



# **Correlation of Histopathological Metastatic Invasive Prognosticators with Five Years Survival of Oral Squamous Cell Carcinoma**

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## **Author's contribution**

*The sole author designed, analysed, interpreted and prepared the manuscript.*

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**Study Protocol**

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## **ABSTRACT**

**Background:** OSCC is the 3rd widespread malignancy in India followed by cervical and breast cancer. Histopathological findings in the tumor are the most prominent factors identified for OSCC progression. Clinical and histopathological prognosis in OSCC like perineural invasion, vascular invasion, lymph node invasion have been studied extensively by many researchers separately or in combination since many years. Bone invasion, muscle invasion and salivary gland invasion are explored less. In order to collectively correlate the role of all prognosticators with 5 years survival, the later prognosticators are included in our study in isolation which may predict accurately the probability of 5 year survival of OSCC. Also we have to search role of the prognosticator which is most commonly affecting 5 years survival of OSCC cases so that it may modify the potential consequence of management of OSCC.

**Objectives:** The aim of this study is to assess the relevance of histopathological invasive prognosticators on 5 years survival of oral squamous cell carcinoma (OSCC) patients visiting Sharad Pawar Dental College and Hospital, Sawangi, Wardha (MS).

**Methodology:** Departmental reports will be screened and specimen mounted slides of histopathologically diagnosed 200 OSCC patients, who undergone surgical resection will be observed under binocular microscope. Data of dead and survived OSCC patients undergone surgery 5 years back will be collected by telecommunication. Histopathological invasive prognosticators will be analyzed and correlated with 5-years survival after treatment.

**Expected Results:**

- Collectively correlating the role of histopathological invasive prognosticators in our study may predict the probability of 5 years survival of OSCC cases more accurately.
- Discovering diversified histopathological patterns of all metastatic prognosticators and their correlation with 5 years survival.
- Identification of most effective histopathological invasive prognosticator predicting 5 year survival.

**Conclusion:** The most commonly found prognosticators in OSCC patients who died within 5 years versus others who survived for 5 years will be discovered.

In addition the most common histopathological pattern related to dead and survived patients after 5 years will be found which can modify the potential consequence of management of OSCC.

*Keywords: Oral squamous cell carcinoma; histopathological invasive prognosticators; 5 years survival.*

## 1. INTRODUCTION

Oral malignancies in today's scenario represent a major challenge in their management. The five-years survival rate for OSCC is about 60% despite several advances in diagnosis and management and there is no significant improvement since 20 years. However younger population is more succumbed to OSCC now a days. So there is a need for exploring potential valuable markers in OSCC [1]. Researchers had studied metastatic invasive prognosticators histopathologically-Perineural invasion, Vascular invasion, Lymph node invasion, Bone invasion, Muscle invasion & Salivary gland invasion singly or in combination of 3 or 4 in H & E stained sections but no potential prognosticator identified to be a sufficiently strong indicator of 5 years survival. Variations in the criteria of invasive prognosticators in advancing OSCC and potential consequences of treatment suggest a lack of consent regarding postoperative adjuvant therapy, as well as the need for additional study. Researchers have not evaluated patterns for all invasive prognosticators in a single study and very few studies had correlated the role of muscle, bone and salivary gland invasion for 5 years survival. So they are need to be researched for their predictability. In order to collectively correlate their role in 5 years survival along with few more prognosticators like muscle invasion, bone invasion and salivary gland invasion, these are included in our study in isolation which may predict more accurately the probability of 5 year survival of OSCC cases.

### 1.1 Objectives

1. To collectively correlate role of all prognosticators with 5 years survival

2. To find the predominant histopathological prognosticator for 5 years in survived and dead patients.
3. To evaluate the histopathological patterns of following histopathological prognosticators in OSCC cases:
  - a. Perineural invasion
  - b. Vascular invasion
  - c. Lymph node invasion
  - d. Bone invasion
  - e. Muscle invasion
  - f. Salivary gland invasion
4. To correlate the above patterns with postoperative 5 years survival in OSCC cases.

## 2. METHODS

The present retrospective cohort study will be carried out at the 'Department of Oral and Maxillofacial Pathology and Microbiology, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Medical Sciences, Deemed to be University, Sawangi (M), Wardha, Maharashtra, India.' Two hundred cases of surgically treated cases of OSCC from year 2010 to 2015 will be retrieved from the archival of the department. H and E stained section slides of OSCC patients will be reviewed to see histopathological invasive prognosticator individually. These findings will be then evaluated and linked with five-year survival of patients of OSCC.

### 2.1 Participants

#### 2.1.1 Inclusion criteria

1. Registered histopathologically diagnosed and surgically treated cases of OSCC.
2. Patient who were on regular follow up.

3. Patients whose records are documented.

### 2.1.2 Exclusion criteria

1. OSCC patients with other systemic lesions.
2. Patient who lost to follow up.
3. Patients whose records are not documented.

### 2.2 Variables

- Outcome – 5 years survival
- Exposure –OSCC.
- Dependent variable Vascular invasion, lymph node invasion, perineural invasion, bone invasion, muscle invasion and salivary gland invasion
- Confounding factors– Any other habit, genetic susceptibility, any other inflammatory condition, blood pressure, diabetes, diseases causing morbidity etc.

### 2.3 Qualitative Variables

Vascular invasion, lymph node invasion, perineural invasion, bone invasion, muscle invasion and salivary gland invasion by tissue processing of excised tissue from OSCC patients and observing slides under H and E staining.

### 2.4 Statistical Methods

This retrospective cohort study will include OSCC patients who underwent surgical treatment in AVBRH, Sawangi, Wardha.

The obtained data will be analysed by:

1. Chi-square test (for qualitative analysis), and
2. Pearson Correlation (to see correlation of prognosticators with each other and with 5 year survival)

A significant level of  $\alpha = 0.05$  will be used.

Oral cancers continue to represent a significant trouble in the oncologic management [2]. Although there is revolution in the identification and management of OSCC, 5 years survival rate in those patients is near 60%. No significant improvement could be seen in the last 20 years. However younger crowd is showing more inclination towards OSCC nowadays. Therefore potential valuable markers in OSCC must be discovered for risk evaluation [1]. Researchers

had studied metastatic invasive prognosticators histopathologically-Perineural invasion, Vascular invasion, Lymph node invasion, Bone invasion, Muscle invasion & Salivary gland invasion singly or in combination of 3 or 4 in H & E stained sections but no potential prognosticator was identified to be a sufficiently strong indicator of 5 years survival. There is a lack of harmony regarding postoperative adjuvant therapy seeing variations observed in the criteria of invasive prognosticators for high-risk disease and therefore it need more additional studies. Researchers have not evaluated patterns for all invasive prognosticators in a single study and very few have correlated role of muscle, bone and salivary gland invasion with 5 year survival. So they are need to be researched for their predictability. In order to collectively correlate their role in 5 years survival along with few more prognosticators like muscle invasion, bone invasion and salivary gland invasion, these are included in our study in isolation which may predict more accurately the probability of 5years survival of OSCC cases.

## 3. EXPECTED RESULTS AND DISCUSSION

OSCC is the most common epithelial malignancy in the head and neck carcinomas. Nearabout three lac new cases were diagnosed universally in the year 2012, with death of 145,400 patients. Even after upgradation for therapeutic protocols the 5-year survival rate is constant [3].

### 3.1 Neural Invasion

PNI is a main histopathological parameter indicative of poor prognosis. Researchers found variations in prognostic significance due to lack of number of cases analysed, conflicting methodology and method to detect PNI. Researchers concluded that research is needed further [3]. In 1985, Batsakis et al defined PNI as infiltration of malignant cells inside, surrounding and in course of peripheral nerves. Liebig has concluded that PNI represents presence of tumor cells within any of the 3 layers of nerve sheath. He discovered 2 histologic patterns 'type A and type B' of nerve involvement. In type A tumor cells were infiltrated into the three nerve sheath layers and in type B tumor cells were observed in close association with nerve involving at least 33% of its perimeter. When invasion was seen in the innermost endoneurium 'intra-neural invasion' term was used. Presently data is

lacking to decide whether intraneural invasion is more destructive compared to other types of PNI [4]. Comment on both extratumoral and intratumoral PNI should be written separately in the histopathological reports [5]. BK Varsha et al. in 2015 carried out retrospective study on PNI location, PNI density and various PNI patterns in 117 cases of primary and recurrent cases of OSCC. Their study revealed PNI in 47 out of 117 patients. Out of 69 cases (49.3%) of clinically positive nodes PNI was observed in 34 cases. The location of nerves were intratumoral in 79% of the nerves involved. PNI density of 1–3 nerves per section was seen in 80% of the cases and the most common pattern of PNI noted in their study was incomplete and/or “crescent-like” encirclement. Every surgical specimen with OSCC should be checked for PNI as it has prognostic value, it helps clinician to manage the treatment plan and can guide him about recurrence and distant metastasis. The presence of PNI indicates aggressive surgical resection, concurrent management of cervical lymph nodes and additional adjuvant therapy [6]. G Deepthi et al studied patterns of PNI and PNI related to size – ‘small nerve (diameter <1 mm) and large nerve (>1 mm)’. extent – “focal (1 focus of PNI), moderate (2-5 foci of PNI) and extensive (>5 foci of PNI)” and distance between the tumor edge and nerve. The PNI patterns were named as complete encirclement, incomplete “crescent-like” encirclement, sandwiching “onion-skin,” partial invasion and neural permeation. Researchers found intratumoral encirclement in 21 cases, complete encirclement in 13 cases, incomplete “crescent-like” encirclement, sandwiching “onion-skin,” in 20 cases, partial invasion in 27 cases and neural permeation in 3 cases [7]. Researchers found LVI and LNM both were associated with PNI in cervical cancer and so postoperative radiotherapy was advised for such patients [8].

### 3.2 Lymphatic and Vascular Invasion

Lymphatic invasion was found to be 28(5%) and vascular invasion was 16(3%) in the study carried out by Mohamad Adel et al in 2015 on 571 OSCC patients who underwent surgical resection with or without adjuvant therapy. They found that these parameters had no effect on loco-regional recurrence and distant metastasis in posttreated OSCC patients [9]. Many studies have concluded that tumor budding, depth of invasion, and lymphovascular invasion (LVI) are predictors of lymph node metastasis (LNM). In LVI cancer cells invade an endothelium-lined

area of vessels [1]. LVI can be seen both ‘intratumoral and extratumoral’. Pathologist should comment separately about this in the reports [5]. M Manjula, et al assessed 105 archival specimens of OSCC patients who had done surgical excision and radical neck dissection. In 29% cases N1 was identified and associated with, lymphovascular invasion. Perineural and intraneural invasion were significantly associated with tumor size [10]. Lizandra Jimenez et al found that patient’s survival was not affected by vascular invasion but it was worse if lymphatic invasion was present [11]. PNI was observed in 2% of cases in a study done on 100 histopathologically confirmed OSCC cases. There was no evidence of vascular invasion in any of the cases examined [12].

### 3.3 Lymph Node Invasion

418 lymph node sections of 40 OSCC patients were studied of which 24 were metastatic and 394 nonmetastatic. Six morphologic patterns (MP) identified were- “Germinal Center Predominance (GCP), Lymphocyte Predominance (LP), Lymphocyte Depleted (LD) Sinus Histiocytosis (SH), Vascular Transformation of Sinuses (VTS), and Granulomatous Reaction (GR).” The predominant MP seen was of VTS (116 nodes) then GCP (105); LP (90), LD (52), SH (43) and GR [12]. LN status and the MPs. showed significant association. Lymph node metastasis (LNM) with LP was 13% and with GCP it was 79%. GCP pattern seemed to be predominant in metastatic tumors. LP or VTS/SH seemed to be common in nonmetastatic cases [13]. Histopathology reports of postoperative 50 OSCC patients were retrieved from January 2018 to June 2018 and pattern of cervical LNM was observed which showed 24 patients (48.0%) had neck node metastasis. Tumor size >1cm in 59.4% cases. Tumors with the depth of invasion >3mm were prone for high risk of metastasis. Metastasis was present in single node (N1) in 17 out of 24 OSCC patients. In 14 patients level 1 and level 2 were commonly involved sites. It was inferred that ‘Elective neck dissection’ can be done when tumor thickness is more than 3mm [14]. B. S. Siriwardena et al in 2018 studied 465 OSCC cases with neck dissection in which they found ‘metastasis and extracapsular invasion’ were linked with level of differentiation and invasion pattern ( $p < 0.001$ ). They anticipated that it will guide clinicians to do radical or prophylactic neck dissection in

OSCC patients if histological prediction model can guess the possibility of developing metastasis [15].

### 3.4 Bone Invasion

25 OSCC patients in which mandibular resection was done revealed mandibular invasion. The After decalcification serial sectioning of tissue specimen was done at 1 cm interval to spot mandibular bone invasion. The pattern of mandibular bone invasion was “infiltrative in 14(56%), erosive in 11(44%), cortical in 5(20%), marrow involvement was seen in 15(60%) while 5(20%) had spread through the inferior alveolar canal.” 24 out of 25 lesions were located within 1 cm of the mandible. In their study in 20% cases, mandible was invaded through the inferior alveolar nerve. Therefore it is suggested that before mandibular preservation by surgeons it should be thoroughly examined for possible involvement [16]. A study was undertaken on 323 OSCC patients. Cases were classified as based on tumor size. Bone invasion was categorized as ‘absence of bone, presence of bone on one side and presence of both buccal and lingual bones’ and correlated with disease progression. It was observed that in tumors measuring 4 cm or less, bone invasion was not significantly associated with disease progression whereas worse prognosis was found if both buccal and lingual bones were invaded [17]. Histopathologic type of bone invasion by OSCC is commonly classified as erosive type and infiltrative type. Conventional classification focuses on how tumor has invaded bone. However, the current study proposed the new classification called “Histopathologic pattern of peritumoral bone change” for how it responds to OSCC in terms of mandible instead of tumor. Understanding peritumoral bone change and its distinction from true tumor mass may be important in the surgical management and may lead to minimally invasive surgical procedure [18]. The pattern of histopathology of mandibular invasion in OSCC was infiltrative or an erosive. The infiltrative pattern exhibited ‘small islands of tumor cells along an tumor edge’ and the erosive pattern showed a ‘broad, pushing tumor front.’ A study was carried out retrospectively on 68 OSCC patients with mandibular invasion who were treated by mandibulectomy. They concluded that the ‘infiltrative pattern’ of invasion in the mandible in OSCC showed a more aggressive behavior with increased chances for ‘positive margins, recurrence and mortality’. So they recommended that pathologists should give

opinion on the histopathological pattern seen in mandibular invasion while reporting OSCC [19].

### 3.5 Muscle Invasion

In OSCC clinical and histopathological invasive prognosticators of oral squamous cell are the topics gaining much attention. One such parameter is muscle invasion (MI). It was found in many studies that muscle invasion is one of the most important predictors of a lymph node metastasis and a poor prognosis. MI is defined as the histopathological permeation of skeletal muscle by tumor. Researchers hypothesized that muscle contractures by these invaded malignant cells may facilitate the drainage of cells into cervical lymph nodes. The study also demonstrated better survival outcomes in patients without MI [20]. Seung-Ki Min et al in 2016, evaluated the association between muscle invasion of 26 OSCC patients of the posterior mandibular alveolar ridge and cervical lymph node metastasis by MRI. They found that cervical LNM was related to muscle invasion (mylohyoid and/or buccinator). Lymphatic vessels were positioned near the tumor invasion front in the muscles. So further studies are needed to assess the relation between MI and prognosis in OSCC [21].

### 3.6 Salivary Gland Invasion

Lining of oral epithelium and excretory ducts of the salivary glands can be affected by chemical carcinogens. Thus, there could be dysplastic changes in the salivary gland ductal epithelium which may turn into malignancy. Sunil Paramel Mohan et al in 2016 analysed 278 archival cases of “mild, moderate and severe epithelial dysplasia, carcinoma in situ, verrucous carcinoma and OSCC” which were evaluated under microscope to see the changes such as squamous, mucous and oncocytic metaplasia, simple hyperplasia of excretory ducts of minor salivary glands and invasion of malignant cells. The most common location involved was cheek mucosa. They observed dysplasia in all the ducts of the gland. Salivary gland tissue changes should be observed by pathologists which could help surgeons in the treatment and preventing recurrence of the carcinomas [22]. Approximately one third OSCC patients go for resection of gland in neck dissection and experience xerostomia. Metastasis to submandibular lymph nodes in such patients is common but invasion is rare in submandibular gland. Patients are benefitted if gland is saved. Out of 90 OSCC patients studied

48.9% had stage IVa (AJCC). Only 28.9% patients showed positive submandibular lymph nodes whereas these were negative in 71.1% cases. Only 5 patients presented with submandibular gland involvement [23].

Researchers studied 5 year survival of 1,383 OCSCC patients and their relationship with primary subsites and pathological features. They noted that in early stage OCSCC patients especially in tongue, perineural invasion had worse prognosis whereas in advance stage of OSCC patients of buccal mucosa and tongue lymphovascular invasion had poor survival [24]. R. Larsen et al analysed that clinical diagnosis of 36% LNM was significantly associated to “grade, neural and vascular invasion; surgical margins and depth of tumor” [25]. The surgical margins studied in 115 T1/T2 OSCC cases showed that 21 had vascular invasion, 9 had nerve invasion and 3 had bony invasion. 8/10 patients died of local metastasis and 8/11 patients died of distant metastasis [26]. According to a net based search on survival rate and OSCC researchers found association of all prognosticators but were not able to predict the prognosis independently. They concluded that, clinicopathological indicators were necessary for prognosis [27]. In Taiwan 341 operated patients of OSCC showed adverse clinicopathologic features like depth of invasion, LVI, PNI, margin status, and extra-nodal extension which had considerably affected outcome of survival [28] NA Agni et al studied the incidence of perineural invasion of OSCC along the inferior alveolar nerve and found histopathologic infiltration of the inferior alveolar nerve by the OSCC in 25 of 26 cases in their study [29]. The bonding of the the surgeon and the pathologist, need of standardisation of all scales of histopathological parameters and precise documentation of the findings is the need of hour [30] A proper clinicopathologic protocol has to be designed to validate the histological prognosticators [20].

#### 4. CONCLUSION

1. Collective correlation of all prognosticators with 5 years survival is not documented in a single study
2. Different patterns of all 6 histopathological invasive prognosticators is not documented in a single study.
3. The overall impact of histopathological patterns of all these metastatic prognosticators on the prognosis and

survival of OSCC patients had not fully clarified and documented.

So an attempt is made to throw a light on correlation of all prognosticators and their histopathological patterns with 5 year survival of OSCC patients.

#### CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline Patient’s consent and ethical approval has been collected and preserved by the authors.

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

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