Original Article

Association of Tumour Necrosis with Histopathological Prognostic Parameters in Oral Squamous Cell Carcinoma

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Abstract

Background-Oral squamous cell carcinoma (OSCC) is the most common cancer in India but to the dismay, it has limited treatment modalities. This is a retrospective study on 50 cases of OSCC to evaluate association of tumour necrosis with histopathological parameters like tumour size, nodal involvement and depth of invasion.

Methods-This was a retrospective study in which all resection specimens of OSCC operated over a one year period were included. The tumours were graded and staged according to the WHO classification. Tumour necrosis was graded semi-quantitatively as Grade 0- no necrosis, grade1- focal or <10% of total tumour area, moderate or grade 2- necrosis comprising 10-30% of the tumour area and extensive or grade 3- necrosis >30% of the tumour area. Necrosis grade was categorised into- low (Grade 0 and 1) and high (Grade 2 and 3). The association between tumour necrosis and histopathological parameters was evaluated using the Chi square test.

Results-A total of 50 resection specimens were included in the study. Out of 50 cases, 14 (28%), 7 (14%), 21(42%), 8 (16%) were T4, T3, T2 and T1 respectively. 28(56%) cases showed low grade necrosis while 22(44%) cases exhibited high grade necrosis. The grade of necrosis showed significant association with depth of invasion, primary tumour size and grade of tumour. However, no association could be elicited between tumour necrosis and nodal status.

Conclusions-Tumour necrosis is an easily recognizable histopathological variable which must be included in routine reporting of OSCCs. A higher grade of tumour necrosis is associated with greater tumour size, grade and depth of invasion.

Keywords

Carcinoma; Invasion; Necrosis; Nodal; oral; Squamous; Tumour

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Introduction

Oral cancer accounts for 2-4% of all cancers in the world while in India it accounts for an overwhelming 45% of all cancers. Squamous cell carcinoma (OSCC) is estimated to be more than 90% of all oral neoplasms[1]. Despite advancements in surgery and therapy, there is no significant improvement in morbidity and mortality in these patients. Studies on prognostic factors on oral squamous cell carcinoma show higher prevalence of OSCC in males and they also present with higher T stage, however 5- year survival rate by gender show no statistical difference[2,3]. Similarly, effect of age as prognostic indicator is controversial. Studies on primary site of OSCC highlights that carcinomas on mucosal surface of lip showed good prognosis, most of the tongue lesions presented with lower T stage while SCC of retromolar trigone showed lowest survival rate[4]. Till date, TNM staging has shown to be the most significant factor in prognosis of OSCC[5,6]. Several studies on cervical lymph node status has shown better survival with N0, N1 status than N2, N3[3,4]. Initially, emphasis was laid on only the tumour cell and its characteristics for prognostication of cancer but now there is enough evidence that the tumour

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microenvironment leads to poor prognosis. Tumour necrosis is undergoing an extensive research to be qualified as prognostic marker in many cancers. Previous literature shows histological tumour necrosis as a diagnostic tool in evaluating patient outcome after liver resection in hilar cholangiocarcinoma and not only the presence but severity of tumour necrosis corelates with the significantly decreased and overall recurrence free survival[7]. Richards et al elicited extensive tumour necrosis as a poor prognostic marker in clear cell RCC along with association with aggressive tumour characteristics such as grade, size, pathological grade and vascular invasion. Similar evidence is seen with tumour necrosis and other high risk pathological features in invasive breast cancer, lung cancer and colorectal cancer[8]. An impressive study on tumour necrosis in endometrial cancer not only establishes the association between tumour necrosis and aggressive clinicopathological features and reduced patient survival but also shows its correlation with gene expression pattern, markers of angiogenesis, hypoxia and inflammation and potential therapeutic targets in the presence of necrosis[9]. There also have been conflicting reports related to tumour necrosis. Tumour necrosis was neither predictive nor prognostic in muscle invasive bladder cancer[10]. This study aims to evaluate association of tumour necrosis in OSCC with histopathological parameters like grade, tumour size, nodal involvement and depth of invasion.

Material and Methods

This was a retrospective study conducted in Department of Pathology. All resected specimens of histologically proven oral squamous cell carcinomas between April 2021 to March 2022 were included. Any cases which received any neoadjuvant chemotherapy or radiotherapy were excluded from the study.

Tumour area was completely processed and was graded and staged according to conventional pTNM classification by WHO[11]. The assessment of tumour necrosis was done semi-quantitatively based on a method by Polheimer et al as Grade 0-no or 0% necrosis, grade1- focal or <10% of total tumour area, moderate or grade 2- necrosis comprising 10-30% of the tumour area and extensive or grade 3-necrosis >30% of the tumour area[12-14]. Chi Square test was used to establish the association between tumour necrosis and histopathological parameters like tumour size, nodal involvement and depth of invasion.

Results

A total of 50 resection specimens were included in the study. The mean age was 58.8 ± 8.2 years with a male to female ratio of 2.8:1. Buccal mucosa was the most common site with 35 cases (70%) followed by tongue (30%). Out of 50 cases, 14 (28%), 7 (14%), 21(42%), 8(16%) were T4, T3, T2 and T1 respectively. Based on grade, there were 17(34%), 13(26%) and 20 (40%) cases of well differentiated, moderately differentiated and poorly differentiated squamous cell carcinoma respectively. No nodal involvement (N0) was seen in 33 (66%) cases while 10 (20%), 4 (8%) and 3 (6%) cases were classified as N1, N2 and N3. Necrosis grade was categorised into- low (Grade 0 and 1) and high (Grade 2 and 3) and compared with the depth of invasion, tumour size and nodal involvement.28 (56%) cases showed low grade necrosis while 22 (44%) cases exhibited high grade necrosis (Figure 1). The grade of necrosis showed significant association with depth of invasion, primary tumour size and grade of tumour (Table 1, 2, 3). However, no association could be elicited between tumour necrosis and nodal status (Table 4).

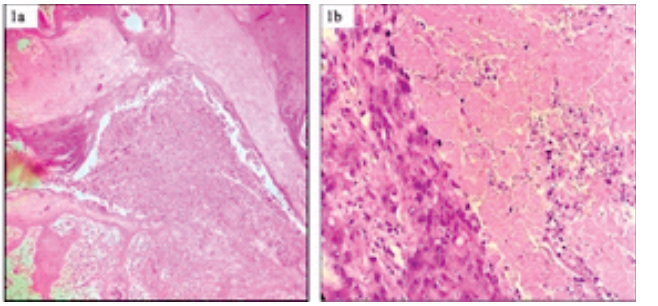

Figure 1 a. Tumour necrosis (Grade 3) in a case of well differentiated squamous cell carcinoma . (Haematoxylin and Eosin, x 10), 1b. Tumour necrosis (Grade 2) in a case of moderately differentiated squamous cell carcinoma. (Haematoxylin and Eosin, x 40).

Table 1 : Association between depth of invasion and tumour necrosis

	Low	High	p value
DOI* <4	11 (22%)	3 (6%)	0.04
DOI >4	17 (34%)	(38%)	

*Depth of Invasion

Table 2: Association between tumour size and tumour necrosis

Tumor Stage	Low	High	p value
T1 & T2	22 (44%)	7 (14%)	0.0008
T3 & T4	6 (12%)	15 (30%)	

Table 3: Association between tumour grade and tumour necrosis.

	Low	High	p value
Well Differentiated	14(28%)	3(6%)	0.02
Moderately Differentiated	6(12%)	7(14%)	
Poorly Differentiated	8(16%)	12(24%)	

Table 4: Association between nodal involvement and tumour necrosis

	Low	High	p value
No Nodal Involvement [N0]	21 (42%)	12 (24%)	0.12
Nodal Involvement [N1, N2, N3]	7 (14%)	10 (20%)	

Discussion

Tumour necrosis is histologically identified as presence of microscopic coagulative necrosis characterized by clusters and sheets of degenerating and dead cells[15]. It occurs when tumours outgrow their vascular supply subsequently compromising their oxygen and nutritional support leading to untimely death of cells. This results in release of proinflammatory cytokines and recruitment of inflammatory cells in the tumour microenvironment. This inflammation is not only one the seven hallmarks of cancer but also associated with poor prognosis in many of the tumours[8]. Electron microscopy is the gold standard to identify specific features of cell death according to the recommendations of Nomenclature Committee on Cell Death (NCCD)[16].

It has been proposed that tumour necrosis is caused by chronic ischaemia, due to vascular collapse, high interstitial pressure or rapid tumour growth exceeding its blood supply. However, tumour necrosis has also been observed in areas of increased microvascular density, particularly in breast carcinomas and glioblastoma[17]. Caruso et al. hypothesized that hypoxia in tumour cells harbouring TP53 mutation induced tumour necrosis via mitotic catastrophe[18].

In the present study, a significant association was seen between tumour necrosis with depth of invasion, primary tumour size and grade of tumour which determines the prognosis. There have been no earlier studies which evaluated association of tumour necrosis in oral squamous cell carcinomas. However, necrosis has been evaluated in other tumours as a prognostic marker. Our data in oral squamous cell carcinomas was in concordance with Pollheimer et al who found the extent of necrosis to be significantly associated with high T classification, high N classification and larger tumour size in their study on colorectal cancer[12]. Sengupta et al also observed similar results in their study on renal carcinomas where tumour necrosis was significantly associated with tumour size, perinephric fat invasion, higher nuclear grade, stage, sarcomatoid differentiation and a poorer 10 year survival in clear cell and chromophobe carcinoma but not in papillary renal cell carcinomas[19]. Pichler et al observed similar results in clear cell and papillary renal carcinomas[15].

Tollefson et al. in their study on clear cell renal carcinoma concluded that Ki-67 and tumour necrosis are independent prognostic markers although these two markers highly correlate with each other[20]. Previous studies have shown that tumour necrosis in epithelial tumours has an independent effect on metastasis free survival in patients[21]. The presence of tumour necrosis in hepatocellular carcinoma is associated with poorer cancer specific overall survival and recurrence free survival[22]. Hiraoka et al in their study on pancreatic cancer concluded that tumour necrosis was an independent predictor of poorer disease free survival [23].

Tumour necrosis reflects an aggressive tumour phenotype in NSCLC and may improve the prognostic power of the TNM staging system was indicated in a study on lung cancer[23]. Since India carries the burden of having the highest number of oral cancers, this may be an important step towards improving the staging system for prognosis. Till date, surgical resections are the only effective treatment modality in oral squamous cell carcinoma. Targeted therapies are being tested in many clinical trials but with no significant promise till date. Additional studies on necrosis and local and systemic inflammatory response to necrosis also shows promise in adding evidences to necrosis as a major histological parameter.

Limitations of the study

The current study was limited in analysis of distant metastasis and necrosis as most of the cases were studied retrospectively. Further research is needed to understand the potential of tumour necrosis in oral squamous cell carcinomas.

Conclusions

Tumour necrosis is an easily recognizable histopathological variable which must be included in routine reporting of OSCCs. A higher grade of tumour necrosis is associated with greater tumour size, grade and depth of invasion. The present study shows necrosis as a promising histological factor in oral squamous cell carcinoma. Assessment of necrosis is simple and it can be incorporated as a one of the histological parameter

for assessing prognosis in addition.

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