ORAL CANCER BACKGROUND PAPERS

Chapter V: Early Detection, Diagnosis and Staging

Working Draft

A. State of the Science

Screening and Early Detection

Screening for oral cancer should include a thorough history and physical examination.[1,2] The clinician should visually inspect and palpate the head, neck, oral, and pharyngeal regions. This procedure involves digital palpation of neck node regions, bimanual palpation of the floor of mouth and tongue, and inspection with palpation and observation of the oral and pharyngeal mucosa with an adequate light source; mouth mirrors are essential to the examination. Forceful protraction of the tongue with gauze is necessary to visualize fully the posterior lateral tongue and tongue base.

The clinician should review the social, familial, and medical history and should document risk behaviors (tobacco and alcohol usage), a history of head and neck radiotherapy, familial history of head and neck cancer, and a personal history of cancer. Patients over 40 years of age should be considered at a higher risk for oral cancer.[3]

Diagnosis can be delayed by several months or more if the clinician treats the patient's complaints empirically with drugs instead of providing a thorough physical examination and workup. Patients with complaints lasting longer than 2-4 weeks should be referred promptly to an appropriate specialist to obtain a definitive diagnosis. If the specialist detects a persistent oral lesion, a biopsy should be performed without delay.

The many signs and symptoms of oral cancer are usually divided into early and late presentation. They can be so diverse that the differential diagnosis may not lead to oral malignancy. Table 1 summarizes the signs and symptoms.

Table 1:
Frequent Signs and Symptoms of Oral Cancer

Early	Late
Persistent red and/or white patch Nonhealing ulcer Progressive swelling or enlargement Unusual surface changes Sudden tooth mobility without apparent cause Unusual oral bleeding or epistaxis Prolonged hoarseness	Indurated area Paresthesia, dysesthesia of the tongue or lips Airway obstruction Chronic earache (chronic serous otitis media)/otalgia Trismus Dysphagia Cervical lymphadenopathy Persistent pain or referred pain Altered vision

Because patients may be at risk for developing multiple primary tumors simultaneously or in

sequence, the entire visible mucosa of the upper aerodigestive tract must be examined. In addition, lymph nodes in the head and neck area—particularly along the jugular chain—must be palpated. Approximately 90% of patients with squamous cell carcinoma in a lymph node in the neck area will have an identifiable primary tumor elsewhere, and about 10% will have cancer in the neck lymph node as an isolated finding ("unknown primary").[4] Thus, most cancers in the neck node represent a metastasis from a primary tumor located in the head and neck region; this primary site must be identified.

Toluidine blue (vital staining) also is a useful adjunct to clinical examination and biopsy.[5,6] The mechanism is based on selective binding of the dye to dysplastic or malignant cells in the oral epithelium. It may be that toluidine blue selectively stains for acidic tissue components and thus binds more readily to DNA, which is increased in neoplastic cells.

Toluidine blue has been recommended for use as a mouthwash or for direct application on suspicious lesions; its value comes from its simplicity, low cost, noninvasiveness, and accuracy (Table 2).[9] In addition, it can help to determine the most appropriate biopsy sites and to surgically delineate margins. Meta-analysis of toluidine blue staining in oral cancer screening found that its sensitivity ranged from 93.5% to 97.8%, and specificity from 73.3% to 92.9%.[7]

The disadvantages of toluidine blue include the risk of obtaining a false negative reaction in a case where the patient is not followed up adequately. In contrast, the infrequent false-positive only subjects the patient to a biopsy. No in vivo observations or reports have suggested a mutagenic effect from this stain.[8]

Table 2: Comparison of Toluidine Blue Uptake with Microscopic Diagnosis[9]

Biopsy Diagnosis	No. Lesions	Positive	Negative	Correct
Carcinoma	62	58	4	94%
Dysplasia	13	11	2	85%
Benign	94	6	88	94%
Total	169			93%

Diagnosis

Currently, the most effective way to control oral cancer is to combine early diagnosis and timely and appropriate treatment. Because more than 90% of all oral cancers are squamous cell carcinomas, the vast majority of oral cancers will be diagnosed from lesions on the mucosal surfaces.

The clinician's challenge is to differentiate cancerous lesions from a multitude of other red, white, or ulcerated lesions that also occur in the oral cavity. Most oral lesions are benign, but many have an appearance that may be confused with a malignant lesion, and some previously considered benign are now classified premalignant because they have been statistically correlated with subsequent cancerous changes.[10] Conversely, some malignant lesions seen in an early stage may be mistaken for a benign change.[11] Any oral lesion that does not regress spontaneously or respond to the usual therapeutic measures should be considered potentially malignant until histologically shown to be benign. A period of 2-3 weeks is considered an appropriate period of time to evaluate the response of a lesion to therapy before obtaining a definitive diagnosis.

A definitive diagnosis requires a biopsy of the tissue. Biopsies may be obtained using surgical scalpels or biopsy punches and typically can be performed under local anesthesia. Incisional biopsy is the removal of a representative sample of the lesion; excisional biopsy is the complete removal of the lesion, with a border of normal tissue. The clinician can obtain multiple biopsy specimens of suspicious lesions to define the extent of the primary disease and to evaluate the patient for the presence of possible synchronous second malignancies. Useful adjuncts include vital staining, exfoliative cytology, fine needle aspiration biopsy, routine dental radiographs and other plain films, and imaging with magnetic resonance imaging (MRI) or computed tomography (CT). Table 3 presents a suggested protocol for patient evaluation.

Most carcinomas of the oral cavity do not need a "panendoscopy" for definitive diagnosis. Such a procedure, which consists of direct laryngoscopy, esophagoscopy, and bronchoscopy, is usually performed as a diagnostic and staging procedure in patients with carcinoma of the oropharynx.

Imaging the Oral Cavity

A diagnostic imaging evaluation consisting of either computer tomography (CT) scanning or magnetic resonance imaging (MRI) is also used to assess the extent of local and regional tumor spread, the depth of invasion, and the extent of lymphadenopathy.[12,13] CT is superior in detecting early bone invasion and lymph node metastasis, but MRI is preferred for assessing the extent of soft tissue involvement and for providing a three-dimensional display of the tumor. MRI is also the preferred technique for imaging carcinoma of the nasopharynx or lesions involving paranasal sinuses or the skull base.

Table 3: Patient Work Up

1 - History and physical examination, including risk factor analysis and exposure to carcinogens.

2 - Head and neck examination:
- direct visualization
- mirror examination
- manual palpation
- toluidine blue staining

3 - Laboratory tests:
- CBC
- liver function

4 - Radiology:
- CT or MRI of head and neck
- chest x-ray
- dental films
- bone scan when indicated

5 - Pathology
- incisional biopsy
- excisional biopsy
- fine needle aspiration biopsy
- molecular markers
- flow cytometry

6 - "Panendoscopy:"
- define T-stage
- draw schematic tumor map
- evaluate for second malignancies

7 - Pre-therapy consultation with:
- radiation oncology
- medical oncology
- head and neck surgery
- reconstructive surgery
- dental oncology
- speech pathology
- psychosocial service

8 - Multidisciplinary Tumor Board:
- finalize staging
- formulate treatment plan

Diagnostic imaging often detects subsurface masses and intraosseous lesions. Although imaging of pathologic lesions does not produce a definite diagnosis, it frequently helps to define the extent of the

tumor. For example, patients who have an unexplained neck node and a negative head, neck, and oral examination may undergo CT scanning followed by a biopsy of the nasopharynx or base of tongue that reveals a suspicious area or tissue change.

Both CT and MRI have limitations as well as advantages, a fact that frequently makes them complementary rather than competitive studies. The advantages of CT include its rapid acquisition time (2-3 seconds per section), patient tolerance, relatively low cost, and superior osseous detail compared with MRI. However, the soft-tissue contrast resolution of CT is relatively poor, which makes it difficult to distinguish between tumor and normal muscle. CT also may require the administration of intravenous contrast material to differentiate vessels from lymph nodes, thereby increasing the risk of an allergic reaction. In addition, CT is frequently degraded by scattered artifacts because of metallic dental appliances.[14]

MRI's several advantages over CT have helped it evolve into a reliable alternative for imaging normal and pathologic head and neck anatomy. The superior soft-tissue resolution of MRI allows high-contrast differentiation between neoplasms and adjacent muscle. In addition, MRI can be obtained in multiple planes (sagittal, axial, coronal, and oblique), which is often helpful in assessing tumor volumes during and after therapy. Finally, the need for intravascular contrast administration is avoided because patent vessels have absent signal, or "signal void," within their lumen, which easily distinguishes them from surrounding soft tissue structures.

However, MRI is not without its drawbacks. Because all the images within a given MRI sequence are obtained simultaneously rather than sequentially, patient movement during an MRI is less well tolerated than with CT. In addition, although the soft-tissue contrast is superb with MRI, fine-bone detail is inferior to that obtained with CT.

Cytology

Under certain conditions, exfoliative cytology (cell scrapings) serves as an adjunct to clinical diagnosis, as it enables more extensive screening and provides microscopic material if there is a delay in or contraindication to biopsy. However, cytologic smears are used infrequently, and patients are not treated on the basis of cytologic findings alone. Smears are most helpful in differentiating inflammatory conditions, especially candidiasis, from dysplastic or neoplastic surface lesions. In addition, cytology may be helpful in detecting field change in oral cancer, especially if this method is used in conjunction with vital staining. Cytology may also be helpful when ulcerations following radiation are suspicious and biopsy is delayed.

Fine needle aspiration biopsy of subsurface masses is also an accepted diagnostic test, one that has increased in popularity over the past few years. This technique is extremely useful in evaluating clinically suspicious changes involving salivary glands and lymph nodes. It expedites diagnosis and

staging and avoids incisional or excisional biopsies that may interfere or complicate definitive treatment. When used by a skilled clinician, fine needle aspiration can often be the best way to establish a definitive diagnosis of unexplained masses of the neck or salivary glands. It is also valuable in following up cancer patients with suspicious enlargements.[15]

Staging of the Disease

The stage of the disease depends on several factors, including the size of the primary lesion, local extension, lymph node involvement, and evidence of distant metastasis. Tumor size, the organ or tissue affected, and the extent of spread are considered to be the best indicators of the patient's prognosis. Table 4 summarizes the most widely accepted staging protocol, the tumor-node-metastasis (TNM) classification of oral cancer. This system has 3 basic clinical features: the size (in centimeters) of the primary tumor; the presence, number, size, and spread (unilateral or bilateral) to the local lymph nodes; and the presence or absence of distant metastasis.

Table 4: Tumor-Node-Metastasis (TNM) Staging System for Oral Carcinoma[16]

	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
T4	(lip) Tumor invades adjacent structures (e.g., through cortical bone, tongue, skin of neck)
T4	(oral cavity) Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)
	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 greater dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; 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 greater dimension
	Distant Metastasis (M)
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

The individual clinical parameters in the TNM classification system are grouped to determine the appropriate disease stage (Table 5); stages are ranked numerically from 0 (which has the best prognosis) to IV (the worst prognosis). In general, oral staging classifications do not use histopathologic findings except to determine the definitive diagnosis.

Table 5: TNM Clinical Stage Grouping[16]

Stage	Tumor Size	Nodal Involvement	Distant Metastasis
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N1	M0
	T1	N1	M0
	T2	N1	M0
	Te	N0	M0
Stage IV	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

Schematic drawings of the tumor (tumor maps) are frequently prepared to document the site and size of the tumor at the initial time of diagnosis. This initial documentation is later complemented by histopathologic findings and imaging preformed during the treatment phase.

Although the risk of distant metastasis is generally low in patients with oral cancer, there is a correlation between the incidence of distant metastasis and tumor (T) and neck (N) stage.[17] When they do occur, the most frequently involved organs are the lungs, bone, and liver. Patients with advanced T or N stages may be at risk for developing metastases outside the head and neck region; a limited workup (chest x-ray, CBC and liver function tests, bone scan) to exclude such a metastasis may be indicated.

After completion of the initial workup, the final T, N, M (metastasis), and overall stage assignment should be formally determined and documented prior to treatment. Because rehabilitation planning starts with staging and treatment, a multidisciplinary approach is essential (see Chapters VII and VIII).

Disease Progression

Oral squamous cell carcinoma spreads primarily by local extension and somewhat less often by the lymphatics. The extent of tumor invasion depends upon the anatomic site, the tumor's biologic aggressiveness, and host response factors.

The lymphatic system is the most important and frequent route of metastasis. Usually the ipsilateral cervical lymph nodes are the primary site for metastatic deposits, but occasionally contralateral or bilateral metastatic deposits are detected. The risk for lymphatic spread is greater for posterior lesions of the oral cavity, possibly because of delayed diagnosis or increased lymphatic drainage at those sites, or both. Cervical lymph nodes with metastatic deposits are firm-to-hard, nontender enlargements. Once the tumor cells perforate the nodal capsule and invade the surrounding tissue, these lymph nodes become fixed and non mobile.

Metastatic spread of tumor deposits from oral carcinoma usually occurs in an orderly pattern, beginning with the uppermost lymph nodes and spreading down the cervical chain. Because of this pattern of spread, the jugulo-digastric nodes are most prone to early metastasis. Carcinomas involving the lower lip and floor of the mouth are an exception, as they tend to spread to the submental nodes. Although lymph node metastasis is not an early event, as many as 21% of individuals with oral cancer present at diagnosis with nodal metastasis. (This proportion exceeded 50% in a study of patients evaluated at admission to cancer centers.[18])

Hematogenous spread of tumor cells is infrequent in the oral cavity but may occur because of direct vascular invasion or seeding from surgical manipulation. Perhaps 10-34% of patients present with distant metastasis; this risk increases with advanced disease.[3] Among the most common sites for distant metastasis are the lungs, liver, and bones. These patients cannot be cured and are treated with palliative intent, usually involving chemotherapy, radiotherapy, or both.[3]

Approximately 30% of patients will present initially with highly confined localized disease stages (T_1 or T_2). These patients are treated with curative intent, usually involving surgery, radiation therapy, or both. Only about 20-40% of patients will develop a local or regional tumor recurrence. However, over subsequent years, these "cured" patients appear to be at higher risk for developing a second malignancy than for developing a recurrence of their initial tumor. Tumor recurrences most often occur during the first 2 years after therapy; later recurrences are rare. Second malignancies, on the other hand, will be observed at a steady rate—perhaps 3-5% per year. Thus, with sufficient follow-up time, second malignancies or other medical diseases become greater problems than recurrence of the primary disease. The use of drug therapy to decrease the rate of second malignancies is being actively investigated.

Patients with locoregionally advanced disease (T_3, T_4, N_1, N_2, and N_3) are also treated with curative

intent. Given the advanced stage of their disease, surgery and radiation are utilized unless patients are considered inoperable or have unresectable disease. Despite this aggressive bimodality therapy, the majority of these cancers will recur within the first 2 years of follow-up, most commonly either locally or regionally. Some of these patients may have metastases outside the head and neck area, events that might be predicted by their initial T and N stages. Investigational therapy in this group of patients, therefore, must focus primarily on delivering more effective locoregional care. However, should locoregional control be improved, chemopreventive strategies will need to be pursued in this group of patients as well since, in principle, oral cancer patients are at risk for developing second primary malignancies in the oral cavity, pharynx, and respiratory and digestive tracts.

Multiple Carcinomas

Individuals with one carcinoma of the head and neck region have an increased risk of developing a second malignancy; the frequency of that event varies from 16% to 36%.[19] When a second malignancy occurs at the same time as the initial lesion, it is called a synchronous carcinoma. Metachronous neoplasms, on the other hand, are additional primary surface epithelial malignancies that develop in a later time period than the original tumor. About 40% of second malignancies of the upper aerodigestive tract arise simultaneously and represent a synchronous tumor. The remaining multiple cancers in this population represent metachronous disease and usually develop within 3 years of the initial tumor.[19] Second primary tumors are the chief cause of death in patients with an early-stage diagnosis.[20]

The tendency to develop multiple carcinomas in the upper aerodigestive region is known as "field cancerization."[21] Prolonged and diffuse exposure to local carcinogens, particularly tobacco combined with alcohol, appears to increase the malignant transformation potential of exposed epithelial cells in the upper aerodigestive tract and lungs.[22] The overall risk for developing a second head and neck malignancy is 10 to 30 times higher in populations that use tobacco and alcohol than in the general population.[23]

B. Emerging Trends

Early Detection

At the present time, the most effective approach to reducing morbidity and mortality from oral cancer is early detection. However, progress in this area requires changes in public and professional knowledge, attitudes, behaviors, and practices (see Chapter IX for a full discussion).

Diagnosis

Immunohistochemical Techniques

The use of immunohistochemical techniques to establish a definitive diagnosis has expanded during the past decade and continues to be refined. These diagnostic tests help to establish a definitive diagnosis when, by routine histopathology techniques, a lesion appears morphologically benign or its classification is in doubt. Research on the biochemical, genetic, and cellular levels should yield information that will identify high-risk groups for many types of cancer including oral cancer.

Imaging Techniques

Imaging techniques continue to improve at a rapid rate. Newer imaging techniques hold promise for clinical staging of T_2, T_3 and T_4 lesions, but T_1 lesions are typically too small to be visualized.[24] Improvements that increase definition will promote earlier detection of nasopharyngeal, submucosal, and bone lesions. One such technique appropriate for lymph nodes is positron emission tomography, which may help to define tumor activity in clinically negative areas.[25]

Biochemical and Genetic Factors

No matter which diagnostic technique is used, there is the possibility of a false-negative diagnosis. However, studies are under way to identify key markers that should improve accuracy. The development of monoclonal antibodies that have high sensitivity and specificity for epithelial dysplastic and malignant cells would enhance accuracy of diagnosis in some cases where the usual or typical cellular characteristics of precancer or cancer are not apparent. Such antibodies might also minimize errors about "tumor free" margins of surgical resections, thereby reducing a potential source for recurrence. In addition, assuming that an antibody was specific for a particular cellular tumor antigen, binding of cytotoxic chemotherapeutic agents for killing tumors and sparing normal cells would be a logical and possibly feasible follow-up to surgery and radiation therapy to improve cancer control.

Additional knowledge about various cell markers that reflect growth and suppressor protein presence or activity may also prove to be of great value in predicting cell behavior. Genetic/chromosome evaluations may serve a similar purpose in the identification and treatment of tumors.

Current research is exploring the genetics of biochemical processes that may affect the development of oral cancer. Included are gene mutations such as p53 tumor suppressor gene amplification and overexpression of proto-oncogenes c-myc, EGFR and cyclin D1, as well as loss of heterozygosity of specific chromosome loci. Cellular alteration of response to growth factor and Beta's (TGF-beta) growth suppressor effect on tumor cells may become important as well.

Clinical Photodetection

Photodynamic therapy, also known as PDT, and photodetection of cancer may be useful in the oral cavity. Two important variables that must be considered are the uptake of the dye and the dye contrast by normal and neoplastic tissue after injection.[26]

C. Opportunities and Barriers to Progress

Early Detection

The role that health care professionals who are not physicians or dentists play in oral cancer screening is poorly defined. Potential participants include dental hygienists, physician's assistants, and nurses. There has been some assessment of the role of hygienists, but very little for physician's assistants or nurses. The medical and dental professions need additional information on the most effective ways to provide early detection screening for all patients, including medically underserved populations. In addition, health care professionals need to know how to instruct patients on oral self-examination techniques. Most practitioners are aware that such instruction is reasonable and practical for breast cancer but are unaware of its role in the early detection of oral cancer.

Similarly, most of the general public is poorly informed about the risk of oral cancer and ways to prevent this disease. In a recent NIH study, only 25% of surveyed adults could identify one sign of oral cancer.[27] Much public attention is paid to the dangers of cigarette smoking, where the major emphasis is on lung cancer and cardiovascular disease, less on increased cancer risk in the upper airways and oral cavity. In recent years more information has been directed toward oral cancer risks in smokeless tobacco abusers than in cigarette smokers.

Most people have little interest in estimating their oral cancer risk based on age, sex, race, or even habits such as drinking or smoking. The portion of the public that regularly receives medical and dental care tends to assume it is routinely and adequately screened for all types of disease, including all forms of cancer. These people are generally unaware that to screen properly for oral cancer requires a head, neck, and oral examination. Thus, the failure of a primary care doctor to perform those procedures would likely go unnoticed by the average patient. Similarly, many patients are no doubt unclear as to who should be responsible for screening them for oral cancer.

Although members of the public have been informed to some degree regarding the general warning signs of cancer, they may not know the early signs of oral cancer. Not surprisingly, far too many oral cancer patients do not seek care until their tumors are advanced, which suggests that a much better job must be done of informing patients when and how to seek help.

Diagnosis

Fine needle aspiration biopsy is an accepted procedure for diagnosing many subsurface lesions such as salivary gland tumors and nodal disease. However, it is often used inappropriately; on many other occasions the clinician retrieves nondiagnostic tissue. Increased practitioner training on properly

applying the procedure and using CT scanning to guide tissue retrieval is needed.

Another problem is that many clinicians lack a clear understanding of the criteria for ordering the various types of imaging available today, many of them quite costly. Inappropriate and indiscriminate use of imaging results in millions of dollars wasted annually. In general, except for unusual and occult lesions, sophisticated imaging is not required for early detection, but it may be essential later to enhance clinical staging and treatment. Clinicians also frequently order CTs and MRIs but do not indicate the extent of anatomy essential for staging; thus, the study needs to be repeated.

Because of the well-recognized phenomenon of "field cancerization" in the head and neck region, it is important to refer patients who are diagnosed with a primary squamous cell carcinoma or epithelial dysplasia of the oral cavity for evaluation of a synchronous tumor. In addition, an annual evaluation for detection of metachronous disease should be reinforced for these patients. Such patients should be monitored routinely for high-risk behaviors, including continued tobacco and alcohol consumption, because these behaviors adversely influence survival after the occurrence of a second cancer. Finally, the use of consultations and tumor board services is essential, even in what may be deemed "early cancer."[28]

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