropharyngeal cancer followed by adjuvant RT has been shown to be associated with worse late toxicity than TORS alone [3]

Similarly, the addition of chemotherapy to definitive RT is also associated with increased risk of severe late toxicity[4,5]

AIMS AND OBJECTIVES

To estimate the accuracy of the presence of radiologic extranodal extension (rENE) in reference to pathologic extranodal extension (pENE) in patients with oral cavity squamous cell carcinoma (OSCC).

MATERIAL AND METHODS

The study is conducted on the patients admitted in the department of Surgery of LLR Hospital, GSVM Medical College, Kanpur with diagnosis of carcinoma oral cavity.

Duration : January 2021 to October 2022.
Type of study : Prospective study
Sample size : 50 cases

Place : Department of Surgery G.S.V.M. Medical College, LLR & Associated Hospitals, Kanpur.

The records of 50 consecutive patients with oral cavity cancer (OCC) treated with initial surgical resection and neck dissection between 2020 and 2021 were reviewed.

All patients underwent high-quality, preoperative CT imaging with 100 cc of intravenous (IV) contrast with radiologist interpretation, CT images were acquired at 1.25 mm, reconstructed into axial, sagittal, and coronal series, and read at 2.5 mm. All surgical specimens were reviewed by pathologists specializing in head-and-neck pathology.

Specimens with pathologic nodal ECE had the extent of ECE graded (by K.R.M.) on a scale from 1 to 4 according to the scale of Lewis et al [6]. Pathologic ECE grading was as follows: grade 1, tumor reaching the nodal capsule; grade 2, 1 mm of extranodal extension; grade 3, >1 mm extranodal extension; grade 4, complete replacement of the node with no residual nodal architecture visible (soft tissue metastasis)[6]

Criteria for radiographic ECE documented on preoperative imaging reports were irregular borders and/or perinodal fat stranding and invasion of adjacent structures[7]. Neck dissections were typically selective neck dissections with sparing of the sternocleido- mastoid muscle, internal jugular vein, and cranial nerve XI, if possible[1]

Inclusion criteria

Patients age >18 years
Patients of oral carcinoma.
Consenting patients.
Willing for regular follow-up
Operable patients with bulky lymph nodes.

Exclusion criteria :

Exclusion criteria included patients less than 18 years of age, active non oral cavity malignancy, previous neck dissection, previous RT to the head and neck, non operable patients, non consenting patients, CT imaging without IV contrast, and >90 days from preoperative imaging to surgery.

STATISTICAL ANALYSIS

All the patients was collected in proforma, entered in excel sheet and analysed using SPSS v21 operating on windows 10. The patients

demographic data was presented as frequency, percentage, mean and standard deviations presented using tables, pie charts and bar diagrams. The mean difference between the continuous variables of two group are assessed using unpaired independent t-test and the follow-up data within the group are analysed using paired t-test. a p-value of <0.05 was considered statistically significant.

Characteristic	Number	%age (n=50)
Total	50	100
Age		
Median	60	

Sex		
Male	31	62
Female	19	38

Characteristic	Number	%age (n=50)
Primary site		
Oral Cavity	50	100
Primary subsite		
Retromolar trigone	4	8
Oral tongue	22	44
Alveolar ridge	6	12
Lip	2	4
Floor of mouth	5	10
Buccal mucosa	11	22

Characteristic	Number	%age (n=50)
Clinical T stage		
T1	8	16
T2	12	24
T3	8	16
T4	22	44

Characteristic	Number	%age (n=50)
N0	24	48
N1	8	16
N2	18	36

Characteristic	Number	%age (n=50)
Pathologic T stage		
pT1	14	28
pT2	10	20
pT3	8	16
pT4	18	36

Characteristic	Number	%age (n=50)
Pathologic N stage		
pN0	26	52
pN1	8	16
pN2	16	32

Characteristic	Number	Percentage (%)
Radiographic nodal ECE		
Yes	6	12
Radiographic ECE criteria		
Adjacent structure invasion	4	66.6
Irregular borders/Fat stranding	2	33.4

Characteristic	Number	%age (n=50)
Pathologic nodal ECE		
Yes	11	22

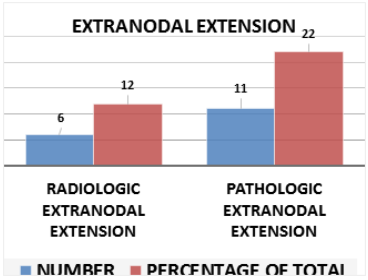
Characteristic	Number	%age (n=50)
Pathologic nodal ECE grade		
0	39	78
2	3	6
3	4	8
4	2	4

In our study, total sample size was 50. Out of 50 patients 31 are male patients constituting 62% of total sample size and 19 females making 38% of total sample size.

Primary site of study is carcinoma of oral cavity. Subsites within oral cavity are as follows; most of the patients are of Carcinoma of tongue 22 (44%) patients out of 50 patients are of carcinoma tongue, 11 (22%) patients are of carcinoma of buccal mucosa, 6 (12%) patients have carcinoma at alveolar ridge, 5 (10%) patients have floor of mouth carcinoma , 4 (8 %) patients have carcinoma of Retromolar trigone, 2 (4%) patients have carcinoma of lip Clinically there are 8 (16%) patients in T1 stage, 12 (24%)patients in T2 stage, 8 (16%) patients in T3 stage, 22 (44%) patients in T4 stage clinically.

52% (n=26) of total patients have image positive nodes16% (n=8) have N1 image positive node, 36% (n=18) have N2 image positive node, 48% (n=24) have image negative node 28% of total patients have (n=14) pathologic TI stage, 20% (n=19) of total patient have pathologic T2 stage, 16% (n= 8) of total patients have pathologic T3 stage, 36% (n = 18) of total patients have pathologic T4 stage No extra nodal extension seen in 39 patient out of 50 patients. It is accounting for 78%. Pathologic Extra Nodal Extension seen in 11 out of 50 patients which is 22% of total population. Out of 11 patients 2 patients (4%) showed Pathologic grade 1 , 3 patients (6%) showed pathological Extranodal extension grade 2, 4 patients (8%) showed pathological Extranodal extension grade 3 and 2 patients (4%) showed pathologic Extranodal extension.

Radiographic ECE was documented in 6 patients (12%), whereas pathologic ECE was found in 11 patients (22%).



Radiographic ENE is seen in 6 out of 50 patients. It accounts for 12% of total patients. 4 out of 6 patients showed adjacent structure invasion in Radiographic ENE (8% of total). Other 2 patients showed Irregular borders/ fat stranding accounting for 4% of total.

RADIOGRAPHIC NODAL EXTRA CAPSULAR EXTENSION (ECE) PREDICTING FOR PATHOLOGIC NODAL ECE

Radiologic ENE	Pathological ENE		Total	P value
	Yes	No		
yes	5	1	6	<0.0001
no	6	38	44	
Total	11	39	50	

Sensitivity	45.4 %
Specificity	97.4 %
PPV	83.3 %
NPV	86.36%
Accuracy	86 %
Chi square value	14.95

Radiographic ECE was documented in 6 patients (12%), whereas pathologic ECE was found in 11 (22%). Sensitivity of radiographic ECE for pECE was 45.4%. Specificity was 97.4%. The PPV, NPV, and accuracy were 83.3%, 86.3%, and 86%, respectively. p Value is <0.0001 which is highly significant

TABLE: RADIOGRAPHIC EXTRANODAL EXTENSION SHOWING ADJACENT STRUCTURES INVASION VERSUS PATHOLOGICAL EXTRANODAL EXTENSION

Radiologic ENE	Pathological ENE		Total	p
	yes	No		<0.001
yes	3	1	4	
no	8	38	46	
Total	11	39	50	

Sensitivity	27.4 %
Specificity	97.4 %

PPV	75 %
NPV	82.6 %
Accuracy	82 %
Chi square value	7.11

Page of Radiographic ECE showing adjacent structures invasion was documented in 4 patients, whereas pathologic ECE was found in 11 (22%). Sensitivity of radiographic ECE with adjacent structures invasion for pECE was 27.4%. Specificity was 97.4%. The PPV, NPV, and accuracy were 75%, 82.6%, and 82%, respectively. p Value is <0.001 which is highly significant

TABLE : RADIOGRAPHIC EXTRANODAL EXTENSION SHOWING IRREGULAR BORDERS/ FAT STRANDING VERSUS PATHOLOGICAL EXTRANODAL EXTENSION

Radiologic ENE	Pathological ENE		Total	P value
	Yes	No		
yes	1	1	2	>0.05
no	10	38	48	
Total	11	39	50	

Sensitivity	91 %
Specificity	97.4 %
PPV	50 %
NPV	79.2 %
Accuracy	79 %
Chi square value	0.9578

Radiographic ECE with irregular borders/fat stranding was documented in 2 patients (), whereas pathologic ECE was found in 11 (22%). Sensitivity of radiographic ECE for pECE was 91%. Specificity was 97.4%. The PPV, NPV, and accuracy were 50%, 79.2%, and 79%, respectively. p Value is >0.05 which is not significant.

TABLE : RADIOGRAPHIC EXTRANODAL EXTENSION SHOWING VERSUS PATHOLOGICAL EXTRANODAL EXTENSION OF GRADE 1-2

Radiologic ENE	Pathological ENE		Total	P value
	Grade 1-2	No		
yes	2	1	3	<0.001
no	3	38	41	
Total	5	39	44	

Sensitivity	40 %
Specificity	97.4 %
PPV	66.67 %
NPV	92.7 %
Accuracy	91 %
Chi square value	9.776

Sensitivity is 40%, specificity is 97.4% PPV, NPV and accuracy are 66.67% 92.7%, 91%. P value is <0.001 which is significant

TABLE: RADIOGRAPHIC EXTRANODAL EXTENSION SHOWING VERSUS PATHOLOGICAL EXTRANODAL EXTENSION OF GRADE 3

Radiologic ENE	Pathological ENE		Total	p Value
	Grade 3	No		
yes	2	1	3	<0.0001
no	2	38	41	
Total	4	39	44	

Sensitivity	50 %
Specificity	97.4 %
PPV	66.7 %
NPV	95 %
Accuracy	93.02 %
Chi square value	12.58

Sensitivity is 50%, specificity is 97.4% PPV, NPV and accuracy are 66.67% 95%, 93.02%.P value is <0.001 which is significant

TABLE : RADIOGRAPHIC EXTRANODAL EXTENSION SHOWING VERSUS PATHOLOGICAL EXTRANODAL EXTENSION OF GRADE 4

Radiologic ENE	Pathological ENE		Total	p Value
	Grade 4	No		<0.001
yes	1	1	2	
no	1	38	39	
Total	4	39	41	

Sensitivity	50 %
Specificity	97.4 %
PPV	50 %
NPV	97.4 %
Accuracy	95.12 %
Chi square value	9.58
P value	<0.001

Sensitivity is 50%, specificity is 97.4% PPV, NPV and accuracy are 50% 97.4%, 95.12%. P value is <0.001 which is significant

DISCUSSION

Lymph node extracapsular extension, also termed extranodal extension or extracapsular spread (ECS) from lymph nodes, is a key characteristic of aggressive phenotype in cancer, carrying a major impact on prognosis. Controversy exists with regards the classification of ECS by different histopathological assessment methods published in the literature [7]

Preoperative CT neck imaging was not sensitive for pECE overall, with a sensitivity of 45.4%, but the specificity, PPV, NPV, and accuracy were reasonable for clinical decision making with values of 97.4%, 83.3%, 86.3%, and 86%, respectively. One patient had false-positive radiographic ECE, for a false-positive rate of 2.01%.

The relatively low prevalence of pECE (22%) in this study led to a robust NPV despite poor overall sensitivity. Radiographic ECE was defined as by 2 criteria: first by irre gular node margin/perinodal fat stranding and second by adjacent structure invasion[7]. We found that adjacent structure invasion was a better predictor of pECE compared with irregular borders/fat stranding with superior sensitivity (27.4% vs 9.1%) and PPV (75% vs 50%). Of the 2 false-positive radiographic ECE, 1 was irregular borders/fat stranding, and only 1 met adjacent structure invasion criteria.

Preoperative CT imaging is the standard of care for clinical staging of most head-and-neck cancers, and therapeutic decisions are made based on the results of imaging assuming robust correlation with pathologic equivalents [8]. However, there is growing body of evidence, both within head-and-neck cancer and in other disease sites, reporting the limitations of CT-based radiographic-pathologic correlation [9,10]. Characterization of the diagnostic test parameters for imaging that is used to guide therapeutic decision making is essential so as to be aware of the risk of misclassification bias and the limitations of the test being used.

Pathologic ECE is a validated poor prognostic factor with significantly higher risk of loco-regional recurrence and death [11]. A combined analysis of 2 large randomized trials solidified adjuvant CRT as the standard of care for patients with resected head-and-neck cancer found to have involved surgical margins and/or pathologic nodal ECE[2].

Pharyngeal primaries represented approximately 50%, 52%, and 35% of the EORTC, RTOG, and MDACC trial populations, respectively. Because of the considerable morbidity of traditional surgical approaches for pharyngeal cancer, organ preservation with definitive CRT was an attractive option for this disease site.

In light of clinical decisions being made based on these imaging findings, we sought to determine the diagnostic test characteristics and accuracy of pre- operative CT imaging-based radiographic ECE for pathologic nodal ECE.

In addition, there is increasing interest among coop- erative groups in TORS as a local therapy modality specifically for human papillomavirus (HPV)-negative oropharyngeal cancer due to significantly worse locoregional control and survival with definitive CRT compared with HPV-positive patients[12,13].

TORS is a Food and Drug Administration-approved local therapy for early-stage, functionally resectable tumors of the oropharynx and larynx. Reported outcomes have improved over time, with a recent large multi-institutional series of 177 patients (78% oropharyngeal tumors) demonstrating a 4.3% margin positivity rate, with 2.3% persistent tracheostomy and 5% persistent enteral tube feeding rates[14]. Neck dissection results and adjuvant therapies were not reported in this series.

A large multi- institutional series of 89 patients (87% oropharyngeal), of whom 76% underwent neck dissection, demonstrated a 0% margin positivity rate. ECE rates were not reported, but 48% of patients did receive CRT, suggesting that a substantial proportion of patients had pECE if adjuvant therapy guidelines were followed[15].

A series by Weinstein et al examined the findings of staged neck dissection 1 to 3 weeks after local therapy with TORS [14]. A total of 31 patients (100% oropharyngeal) underwent 33 neck dissections, with ECE found in 9 patients (29%). Overall, 12 patients (39%) received adjuvant CRT. The reported prevalence of pECE in these series is similar to that in the current study (20%).

We selected patients with oral cavity cancer for this study because of the need for initial surgical resection in this patient population regardless of the preoperative CT imaging findings. Definitive RT/CRT is known to have worse outcomes than initial surgery for patients with OCC, and upfront surgical resection is the standard of care for patients with resectable disease[8].

To reduce the selection bias caused by the influence of radiographic ECE on therapy decisions and neck Patients with grade 1 to 2 ECE had no worse outcomes than those without ECE. The adverse effect of ECE was limited to those with high- grade ECE, primarily grade 4.

CT imaging test characteristics generally improved as the predicted state pECE grade increased. The sensitivity increased from 40% for grade 1 to 2 ECE, to 50% for grade 3, and 52% for grade 4 ECE.

The PPV of radiographic ECE was 66.67% for grade 1 to 2 ECE versus 66.67% and 50% for grade 3 and 4 ECE, respectively. NPV was excellent for all ECE grades because of the relatively low prevalence of pECE in this patient population

Alternatively, PPV would be expected to increase in a patient population with a higher prevalence of pathologic ECE because of the low probability of false-positive radiographic ECE.

The prognostic value of ECE grade for patients with oral cavity has not been well delineated. It is not currently known whether outcomes for patients with these primary sites and high-grade ECE differ by treatment with definitive CRT versus trimodality therapy for management of the neck.

The appearance of radiographic ECE depended on pathologic ECE grade, with adjacent structure invasion being more common with higher-grade ECE. Adjacent structure invasion was noted in 2 of 5 patients (40%) with grade 1 to 2 ECE, 2 of 4 patients (50%) with grade 3 ECE, and 1 out 2 patients (50%) with grade 4 ECE. Adjacent structure invasion was a better predictor for grade 3 to 4 pECE than irregular borders/fat stranding.

Our study results are consistent with those of other published studies demonstrating that the risk of pECE significantly increases with increasing LN size[16]. However, there was not an association between either radiographic LN size or pathologic LN size and ECE grade in patients with pECE (n=11), although the patient numbers in each category were low.

Limitations of this study include the potential for selection bias exists if the finding of radiographic ECE on preoperative imaging influenced the decision to pursue initial surgery. We sought to minimize this bias by including only those patients who were indicated for initial surgical resection as standard-of-care treatment. The prevalence of pECE and rECE were relatively low leading to small patient numbers and wide confidence intervals around the test characteristic point estimate in several subgroup analyses.

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