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The DOI for this manuscript is doi: 10.5858/arpa.2018-0411-SA

The final published version of this manuscript will replace the Early Online Release version at the above DOI once it is available.

Data Set for the Reporting of Oral Cavity Carcinomas

Explanations and Recommendations of the Guidelines From the International Collaboration of Cancer Reporting

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● The International Collaboration on Cancer Reporting is a nonprofit organization whose goal is to develop evidence-based, internationally agreed-upon standardized data sets for each cancer site for use throughout the world. Providing global standardization of pathology tumor classification, staging, and other reporting elements will lead to the objective of improved patient management and enhanced epidemiologic research. Carcinomas of the oral cavity continue to represent a significant oncologic management burden, especially as changes in alcohol and tobacco use on a global scale contribute to tumor development. Separation of oral cavity carcinomas from oropharyngeal tumors is also important, as management and outcome are quite different when human papillomavirus association is taken into consideration. Topics such as tumor thickness versus depth of invasion, pattern of invasive front, extent and size of perineural invasion, and margin assessment all contribute to accurate classification and staging of tumors. This review focuses on the data set developed for *Carcinomas of the Oral Cavity Histopathology Reporting Guide*, with discussion of the key elements developed for inclusion.

(*Arch Pathol Lab Med.* doi: 10.5858/arpa.2018-0411-SA)

With the aim of standardizing evidence-based pathology reports for use throughout the world, the International Collaboration on Cancer Reporting (ICCR) since its formation in 2011 has developed data sets for various organ systems. The ICCR is an alliance formed by major pathology organizations including the College of American Pathologists; the Royal Colleges of Pathologists of Australasia and the United Kingdom; the Canadian Association of Pathologists–Association Canadienne des Pathologists in association with the Canadian Partnership Against Cancer; the American Society of Clinical Pathology; Royal College of Physicians of Ireland, Faculty of Pathology; and the European Society of Pathology. Each data set is composed of an expert panel with international experience, which is particularly important in oral cavity cancers, where there are worldwide geographical differences in presentation due to variations in tobacco use.

Using the ICCR guidelines for the development of the data sets (http://www.iccr-cancer.org/datasets/dataset-development), the series champion appointed a domain chair for a specific anatomic site, together inviting 7 additional members to form the Dataset Authoring Committee. In order to assure geographic diversity, members of the authoring committee were chosen from 5 countries (4 continents), including 8 pathologists chosen from the additional sponsoring organizations of these data sets: the North American Society of Head and Neck Pathology, the American Academy of Oral and Maxillofacial Pathology, the British Society for Oral and Maxillofacial Pathology, and the International Association of Oral and Maxillofacial Pathologists. Some of the pathologists had prior experience in data set development, and inclusion of a head and neck surgeon was deemed essential.

The ICCR oral cavity data set is specific to resection specimens and biopsies of invasive carcinoma of the oral cavity, including lip and tongue. Neck lymph node excisions and dissections are covered in a linked but separate *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours Histopathology Reporting Guide*,[59] as are mucosal melanomas of the head and neck in a *Mucosal Melanomas of the Head and Neck Histopathology Reporting Guide*.[60] The expert panel evaluated which included elements were core and noncore. *Core* elements are considered essential for clinical management, staging, or prognosis and thus are
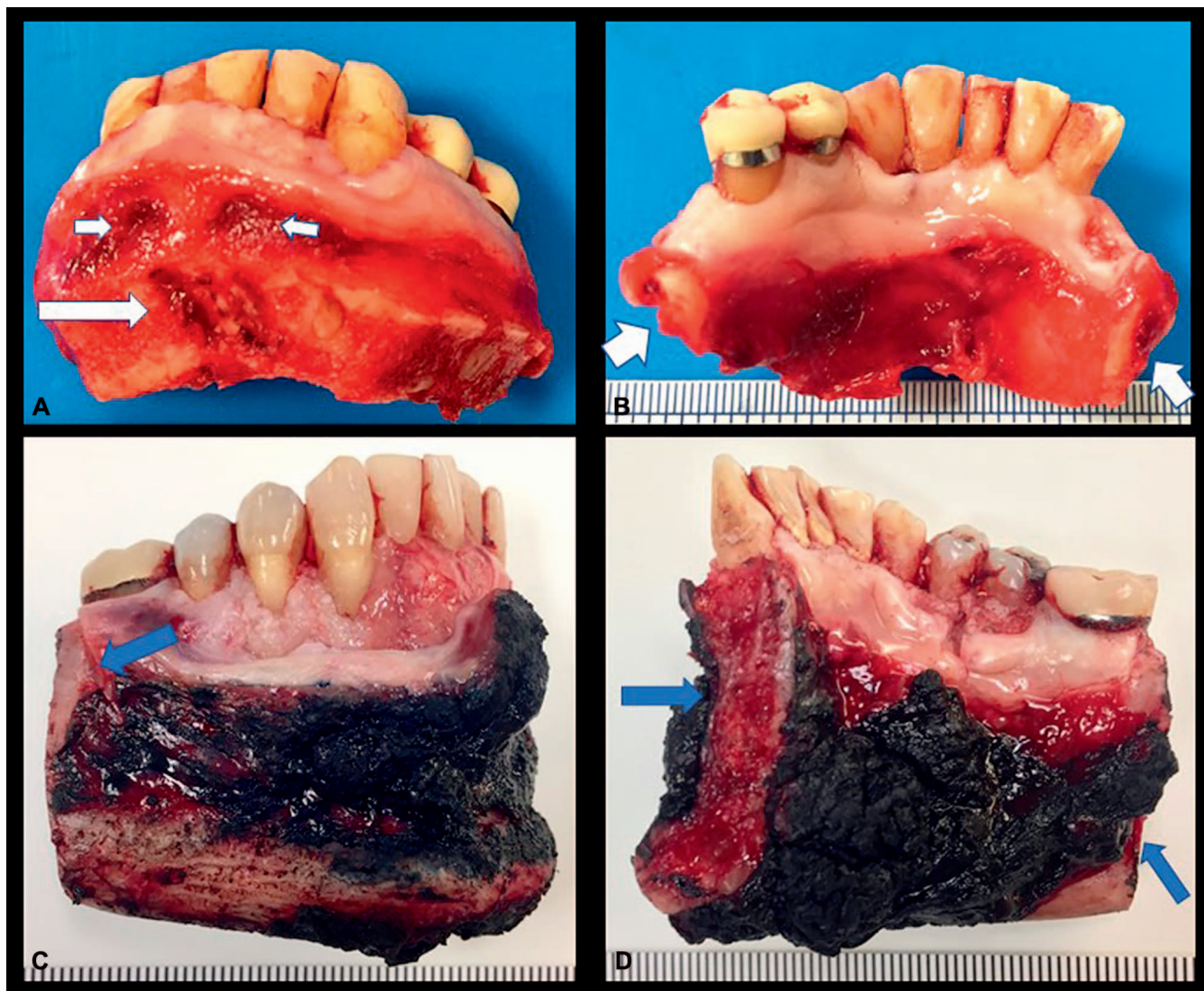
Figure 1. *Gross photographs demonstrating the difference between marginal mandibulectomy and segmental mandibulectomy. A, Marginal mandibulectomy, anterior view (long arrow, inferior bone margin; short white arrows, mentalis muscle bundles). B, Marginal mandibulectomy, posterior view (white arrows, left and right bone margins). C, Segmental mandibulectomy, lateral view (blue arrow, right bone margin). D, Segmental mandibulectomy, medial view (blue arrows, right and left bone margins).*

required reporting items, generally supported by National Health and Medical Research Council evidence level III-2 (based on prognostic factors among patients in a single arm of a randomized control trial) and above.[1] Noncore elements generally are not validated or routinely used in patient management, but are reporting elements that may be clinically important and are recommended as good clinical practice. This review will summarize the ICCR guidelines for the reporting of *Carcinomas of the Oral Cavity* data set with a discussion of the key elements developed for inclusion.[61]

DATA SET ELEMENTS

Core (Required) Elements

Operative Procedure.—It is important to correlate the type of procedure, that is, excisional or incisional biopsy or resection, with the material received. Site-specific designations are required as accurate staging is site dependent and is necessary for cancer registries. The type of resection should be modified as necessary, such as *hemi*glossectomy,

partial glossectomy, *segmental* mandibulectomy, and *partial* maxillectomy (Figure 1, A through D).[2,3]

Specimens Submitted.—The anatomy of the oral cavity is complex and requires clear communication between the pathologists and the treating clinicians. The exact anatomic site of involvement, tumor laterality, and operative procedure are critical for tumor staging and treatment.[4–6] A diagram of the oral cavity with the anatomic subsites designated (Figure 2), further explained in the accompanying data set discussion, ensures uniformity in reporting. For large cancers that involve more than one site, the primary site of involvement should be recorded (Figure 3). Although *not specified* is a choice, it should be used rarely and only after assiduous effort to obtain the requisite information.

Tumor Dimensions.—An important component in pathologic staging, tumor dimension is considered a core element (Figure 4).[7] Both macroscopic and microscopic tumor dimensions are included as key elements. It is acknowledged that at times no macroscopically visible
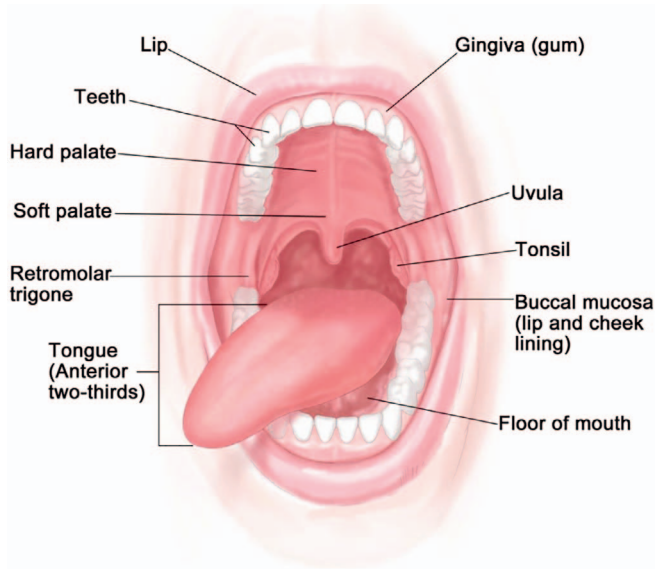
Figure 2. *Anatomic sites and subsites for lip and oral cavity. Reproduced with permission from Terese Winslow. Copyright 2012 Terese Winslow LLC; US Government has certain rights.*

tumor is present, or conversely, microscopic tumor extent exceeds macroscopic measurements. However, the microscopic tumor dimensions should generally be the primary dimensions used for pathologic staging, as 3-dimensional measurements are not always accurately determined. In addition, gross examination of a specimen does not always reflect true tumor extent, as dysplasia, ulceration, or inflammation may appear as tumor on macroscopic examination.

Histologic Tumor Type.—Oral cavity squamous cell carcinoma should be classified according to the most recent edition of the World Health Organization (WHO) *Classification of Tumours of the Head and Neck*[8] (Figure 5). Hybrid lesions, such as verrucous carcinoma and squamous cell carcinoma, are recognized and may affect prognosis.[9] Subtypes should be assigned for both prognosis and cancer registry.[10–12] Minor salivary gland tumors and neuroendocrine tumors should be specified and classified according to the WHO classification.[8] Other carcinomas that may occur in the oral cavity should be entered under ''other.'' Importantly, this data set is for reporting of primary oral cavity carcinomas and is not intended for use with metastases to this site nor for melanomas, sarcomas, or lymphomas. A separate *Mucosal Melanomas of the Head and Neck Histopathology Reporting Guide*[60] would be completed for oral cavity melanomas.

Histologic Tumor Grade.—Based on the WHO classification, 3 histologic grades of conventional squamous cell carcinoma are used: well, moderately, and poorly differentiated.[8] If the tumor has varied histology, the highest grade should be recorded. Grading requires the assessment of keratinization, mitotic activity, cellular and nuclear pleomorphism, pattern of invasion, and host response.[2,13–15] Variants of squamous cell carcinoma (verrucous squamous cell carcinoma, basaloid squamous cell carcinoma, and papillary squamous cell carcinoma) are not graded.

Depth of Invasion.—Depth of invasion (DOI) in oral cavity squamous cell carcinoma, particularly of the tongue, has been identified as an important prognostic indicator and
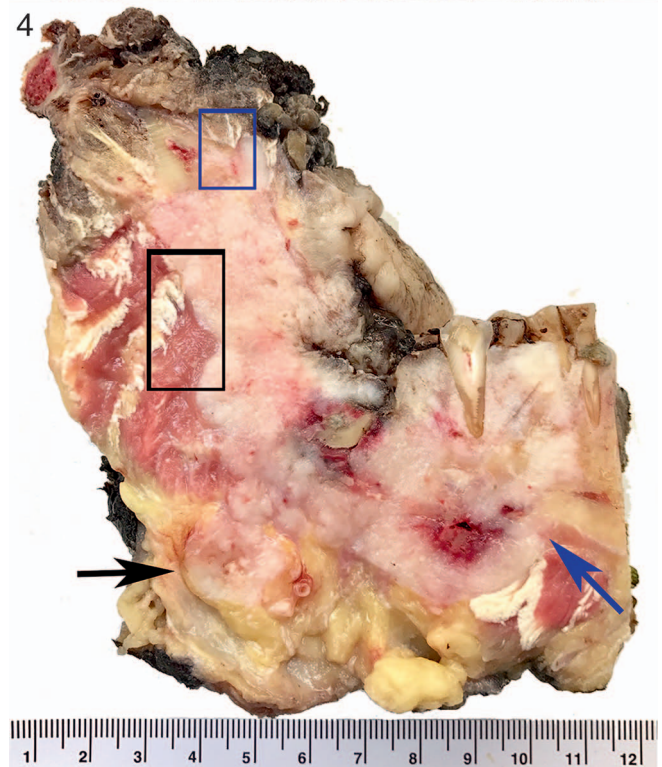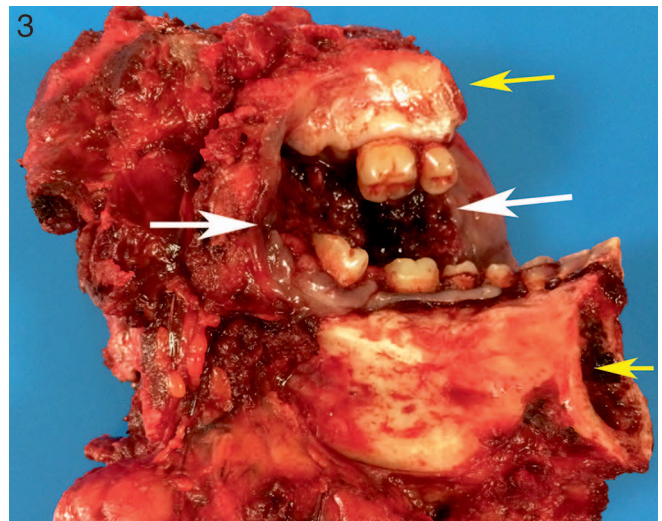

Figure 3. *A large oral cavity tumor involving multiple sites. White arrows, tumor involvement extends from the buccal mucosa to the retromolar trigone. Tumor extends superiorly to the maxillary buccal sulcus and inferiorly to the mandibular buccal sulcus. Top yellow arrow, maxilla; bottom yellow arrow, mandible.*

Figure 4. *The macroscopic tumor dimension is an important component in pathologic staging. This retromolar trigone mucosal lesion measured 3.6 cm. The intraosseous extent of tumor is larger, invading medullary bone of mandible (black box) and masticator space muscle (blue box). Blue arrow highlights primary tumor extension beyond the inferior border of the mandible. Black arrow highlights grossly involved Level Ib lymph node attached to the specimen.*

is a core element.[16–24] In the recent American Joint Committee on Cancer (AJCC) staging manual,[7] the tumor stage (T) has been changed to reflect the importance of DOI. Depth of invasion increases pT by 1 step for every 5 mm, whereby pT1 is tumor 2 cm or smaller and DOI 5 mm or
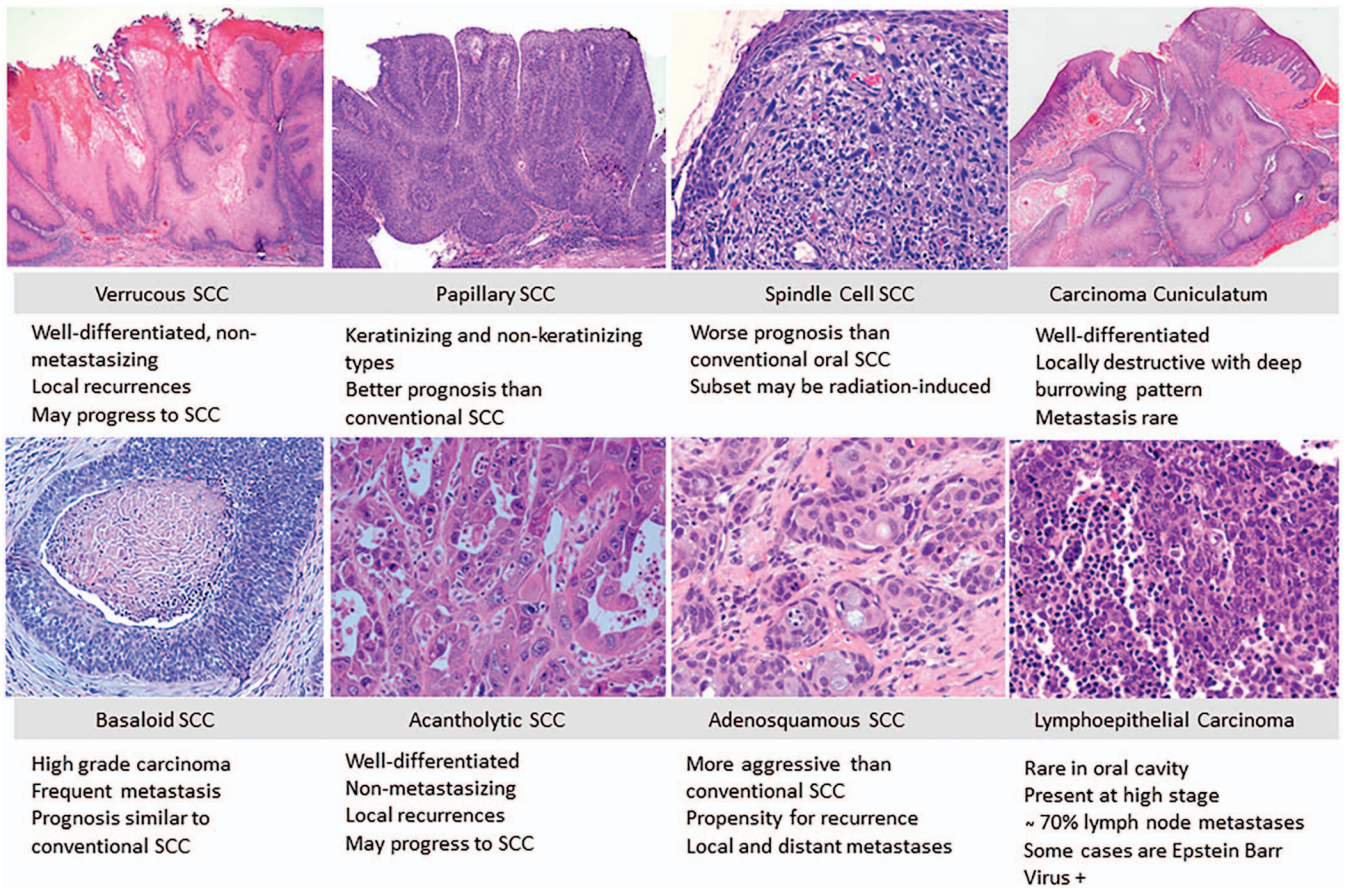
Figure 5. *Oral cavity histologic subtypes of squamous cell carcinoma (SCC) according to the World Health Organization Tumor Classification (hematoxylin-eosin).*
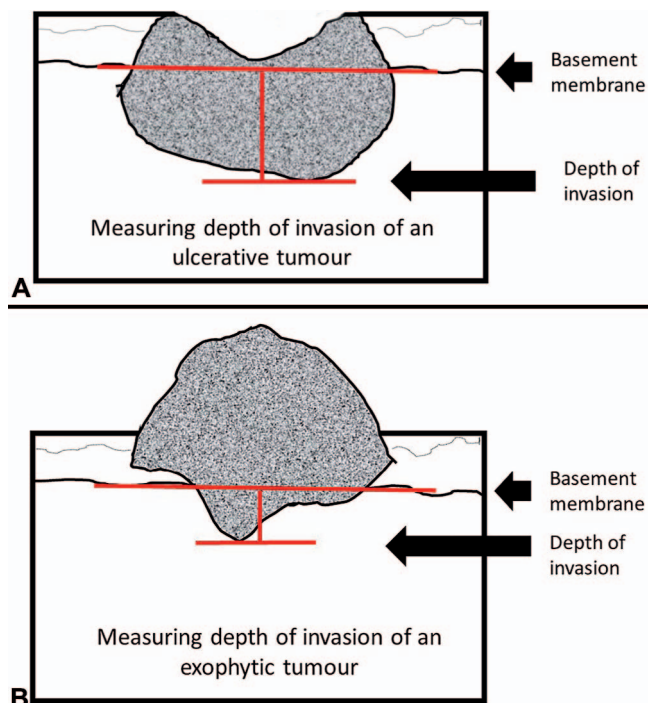

Figure 6. *Measuring depth of invasion: ulcerative (A) versus exophytic (B) tumors.*

less, pT2 is tumor 2 cm or smaller and DOI more than 5 mm and 10 mm or less or tumor more than 2 cm but 4 cm or less and 10 mm or less DOI, and pT3 is tumor larger than 4 cm or any tumor more than 10 mm DOI. Depth of invasion measures the invasiveness of the carcinoma. In the 8th edition of *TNM Classification of Malignant Tumours*[25] published by the Union for International Cancer Control (UICC), DOI is included as a required reporting element but without measurement determination guidance. Therefore, the ICCR data set has adopted the guidance as included in the AJCC staging manual. It is important to note that DOI is not synonymous with tumor thickness. To measure DOI, the basement membrane is identified, and an imaginary line is drawn across the tumor. A vertical or plumb line extends to the deepest part of the tumor, which represents the DOI (Figure 6, A and B). An ulcerative tumor (Figure 6, A) may be thinner than an exophytic tumor (Figure 6, B), but the DOI of the ulcerative lesion may be greater. Importantly, potential confounding problems with DOI determination are extratumoral perineural invasion (may be deeper than tumor front); absence of residual invasion tumor in resection samples, which requires reexamination of biopsy samples; and, when a deep margin is positive, possibly underestimation of the DOI.[26]

Pattern of Invasive Front.—The pattern of invasion in oral squamous cell carcinoma has proven prognostic value and should be reported as cohesive, noncohesive, or widely dispersive (Figure 7).[27–31] It is important to evaluate the most complex area of tumor-stroma interface ("worst" area) and
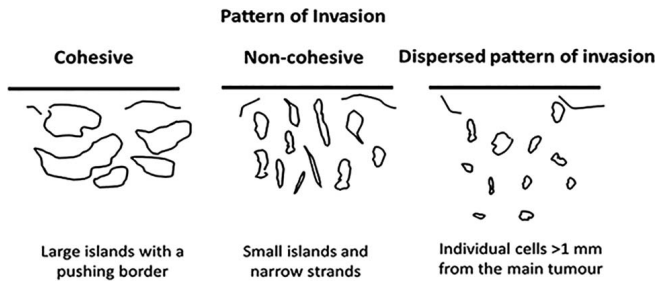
Figure 7. *Patterns of invasive front, showing cohesive, noncohesive, and dispersed patterns.*

Figure 9. *A, Cross section through retromolar trigone region from Figure 8. Intramedullary carcinoma is confirmed; black arrow highlights mandibular canal as reference point to gross photo; blue arrow, mylohyoid muscle. B, Mandibular medullary invasion by squamous cell carcinoma (hematoxylin-eosin, original magnifications ×10 [A] and ×200 [B]).*

consequently, assessment is meaningfully determined only on resection specimens. Cohesive invasion is defined as broad sheets of cancer cells and/or tumor nests more than 15 cells across. Noncohesive invasion shows a spectrum of appearances that includes narrow strands, small groups of fewer than 15 tumor cells, and single infiltrating tumor cells. For stage T1/T2 oral squamous cell carcinoma, particularly those arising in the tongue, there is evidence that tumor satellites 1 mm or more from the main tumor or nearest satellite (worst pattern of invasion 5) are a valid adverse prognostic factor.[29,31]

Bone Invasion.—Infiltrative bone/cartilage involvement by squamous cell carcinoma correlates with a worse prognosis.[32] Bone/cartilage invasion may be a macroscopic feature; however, sampling through the involved bone for histologic examination should be performed to obtain histologic documented evidence (Figure 8, A and B). The presence of bone/cartilage invasion affects tumor staging, and patients with bone invasion often have a worse prognosis. It is important to distinguish between superficial cortical bone erosion and infiltrative invasion to the medullary bone, as this is critical in accurate tumor staging (Figures 9, A and B, and 10). If bone is resected, then bone margins should be reported.

Perineural Invasion (Core and Noncore).—The presence of perineural invasion, regardless of nerve size, is an independent negative prognostic factor associated with locoregional recurrence, poor overall survival, and regional lymph node metastases. Thus, the presence of perineural
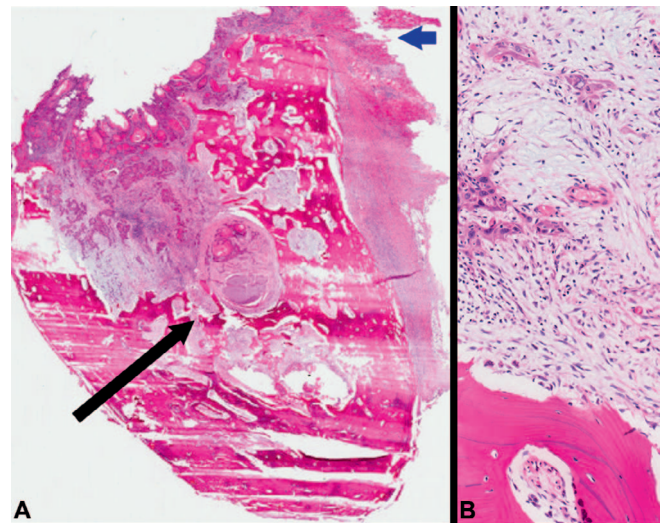
invasion may impact subsequent therapy and prognosis.[2,14,33–35]

Lymphovascular Invasion.—Lymphovascular invasion is identified by the demonstration of malignant cells within the lumina of blood vessels and/or lymphatics.[36,37] It is important to distinguish between intravascular tumor embolization and fixation and/or processing retraction artifact.

Margin Status.—Accurate margin assessment is critical when evaluating a complex surgical resection of oral cavity cancers.[2,13,14,38–41] All surgical margins should be assessed, including the deep soft tissue and bone margins. Documentation of how the surgical margin was measured is important—for example, if the margin was submitted in situ at the time of the operative procedure rather than from the surgical specimen. The presence of high-grade dysplasia/

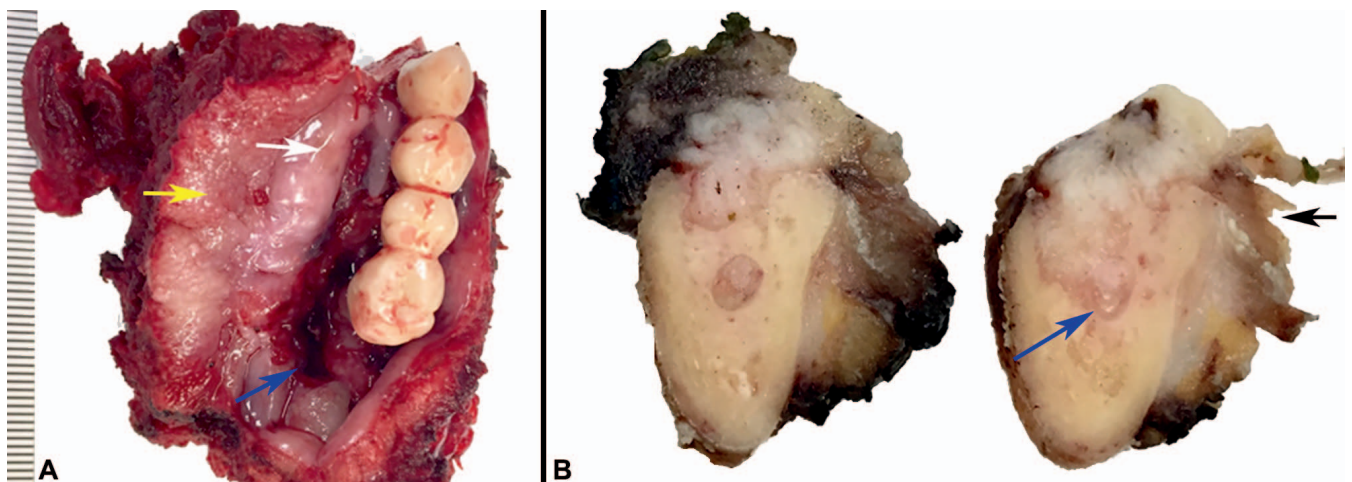**Figure 8.** *Composite mandibular resection for squamous cell carcinoma of the retromolar trigone, posterior floor of mouth, and later oral tongue. A, Yellow arrow, carcinoma; white arrow, ventrolateral tongue; blue arrow, dorsal tongue; B, Cross sections through retromolar trigone region demonstrate bone invasion. Blue arrow, carcinoma extends within bone and abuts mandibular canal; black arrow, mylohyoid muscle.*
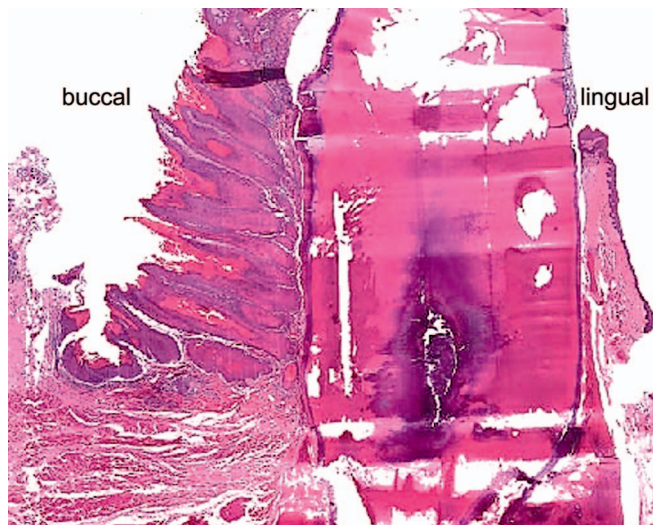
Figure 10. *Cortical erosion from a primary mandibular gingival squamous cell carcinoma extending into the buccal sulcus (hematoxylin-eosin, original magnification ×10).*

carcinoma in situ at the margin is associated with an increased risk of local recurrence, and hence the reason for inclusion. The definition of a close margin is not standardized, but in the oral cavity, from a surgical perspective, more than 5 mm is clear, 1 to 5 mm is close, and less than 1 mm is considered involved. It is well known that fixation and processing distort measurements, with tissue shrinkage changing margin assessment.[42] Bone resection margins must be identified, with margin status reported for carcinoma and high-grade dysplasia. Dysplastic changes include abnormal cellular organization, increased mitotic activity, and nuclear enlargement with pleomorphism. Although terminology varies, oral dysplasia is separated into mild, moderate, or severe dysplasia/carcinoma in situ, according to the most recent WHO classification.[43] The term high-grade dysplasia includes moderate dysplasia, severe dysplasia, and carcinoma in situ.

Pathologic Staging.—There are no differences in the pathologic pT staging systems for oral cavity cancers in the UICC[25] and AJCC[7] 8th editions. As stated earlier, both DOI and bone invasion are critical to obtaining the correct pathologic staging. Invasion through the cortical bone into the medullary bone is staged as pT4a. When neck lymph node dissections are included, a separate, linked data set for *Nodal Excisions and Neck Dissection Specimens for Head and Neck Tumours*[59] would be completed, as applicable.

Noncore (Recommended) Elements

Neoadjuvant Therapy.—History of neoadjuvant therapy is important when assessing histopathology. Histologic changes related to radiotherapy and/or chemotherapy, such as necrosis, may affect interpretation of the tumor. Currently, descriptions of specific pathologic changes in response to neoadjuvant therapy are absent in the literature about oral cavity cancer. In other organ systems, pathologic changes include necrosis, fibrosis, cytologic atypia, and inflammation. With evolving therapies for oral cavity cancer, histologic assessment of response to neoadjuvant treatment will be an important element to be used by treating clinicians and may be better elucidated.

Tumor Focality.—True multifocal or synchronous oral cavity carcinomas are rare.[44–46] Most oral squamous cell carcinomas develop metachronously. Multifocal tumors may be seen in proliferative verrucous leukoplakia, although these tumors are typically connected via dysplastic epithelium.[47]

Coexistent Pathology.—Identifying the presence of dysplasia is recommended. The recognition of dysplasia, particularly high-grade dysplasia/carcinoma in situ, may have significant impact on patient management and/or treatment.[48] The most common sites of dysplasia with the highest risk of malignant transformation are lateral and ventral tongue, floor of mouth, and lower lip. A recently described subset of oral dysplasia is positive for high-risk human papillomavirus (HPV). The epithelium exhibits full-thickness dysplastic changes with karyorrhexis and apoptosis and the cells are strongly positive for p16 by immunohistochemistry.[49] Unlike the oropharynx, p16 immunohistochemistry is not a surrogate marker for high-risk HPV in the oral cavity. Only cases with proven HPV positivity by in situ hybridization confirming the presence of transcriptionally active high-risk HPV should be reported.

Proliferative verrucous leukoplakia is a distinct precursor lesion of unknown etiology with a multifocal presentation and a progressive course associated with high recurrence rates and malignant transformation in up to 70% of cases.[50,51] This diagnosis requires adequate clinical information. Subepithelial fibrosis is a characteristic of oral submucous fibrosis, and increased fibrosis is associated with an increased risk of epithelial dysplasia.[52] Some inherited genetic mutations are associated with a higher risk of oral cancer development, including Fanconi anemia, Li-Fraumeni syndrome, and dyskeratosis congenita. Care must be taken to rule out reactive atypia, which may be seen in epithelium adjacent to ulcers and with fungal infections.[53]

Ancillary Studies.—For most oral cavity squamous cell carcinomas, immunohistochemistry is not required to establish a pathologic diagnosis. Epithelial immunohistochemical markers, including AE1/AE3, CK5/6, p63, and p40, may be required for poorly differentiated or spindle cell carcinoma. Lymphoepithelial squamous cell carcinoma in the oral cavity is rare, and although not all cases are Epstein-Barr virus positive, Epstein-Barr virus–encoded small RNA (EBER) studies are indicated.[54] There is currently no role for routine HPV high-risk type testing in oral squamous cell carcinoma.[43,49,55–57] Some minor salivary gland tumors may require immunohistochemistry to aid in diagnosis.[58]

CONCLUSIONS

Resection specimens from oral cavity cancers may be complex because of the anatomy. Developing internationally standardized data sets should simplify the examination and reporting of these specimens. The international panel of experts serving on the ICCR Dataset Authoring Committee designated 13 core and 5 noncore reporting elements considered essential for the reporting of oral cavity carcinomas. With the goal of restricting required (core) reporting elements to those that are evidence based and agreed upon by the committee, the resulting data set is as concise as possible. Consistency is improved by using a checklist, but free-text comments are encouraged, particularly when there are unusual findings. Harmonization of

existing data sets to develop a generic, evidence-based structured cancer reporting data set is the goal of the ICCR to facilitate comparison of data between countries and will be important for future research and benchmarking.

The authors would like to express their appreciation to the sponsoring societies and organizations and give special thanks to Fleur Webster and Hannah B. Canlas for all their exceptional organizational and editing contributions. The views expressed are those of the authors solely.

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