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Adverse Histologic Features in Oral Cancer

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INTRODUCTION

Squamous Cell Carcinoma **(SCC)** accounts for more than 90% of all oral cancer cases [1,2] and it is widely accepted as one of the most aggressive malignacies, associated with high rates of mortality and morbidity [3]. Despite the considerable advancement in multidisciplinary therapy (surgery, radiation therapy, chemotherapy and the recently developed monoclonal antibody-based immunotherapy) the survival rates remain relatively low, reflecting the significant limitations in achieving adequate oncologic control [4,5]. Listl et al. [4] analyzing data of 15.792 oral cancer patients registered in Germany, did report an 5-year overall survival of 54.6% although including cancer of the lip that is known to have a much better prognosis than other sites of the oral cavity.

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Given that loco-regional recurrence is the leading cause of treatment failure, the main efforts of improving survival rates should be focused in maximizing primary control of the disease [6-10]. With aim to enhance the effectiveness of the initial therapeutic approach various adverse histopathology features have been used in conjunction with clinical parameters [TNM status as described on the 7th edition of the Union For International Cancer Control **(UICC)** and the American Joint Committee On Cancer **(AJCC)** TNM Classification of Malignant Tumours [Table 1], in an attempt to identify patients at risk of residual loco-regional disease who would have survival benefit by adjuvant therapeutic intervention [11-16].

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Lip and Oral Cavity
(7th ed., 2010)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease* (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose (oral cavity) Tumor invades adjacent structures (eg, through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Table 1 - Continued

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for the Lip and Oral Cavity
(7th ed., 2010)
(Nonepithelial tumors such as those of lymphoid tissue, soft tissue, bone, and cartilage are not included)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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Among these features, positive resection margins and advanced neck disease are recognized as "high risk" characteristics [Table 2]. Perineural invasion, lymphovascular emboli (lymphovascular invasion), T2 tumor with a more than 5 mm depth of invasion, bone involvement, nodal dissemination at level 4 or 5, and close resection margins are recognised as "intermediate risk" characteristics [Table 3]. Adjuvant postoperative Radiation Therapy **(RT)** is generally recommended for patients at "intermediate risk" of residual disease and loco-regional recurrence, while adjuvant concurrent Chemo-Radiotherapy **(CRT)** is the standard of care for "high risk" cases. If more than 2 intermediate risk factors present, chemo-radiation should also be recommended [17-21].

Table 2: High risk histologic features.

- Positive margins
- Eracapsular spread (ECS)
- pN2b/c – N3

Table 3: Intermediate risk histologic features:

- Perineural invasion (PNI)
- Lymphovascular infiltration (LVIF)
- Bone invasion
- T2 with > 5 mm depth of invasion
- Close surgical margins (< 5mm)
- pN2a or N1 to levels IV/ V

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The purpose of this chapter is to review the adverse histologic features in oral squamous cell carcinoma and discuss their prognostic significance and their role in guiding multidisciplinary treatment decision-making.

POSITIVE RESECTION MARGINS

The main goal of ablative surgery is the complete resection of the primary lesion with histopathology confirmation of disease-free margins, so as to maximize the chance of local oncologic control [NCCN]. Close or positive margins have been significantly associated with increased risk of local recurrence and decreased survival rates [22]. Resection margin evaluation is typically performed after standard formalin fixation and hematoxylin/ eosin staining of the specimen tissues [23]. Immunostaining techniques are not routinely performed. Oncologically adequate resection is defined as permanent resection margins that are clear of disease for at least 5 mm (clear or negative margin: =/> 5 mm). A less than 5 mm distance from the tumor front is defined as close margin (close margin: < 5 mm). Resection margins that are involved with invasive carcinoma, Ca in situ or severe dysplasia are defined as positive [20,24-29].

Oral cancer patients with positive resection margins are at high risk for loco-regional relapse and should be referred for adjuvant therapeutic interventions [19, 20, and 30]. Based on the results of two large landmark prospective, randomized trials (RTOG #9501 – USA [17] and EORTC #22931-Europe [18] the presence of positive margins is a strong, unequivocal indication for postoperative Chemo-Radiation Therapy **(CRT)**. Close margins could be managed with adjuvant Radiotherapy **(RT)** or close follow-up monitoring, taking under consideration other clinical and histological criteria [20].

NODAL METASTASES / EXTRACAPSULAR NODAL SPREAD

Histological proven cancer dissemination to cervical lymph nodes is the single most important adverse prognostic factor for oral cancer patients [10, 31]. The presence of even a single involved lymph node reduces the expected 5-year overall survival by 50%, while the histological verification of extra capsular tumor spread (ECS) decreases this survival by an additional 50% (75% in total-increased risk of distant metastases) [32, 33]. It is estimated that up to 65% of patients with squamous cell carcinoma of the oral cavity have neck metastasis at initial presentation. Up to 75% of these more than 3 cm in greatest dimension would also have extra capsular dissemination [32]. Approximately 20% to 45% of patients without clinically evident neck disease (cN0) will have occult micrometastases on histological node evaluation following elective neck dissection [10, 34]. The possibility of occult ECS in cN0 patients is estimated 19 - 49% in various studies [32, 35-37]. When the possibility of occult neck dissemination surpasses 20%, an elective neck dissection, based on the cervical lymph node echelons as described by the American Head and Neck Society Guidelines [38, 39] should be performed for staging purposes [40]. Several criteria, including tumor size (T2-4), tumor site, depth of invasion (> 4mm), perineural invasion, lymphovascular infiltration, grade of differentiation, are typically used to identify cN0 patients at increased risk of neck micrometastases [10,31].

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Patients with squamous cell carcinoma of the oral cavity with single node at levels IV/V or more than 3 cm in greatest dimension (pN1 at levels IV/ V or pN2a) should be managed with adjuvant RT based on NCCN recommendations [10,20,31]. Histological proven ECS (ECS+) is a strong and unequivocal indication for postoperative chemo-radiation based on the results of both RTOG #9501 and EORTC #22931 clinical trials [17-19,20]. Patients with two or more positive nodes are also candidates for combined postoperative therapy according to the RTOG #9501 trial [17].

PERINEURAL INVASION / LYMPO-VASCULAR INFILTRATION

Perineural Invasion **(PNI)** is a well-recognized adverse oncologic feature, strongly correlated with aggressive tumor behavior and increased rates of loco-regional treatment failure (50%) [12,23,41-49]. Its role as an independent prognosticator of decreased 5-year disease specific and overall survival has also been demonstrated in various multivariate analysis [11,26,50-52]. Perineural invasion is detected in more than 30% of the oral squamous cell carcinoma cases and could thus reliably affect treatment decisions [53-55]. The Royal College of Pathologists (UK) and the College of American Pathologists, recognizing the important role of nerve involvement in adjuvant therapeutic decisions, have endorsed the identification of perineural invasion in the standard histopathology report for SCCs of the oral cavity and the lips [56,57].

Perineural invasion is considered to be a distinct way of malignant dissemination that characterizes specific tumors with inherent nerve bundle tropism (well referred as neurotrophic malignancies), and is typically defined as (1) the identification if cancer cell in any of the three nerve sheath layers and/ or (2) the identification of cancer cell in more than one third of the nerve circumference [55,58]. Immunostaining techniques are not routinely used for PNI detection [15, 55]. Perineural invasion may regard small-diameter (<1 mm) or large (named) nerve bundles [15, 41]. Cancer dissemination through the invaded bundles could potentially occur in a retrograde (toward the skull base) or antegrade (toward peripheral branches) way of spread (perineural spread); the antegrade pattern is the mainly observed pattern in oral cancer cases [49,59].

Lymphovascular Infiltration **(LVIF)** is also recognised as an adverse histologic prognosticator in oral SCC patients, correlated with residual disease and decreased survival rates [11, 12, 26, 50-52, 60, 61]. Lymphovascular infiltration is defined as (1) the presence of cancer cell within the lymphatic or vascular endothelial lining and/ or (2) the presence of tumor emboli within the involved vessels [56,57].

The identification of PNI and/ or LVIF has been demonstrated as indicators for cT1/2N0 patients at risk of occult neck metastasis in various studies [11,12,50,51,61-64]. These patients have been found to have significant overall and disease-free survival benefit when managed with elective neck dissection [40,52, and 64]. Although the European Organization for Research and Treatment of Cancer **(EORTC)** did include PNI and LVIF among the recommended criteria for adjuvant CRT in its 22931 trial [18], the other relevant USA study [17] did fail to demonstrate

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significant benefit to patients managed with CRT. According to 2015 NCCN practice guidelines [NCCN, 2015] patients with isolated perineural or lymphovascular invasion should only be considered for adjuvant RT, while recent multivariate analysis advocate on even close follow-up monitoring [26,50-52,64-69]. PNI and LVIF are among the enrollment criteria for receiving adjuvant IMRT +/- Cetuximab in a currently conducted prospective randomized clinical trial (RTOG #0920) [21].

DEBTH OF INVASION / MUSCLE INVASION

Tumor depth of invasion is considered an adverse histologic feature with predictive significance for regional nodal disease and survival in oral cavity cancer patients [31, 70, and 71]. Measuring depth of invasion with precision requires successive histologic sections of 3- to 4- mm of the lesion in order to detect the deepest point of invasion [72]. Any exophytic portion or excessive keratin layer should be ignored and measurement should occur from the original surface plane. Likewise, in ulcerated lesions dimension is measured from the initial surface level [73].

Many studies have attempted to predict the statistical significant point of depth of invasion, particularly for tongue and floor of mouth sites that is associated with increased risk of neck disease, thus proving the benefit of elective neck dissection [30, 70, 74, and 75]. First, Spiro et al, without considering the T stage reported that lesions of the tongue and floor of mouth with depth of invasion more than 2mm had a higher incidence of lymph node metastasis [74]. In 2003, O'Brien and associates found that in clinically T1 and T2 oral cancers a depth of invasion of 4mm and more is related to poorer loco regional control and decreased survival rates [70]. Ord et al, based on data from the University of Maryland demonstrated that T1 cancers with N0 neck and >3-4mm depth are at high risk of cervical metastasis and SOHND is indicated [30]. Another histologic feature in relevance to the depth of invasion is muscle invasion. Judging from the publications, the term is less studied. However, an interesting study reports that muscle invasion in oral tongue carcinoma had a higher positive predictive value of local recurrence compared to depth of invasion. This characteristic might guide wider excision in primary site [76]. Depth of invasion greater than 4mm has been significantly associated with decreased regional control and survival rates and suggested postoperative radiotherapy [68]. Although there is no general convergence, patients with T2 oral cancer with >5mm depth are considered to be at intermediate risk of residual disease and potentially have benefit of adjuvant postoperative radiotherapy [21].

BONE INVASION

The cortical (mandible or maxilla) bone is considered to be at risk of tumor invasion when squamous cell carcinomas of the oral cavity are in close proximity or fixed to the cortical bone, irrespective of radiological confirmation of bone destruction in CT scans [10,31,77,78]. Approximately 12% - 56% of oral cancer patients have bone involvement [79]. In case of increased risk of bone invasion, the landmark study by McGregor and MacDonald [80] could help the surgeon understand the pattern of bone invasion and decide whenever a segmental

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mandibulectomy should be performed or when the continuity of the lower border of the mandible would be preserved (marginal mandibulectomy). In general, cancellous bone invasion, invasion of the inferior alveolar nerve or canal, tumor fixed to an atrophic or a post-radiation mandible, gross soft tissue disease in close proximity to the mandible are among the main indications for segmental mandibulectomy (Table 4) [10,31,81,82].

Histological verification of tumor invasion through the cortical bone is an adverse oncologic feature associated with locally advanced stage (T4a-NCCN Guidelines, version 01.2015) and increased risk of residual disease. These patients have a strong indication for postoperative radiotherapy, in an attempt to achieve adequate primary oncologic control [20].

CONCLUSION

Various other factors, including degree of differentiation, tumor thickness, front of infiltration, and cancer related metabolic (e.g. lactate dehydrogenase 5 - LDH5, hypercalcaemia) [83,84] and oncogenic markers (e.g. nerve growth factor - NGF, high-affinity receptor tyrosine kinase A - TrkA, pyruvate kinase M2 - PKM2) [47,84], have also been correlated with oral squamous cell carcinoma aggressiveness, but they failed to prove their survival significance in multivariable analyses and thus reliably guide adjuvant therapy decision making. However, as our knowledge regarding the nature of this malignant entity is still limited, well-organized prospective randomized trials seem to be necessary to clarify the most effective multidisciplinary approach based on each case specific clinical and histological parameters.

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