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Oral Cancer: Comprehending the Condition, Causes, Controversies, Control and Consequences

7. Staging and Diagnostic Clinical Aids

Conventional oral exploration (visual and palpation examination) constitutes the current *gold standard* for oral cancer screening, while biopsy and histopathological examination are indispensable for case detection. There are also a number of other techniques, that may contribute to the diagnosis of oral cancer, discussed below.

Biopsy and histopathology

The accurate diagnosis of potentially malignant and malignant oral lesions depends on the quality of the biopsy, adequate clinical information, and correct interpretation of biopsy results (Figure 1).

Oral biopsy is discussed in Article 5. Specimens can be affected by crushing, fulguration, injection, or incorrect fixation and freezing. There is controversy regarding incisional *versus* excisional biopsy and surrounding the use of the most appropriate surgical instruments. Excisional biopsy is theoretically preferable because it allows histopathological examination of the entire lesion, but it risks incomplete treatment of malignant lesions and
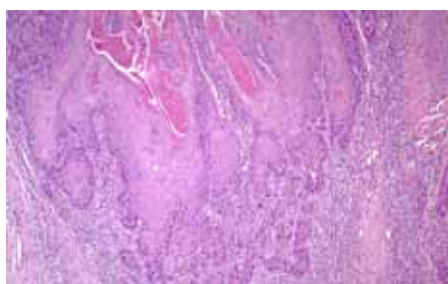
Figure 1. Histopathological image showing well-differentiated oral squamous cell carcinoma (OSCC) in an incisional biopsy specimen (H&E stain x100).

Figure 2. Toluidine blue-positive staining in oral squamous cell carcinoma.

overtreatment of benign ones. It has been suggested that neck metastasis from OSCC may increase after incisional biopsy because tumour cells appear in the peripheral blood 15 minutes after incisional biopsies using a conventional scalpel. Other means of obtaining biopsy material might minimize

seeding of cells. Electrocautery or CO_2 laser, however, can produce thermal cytological artefacts.

Toluidine blue staining (see below) is best for selecting the site(s) for biopsy in large lesions and multiple biopsies and reducing the percentage of

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TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	Carcinoma *in situ.*
T1	Tumour 2cm or less in greatest dimension.
T2	Tumour more than 2cm but not more than 4cm in greatest dimension.
T3	Tumour more than 4cm in greatest dimension.
T4	Lip : Tumour invades adjacent structures, eg through cortical bone, inferior alveolar nerve, floor of mouth, skin of face. Oral Cavity : Tumour invades adjacent structures, eg through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, skin (superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4).

Table 1. TNM staging. T – Primary Tumour.

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension.
N2	N2a Metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6cm in greatest dimension. N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6cm in greatest dimension. N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension.
N3	Metastasis in a lymph node more than 6cm in greatest dimension.
Nomenclature of anatomical site of lymph node	
Level I	Contains the submental and submandibular triangles bounded by the posterior belly of the digastric muscle, the hyoid bone inferiorly and the body of the mandible superiorly.
Level II	Contains the upper jugular lymph nodes and extends from the level of the hyoid bone inferiorly to the skull base superiorly.
Level III	Contains the middle jugular lymph nodes from the hyoid bone superiorly to the cricothyroid membrane inferiorly.
Level IV	Contains the lower jugular lymph nodes from the cricothyroid membrane superiorly to the clavicle inferiorly.
Level V	Contains the posterior triangle lymph nodes bounded by the anterior border of the trapezius posteriorly, the posterior border of the sternocleidomastoid muscle anteriorly and the clavicle inferiorly.
Level VI	Contains the anterior compartment lymph nodes from the hyoid bone superiorly to the suprasternal notch inferiorly. On each side the lateral border is formed by the medial border of the carotid sheath.
Level VII	Contains the lymph nodes inferior to the suprasternal notch in the upper mediastinum.

Table 2. TNM staging. N – Regional Lymph Node involvement.

Pulmonary	PUL	Bone marrow	MAR
Osseous	OSS	Pleura	PLE
Hepatic	HEP	Peritoneum	PER
Brain	BRA	Adrenals	ADR
Lymph nodes	LYM	Skin	SKI
Others	OTH		

Table 4. Sites of metastases.

RX	Presence of residual tumour cannot be assessed.
R0	No residual tumour.
R1	Microscopic residual tumour.
R2	Macroscopic residual tumour.

Table 5. Residual tumours.

underdiagnoses.

Imaging techniques (DPT, CT, MRI) are also often used to supplement the clinical evaluation and tumour staging.

MX	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastases.

Table 3. TNM staging. M – Distant Metastasis.

CT is the technique of choice to evaluate bone invasion. Cone beam CT (CBCT) helps determine the invasion and extension of a lesion towards jaw bones, with the added advantages of lower cost and a lower radiation dose than conventional CT. MRI is more informative when evaluating soft tissue invasion, neurovascular infiltration, or cervical lymph node involvement.

Staging

Quality management of cancer requires universal, accurate TNM (Tumour; Node; Metastasis) staging, which must be documented in the clinical notes and on the database (Tables 1–3).

Clinical palpation of the cervical lymph nodes is generally regarded as inaccurate (sensitivity and specificity 60–70%), and micrometastases may be present. CT has a higher sensitivity in detecting metastatic disease (69–93%) than physical examination. MRI is even better than CT but less readily available. Ultrasound Guided Fine Needle Aspiration Cytology (US-guided FNAC) requires particular expertise and experience, but can have a sensitivity of 76% and a specificity of 100%. PET/CT scanning is currently under evaluation.

Metastases may be further specified according to site (Table 4).

Careful examination of the upper aerodigestive tract is mandatory and can identify primary tumours in 40–50% of patients presenting with a metastatic cervical lymph node but no other symptoms. Panendoscopy should include the oral cavity, pharynx, larynx, and upper oesophagus. Chest radiology should be performed to look for metastases and any second primary tumours (SPTs). CT or MRI scan of the chest should be carried out in suspected metastases.

The absence or presence of residual tumour after treatment may be

described by the symbol 'R' (Table 5).

Additional diagnostic aids

A number of possible diagnostic aids have appeared on the market but as yet none has been accompanied by scientific studies that has convinced the clinical community of their usefulness over and above clinical examination (Table 6).

Toluidine blue (TB)

Toluidine blue (tolonium chloride) (Figure 2) has been evaluated as a diagnostic aid in many studies over many decades. A meta-analysis based on data available up to 1989, assessing the effectiveness of TB, revealed a sensitivity for identifying oral squamous cell carcinomas between 93% and 97% and a specificity between 73% and 92%. However, many of these studies had serious methodological flaws.

Light-based detection systems

Light-based detection systems were introduced on the assumption that the mucosal structural and metabolic changes during carcinogenesis give rise to distinct profiles of absorption and refraction when exposed to different types of light or energy (Table 6). Sadly, few reliable studies have appeared before their release for clinical use.

Chemiluminescence

ViziLite® (Zila Pharmaceuticals, Phoenix, Arizona, USA) is the best known system. It appears to have a high sensitivity (100%), but its specificity (0%–14.2%) and positive predictive value

- ■ TOLUIDINE BLUE
- ■ LIGHT-BASED SYSTEMS
  - Chemiluminescence (ViziLite Plus®; Microlux/DL®)
  - Tissue Fluorescence Imaging (VELscope®)
  - Tissue Fluorescence Spectroscopy
- ■ EXFOLIATIVE CYTOLOGY OR BRUSH BIOPSY (OralCDx®)

Table 6. Main techniques that theoretically contribute to the diagnosis of oral cancer in addition to conventional oral exploration (visual and palpation examination), biopsy and histopathology.

are low. ViziLite® does not help overall in the identification of malignant and premalignant oral lesions and therefore the combination with TB (ViziLite Plus®) was proposed to reduce the number of false positives. Although the specificity and positive predictive value of this combination have improved, there is little supporting scientific evidence.

Microlux/DL® consists of a battery-powered, light-emitting diode (LED) transilluminator with an autoclavable light guide that produces diffused light (Microlux/DL®, AdDent Inc, Danbury, Connecticut, USA). In a prospective study, the sensitivity and specificity for the detection of oral cancerous and precancerous lesions were 77% and 70%, respectively.

Tissue fluorescence imaging

VELscope® (Visually Enhanced Lesion Scope; LED Dental Inc, White Rock, British Columbia, Canada) detects the loss of fluorescence in visible and non-visible high-risk oral lesions, such as cancers and precancers, by applying direct fluorescence. Reported sensitivity values of 97% to 100% and specificities of 94% to 100% are encouraging but there are no

studies that have demonstrated the utility as a diagnostic aid in lesions in low-risk patients or when used by general dentists.

Tissue fluorescence spectroscopy

Autofluorescence spectroscopy consists of a small optical fibre that produces various excitation wavelengths and a spectrograph that receives the data and records it on a computer. This eliminates the subjective interpretation of the changes in tissue fluorescence resulting in a high sensitivity and specificity in differentiating healthy mucosa from malignant oral lesions.

Exfoliative cytology

OralCDx® brush biopsy (OralCDx® Laboratories Inc, Suffern, New York, USA) is a transepithelial 'biopsy' system. The sensitivity of this system for the detection of abnormal cells has been of 52–100% and specificity of 29–100%.

Most clinicians, faced with a doubtful mucosal lesion, will elect to undertake a biopsy with scalpel or punch, rather than undertake a procedure which is costly and is not as reliable at excluding neoplasia.