Data Set for the Reporting of Malignant Odontogenic Tumors

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

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• A data set has been developed for the reporting of excisional biopsies and resection specimens for malignant odontogenic tumors by members of an expert panel working on behalf of the International Collaboration on Cancer Reporting, an international organization established to unify and standardize reporting of cancers. Odontogenic tumors are rare, which limits evidence-based support for designing a scientifically sound data set for reporting them. Thus, the selection of reportable elements within the data set and considering them as either core or noncore is principally based on evidence from malignancies affecting other organ systems, limited case series, expert opinions, and/or anecdotal reports. Nevertheless, this data set serves as the initial step toward standardized reporting on malignant odontogenic tumors that should evolve over time as more evidence becomes available and functions as a prompt for further research to provide such evidence.

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As a starting point, an international panel of pathologists with particular experience in the diagnosis and management of malignant odontogenic tumors discussed all issues considered significant in formulating a data set for reporting these neoplasms. The panel was organized under the auspices of the International Collaboration on Cancer Reporting (ICCR), established in 2011 through a collaboration between the College of American Pathologists, the Canadian Association of Pathologists–Association Canadienne des Pathologistes in association with the Canadian Partnership Against Cancer, the Royal Colleges of Pathologists of Australasia and the United Kingdom, joined in 2013 by the European Society of Pathologists, and followed by the American Society of Clinical Pathology and the Royal College of Physicians of Ireland, Faculty of Pathology as sustaining members. The members of the data set authoring committee were nominated from the additional sponsoring organizations: North American Society of Head and Neck Pathology; American Academy of Oral and Maxillofacial Pathology; the British Society for Oral and Maxillofacial Pathology; and the International Association of Oral and Maxillofacial Pathologists. Working via multiple teleconferences and reviewing a series of drafts that included many comments and clarifications, the final data set contained core and noncore elements.[30] A core element (as defined by the ICCR) represents an essential piece of information for the management of the tumor, whereas a noncore element constitutes an element that provides additional useful, but not critical, information about the neoplasm. In some cases, an element was designated noncore because the value was not yet established but may be elevated to the status of a core element in the future. Sometimes, elements can be both. Because this group of tumors is rare, with only limited prognostic data, selection of core and noncore elements was principally based on basic oncologic principles applicable to most malignant tumors and not necessarily on data specifically derived from studies of large prospective cohorts

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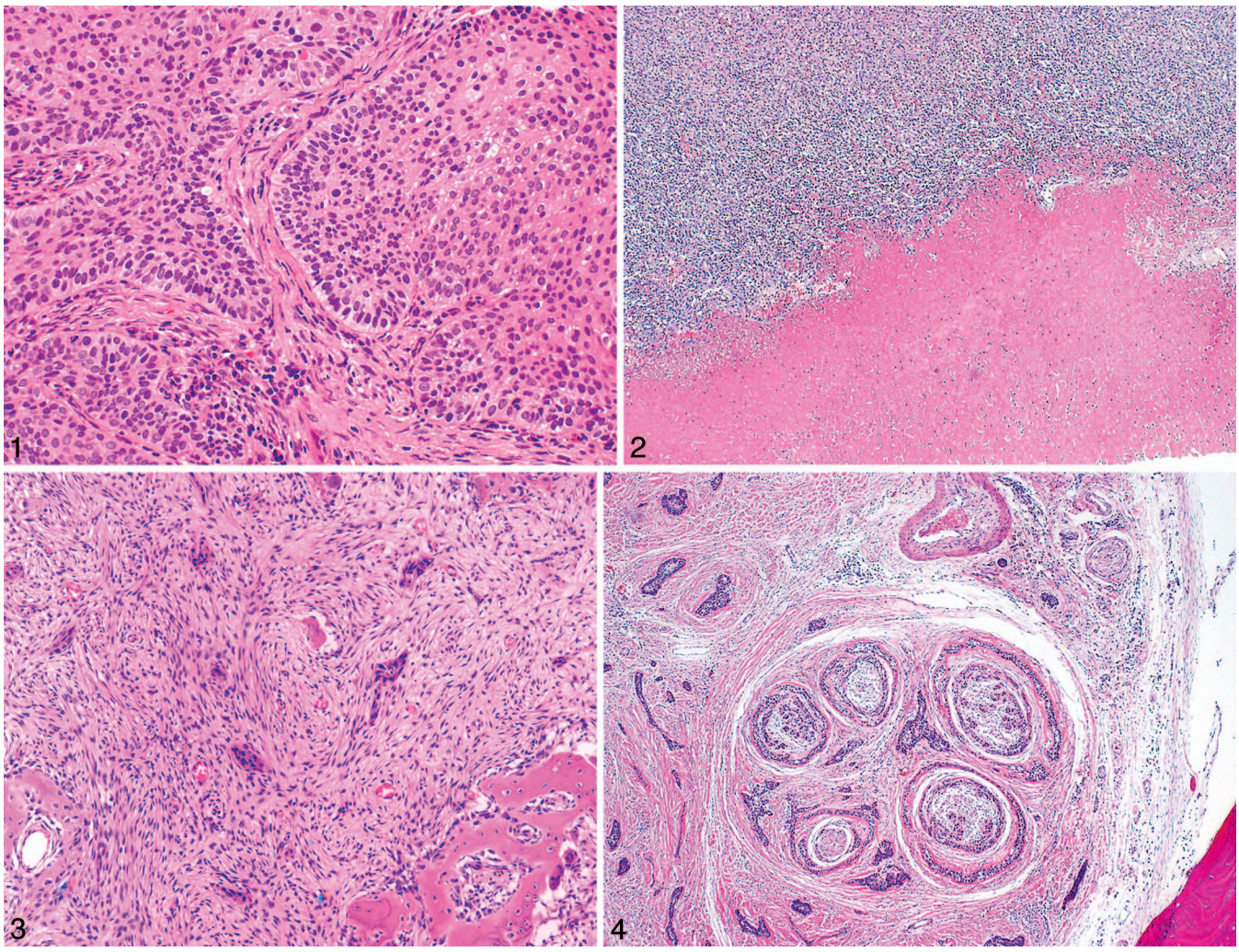

Figure 1. *Ameloblastic carcinoma showing the pattern of ameloblastoma but also cytonuclear atypia, which allows for the distinction between the entities (hematoxylin-eosin, original magnification ×400).*

Figure 2. *Area of necrosis in spindle cell–type ameloblastic carcinoma (hematoxylin-eosin, original magnification ×150).*

Figure 3. *Histology of sclerosing odontogenic carcinoma: inconspicuous epithelial strands in a fibrocellular background (hematoxylin-eosin, original magnification ×400).*

Figure 4. *Ameloblastic carcinoma showing perineural invasion of the inferior alveolar nerve (a named nerve) (hematoxylin-eosin, original magnification ×40).*

of malignant odontogenic tumors. In this way, the policy of the ICCR was implemented, namely, that generic descriptors that apply to all cancer types should be included in data sets irrespective of the level of evidence in the literature to support their inclusion. Hopefully, in due time, higher levels of evidence may be achieved. Currently, the level of evidence is mainly based on small case series and "expert opinion."

DATA SET ELEMENTS

Core (Required) Elements

Specimens Submitted.—As for all pathology specimens, the kind of specimen should be listed, including debulking or curettage, excisional or incisional biopsy, and surgical resection. *Not specified* is used only in rare instances and is to be discouraged. Instead, there should be active personal communication with the treating physicians to obtain the required information. In case of a resection, appropriate and concise terms to be used would be *mandibulectomy* or *maxillectomy* with a prefix indicating the extent (hemi-, partial, or total). In case of a neck dissection submitted together with a tumor specimen, a separate, linked data set for *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours*[31] would be used to describe the neck lymph node findings.

Tumor Site.—The tumor site belongs to standard items listed in agreement with general rules regarding pathology reports, irrespective of the kind of lesion. Giving the exact anatomic site of involvement is most helpful, a finding that may require correlation with clinical and imaging findings.

Tumor Dimensions (Core and Noncore).—Owing to the intraosseous nature of odontogenic lesions, reference to any imaging studies or consultation with a radiologist is recommended in order to achieve the best interpretation of maximum tumor dimension, combining macroscopy, specimen or clinical radiology, and microscopy. Size criteria for

World Health Organization Classification of Malignant Odontogenic Tumors	
Descriptor	**ICD-O Codes[a]**
Ameloblastic carcinoma	9270/3
Primary intraosseous carcinoma, NOS	9270/3
Sclerosing odontogenic carcinoma	9270/3
Clear cell odontogenic carcinoma	9341/3
Ghost cell odontogenic carcinoma	9302/3
Odontogenic carcinosarcoma	8980/3
Odontogenic sarcomas	9330/3

Abbreviation: NOS, not otherwise specified.

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behavior is coded /0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumors.

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possible staging have been suggested.[1] Using data from the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) database for the period 1973–2011, Agarwal et al[2] and Lee et al[3] showed that size was an independent prognostic indicator with smaller tumor size significantly associated with a better overall survival. Patients with tumors greater than 41 mm were twice as likely to die of disease as patients with smaller lesions.[2] The rationale for using both core and noncore is the need to use both pathologic and imaging data to determine the lesion's dimensions, with the latter potentially not easily available to the prosecting pathologist.

Histologic Tumor Type.—The gnathic bones give rise to a variety of neoplasms, including odontogenic and bone/cartilage forming tumors; however, this data set is designed to report only the malignant odontogenic tumors (carcinomas as well as sarcoma) as classified according to the most recent edition of the World Health Organization's (WHO) *Classification of Head and Neck Tumours*[4] (Table). Bone and cartilage forming tumors are classified using a different data set.

Histologic Tumor Grade.—For primary intraosseous squamous carcinoma, the conventional squamous cell carcinoma grade is used.[5,6] Although other malignant odontogenic tumors are generally not graded, the pathologist can still comment on the extent of tissue changes (for these non–squamous cell carcinoma tumors, histologic tumor grade is a noncore item). This especially applies to ameloblastic carcinoma, where there may be varying degrees of cytologic atypia (Figure 1).

Necrosis.—Tumor necrosis is not only a tool to aid in tumor grading, but also the presence of necrosis often helps to confirm a diagnosis of malignancy in odontogenic tumors in general (Figure 2). Thus, while large clinical series of these rare tumors are not available, there is strong support that reporting tumor necrosis aids in diagnosis, grade, and tumor classification.[7,8]

Perineural Invasion.—Perineural invasion is included as a generic descriptor that is considered to be relevant for all types of malignant tumors (Figure 3). Note, however, that the extensive perineural spread seen in sclerosing odontogenic carcinoma does not appear to be a poor prognostic feature (Figures 4 and 5, A and B).[9–11]

Lymphovascular Invasion.—Lymphovascular invasion is generally a feature seen in malignancy, and thus, it is

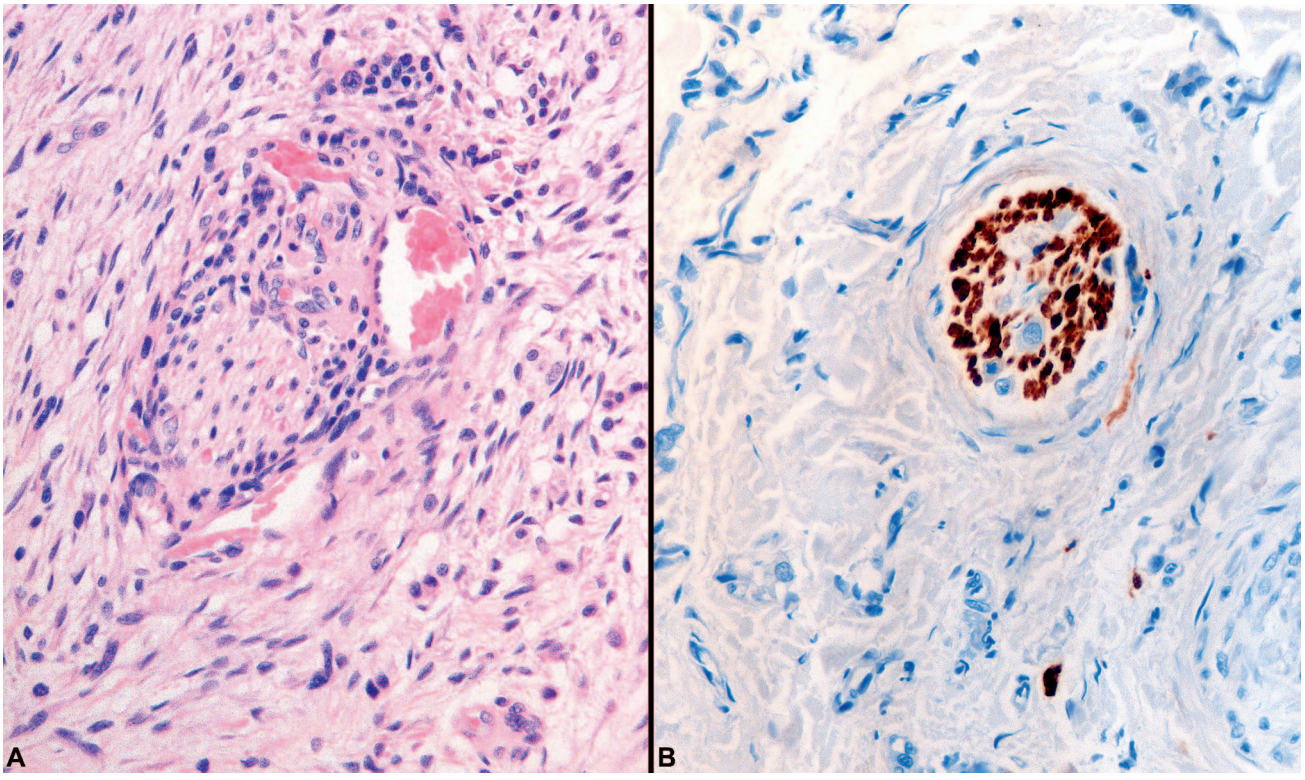
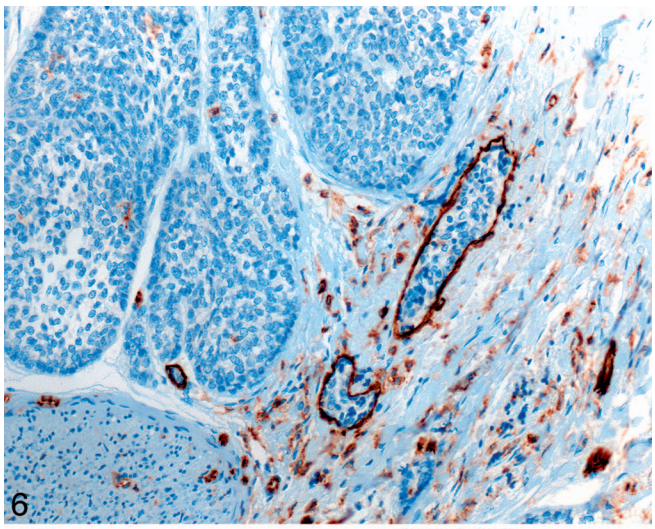


Figure 5. *Perineural growth is a typical feature of sclerosing odontogenic carcinoma (A), highlighted by an S100 protein study (B) (hematoxylin-eosin, original magnification ×600 [A]; original magnification ×600 [B]).*



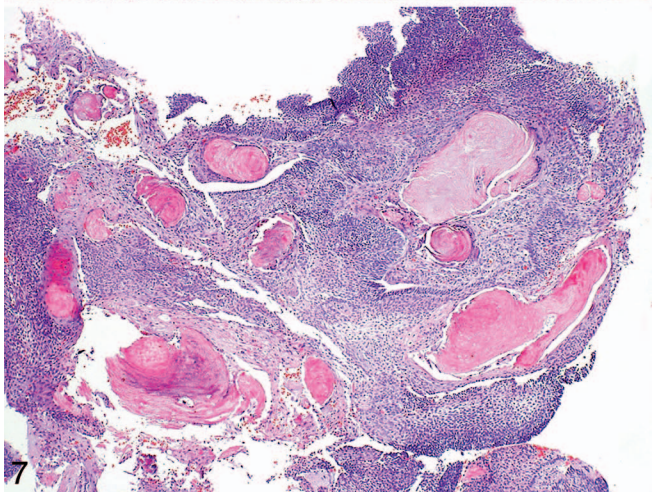


Figure 6. *Vascular invasion in ameloblastic carcinoma can be highlighted by a CD31 immunohistochemistry study, with tumor filling the endothelial lined space (original magnification ×400).*

Figure 7. *A positive margin in ghost cell odontogenic carcinoma (hematoxylin-eosin, original magnification ×100).*

included here, although data specific to malignant odontogenic tumors are not yet reported (Figure 6).

Margin Status.—Margin status is considered a key prognostic factor. Clear margins are commonly achieved only with a thin layer of normal tissue between the tumor and the resection margin. It is therefore of crucial importance to assess whether the excision has an adequate margin around the entire lesion, since if there is focal margin positivity, reoperation may be necessary.

The prognosis is worse when an incomplete excision is located at the infratemporal fossa and/or base of skull and thus, reporting the specific anatomic site of involved margins must be clearly specified (Figure 7).

Noncore (Recommended) Elements

Extent of Invasion.—Extent of invasion is best assessed by a combination of radiographic, macroscopic, and microscopic features (Figure 8). Use of a diagram (Figure 9) is strongly recommended, as the pertinent anatomic landmarks can be easily identified and assessed in the embedding and sectioning protocol.

Ancillary Studies.—There are several immunohistochemical and molecular studies that may be clinically relevant,[12] with some to have potential but unproven therapeutic benefit. Examples include *EWSR1* rearrangements in clear cell odontogenic carcinoma and *BRAF* V600E point mutation in ameloblastic carcinoma.[13,14] Such tests may also increase diagnostic certainty. Thus, if any of these tests are performed, they should be recorded.

DISCUSSION

This data set is based almost exclusively on professional judgement owing to the lack of high-quality evidence to support individual data items. Malignant odontogenic tumors are rare and published series are often not homogeneous by tumor type, classification, stage, or treatment, making conclusions about the value of individual items difficult. In general, the tumors that show aggressive histologic features are more likely to be associated with poor survival, but this tumor group is characterized by unpredictable behavior; low-grade tumors may recur or metastasize many years after excision. For all types, large size, local recurrence, and metastasis are poor prognostic features[2,3,15,16] and outcomes are relatively poor after local recurrence.[17–19] Published mortality rates are generally limited by short follow-up. Ameloblastic carcinomas appear to carry a better prognosis than other tumor types for reasons that are still unclear,[2] although maxillary tumors behave worse than mandibular neoplasms,[20] with up to one-third of maxillary tumors yielding lung metastases. Odontogenic sarcomas are overall of low grade and tend to locally recur rather than to metastasize, but are still associated with significant mortality rates[21–23] owing to local involvement of vital structures.

There are no validated grading systems for odontogenic tumors, although primary intraosseous squamous cell carcinomas are graded by conventional squamous cell carcinoma grading schemes, ostensibly showing some value.[5,6] Tumor necrosis is included as a histologic core feature but is also considered useful in confirming a diagnosis of malignancy in general. Perineural invasion is an included element, although it must be emphasized that in sclerosing odontogenic carcinoma, despite extensive perineural spread, this carcinoma nevertheless carries a relatively good prognosis.[9,10,11]

Margin status after surgical excision is thought to be the key prognostic feature[15,24–27] and the best evidence relates to ameloblastic carcinoma,[2,28] primary intraosseous carcinoma,[5,17] and clear cell carcinoma.[24] Surgical margin clearances may be very small or inadequate and extension into soft tissues beyond the periosteum is usually associated with a significant risk of local recurrence. The prognosis is worse when incomplete excision is seen at the infratemporal fossa and/or base of skull and therefore the anatomic site of involved margins must be clearly specified and marked on a diagram (Figure 9) during macroscopic and microscopic examination.

Tumor dimensions (size) and site are also important prognostic features. Further, carcinomas arising in or limited to cysts carry a better prognosis than those with widespread infiltration.[29]

The role for adjuvant or salvage radiotherapy remains to be defined. The literature does not provide useful information on specific radiotherapy indications or the intent when it has been used. Despite its use to locally control

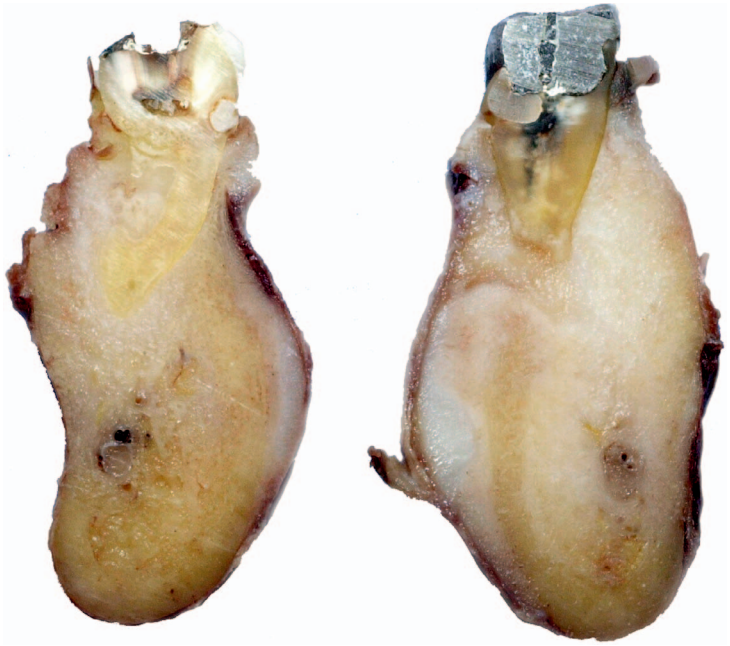


Figure 8. *Gross appearance of clear cell odontogenic carcinoma. Note tumor spread beyond the cortical border of the mandible into the adjacent soft tissues.*

incompletely excised malignant odontogenic tumors, its value appears limited,[24,25] although it has been supported in some large series[2] and is usually considered most effective as part of a multimodality treatment approach. This is true particularly for maxillary lesions in which vital structures may prevent surgical management.

Ancillary studies still play a relatively limited role[12–14]; they are sometimes helpful in diagnosis, while molecular findings may help to guide targeted therapeutic options. However, availability and cost constraints limit widespread adoption, especially in developing nations.

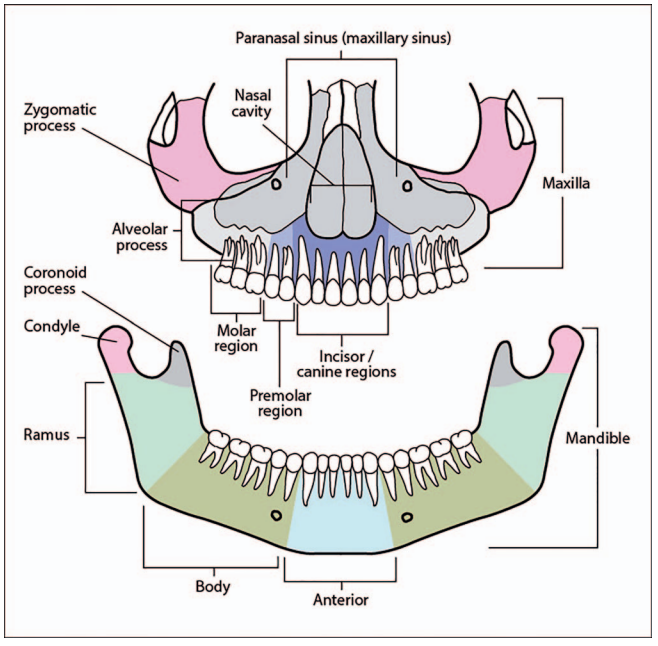


Figure 9. *A diagram depicting anatomic sites, useful in determining the extent of tumor involvement. Reproduced with permission from International Collaboration on Cancer Reporting (ICCR).*

Finally, while ameloblastomas are benign, they often require an oncologic (surgical) approach to management, and thus, the panel recommends discussion of ameloblastomas at a multidisciplinary team meeting (tumor board) to ensure optimal management. Furthermore, this tumor would also benefit from a standardized reporting data set. While this data set was prepared for malignancies, the panel also strongly advocates its use for ameloblastoma.

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References

1. Yang R, Liu Z, Gokavarapu S, Peng C, Ji T, Cao W. Recurrence and cancerization of ameloblastoma: multivariate analysis of 87 recurrent craniofacial ameloblastoma to assess risk factors associated with early recurrence and secondary ameloblastic carcinoma. *Chin J Cancer Res*. 2017;29(3):189–195.

2. Agarwal S, Mark J, Xie C, Ghulam E, Patil Y. Survival and prognosis for malignant tumors of odontogenic origin. *Otolaryngol Head Neck Surg*. 2016; 155(1):113–116.

3. Lee RJ, Tong EL, Patel R, Go LA, Christensen RE. Epidemiology, prognostic factors, and management of malignant odontogenic tumors: an analysis of 295 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;120(5):616–621.

4. El Nagar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: IARC; 2017. *World Health Organization Classification of Tumours*; vol 9.

5. Huang JW, Luo HY, Li Q, Li TJ. Primary intraosseous squamous cell carcinoma of the jaws: clinicopathologic presentation and prognostic factors. *Arch Pathol Lab Med*. 2009;133(11):1834–1840.

6. Odell EW, Allen CM, Richardson M. Primary intraosseous carcinoma NOS. In: El Nagar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: IARC Press; 2017:207–209. *World Health Organization Classification of Tumours*; vol 9.

7. Yoon HJ, Hong SP, Lee JI, Lee SS, Hong SD. Ameloblastic carcinoma: an analysis of 6 cases with review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009;108(6):904–913.

8. Goldenberg D, Sciubba J, Koch W, Tufano RP. Malignant odontogenic tumors: a 22-year experience. *Laryngoscope*. 2004;114(10):1770–1774.

9. Hussain O, Rendon AT, Orr RL, Speight PM. Sclerosing odontogenic carcinoma in the maxilla: a rare primary intraosseous carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116(4):e283–e286.

10. Koutlas IG, Allen CM, Warnock GR, Manivel JC. Sclerosing odontogenic carcinoma: a previously unreported variant of a locally aggressive odontogenic neoplasm without apparent metastatic potential. *Am J Surg Pathol*. 2008;32(11): 1613–1619.

11. Hanisch M, Baumhoer D, Elges S, Fröhlich LF, Kleinheinz J, Jung S. Sclerosing odontogenic carcinoma: current diagnostic and management considerations concerning a most unusual neoplasm. *Int J Oral Maxillofac Surg*. 2017; 46(12):1641–1649

12. Hunter KD, Speight PM. The diagnostic usefulness of immunohistochemistry for odontogenic lesions. *Head Neck Pathol*. 2014;8(4):392–399.

13. Bilodeau EA, Weinreb I, Antonescu CR, et al. Clear cell odontogenic carcinomas show EWSR1 rearrangements: a novel finding and a biological link to salivary clear cell carcinomas. *Am J Surg Pathol*. 2013;37(7):1001–1005.

14. Diniz MG, Gomes CC, Guimaraes BV, et al. Assessment of BRAFV600E and SMOF412E mutations in epithelial odontogenic tumours. *Tumour Biol*. 2015; 36(7):5649–5653.

15. Casaroto AR, Toledo GL, Filho JL, Soares CT, Capelari MM, Lara VS. Ameloblastic carcinoma, primary type: case report, immunohistochemical analysis and literature review. *Anticancer Res*. 2012;32(4):1515–1525.

16. Loyola AM, Cardoso SV, de Faria PR, et al. Clear cell odontogenic carcinoma: report of 7 new cases and systematic review of the current knowledge. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;120(4):483–496.

17. Elzay RP. Primary intraosseous carcinoma of the jaws: review and update of odontogenic carcinomas. *Oral Surg Oral Med Oral Pathol*. 1982;54(3):299–303.

18. Loyola AM, Cardoso SV, de Faria PR, et al. Ameloblastic carcinoma: a Brazilian collaborative study of 17 cases. *Histopathology*. 2016;69(4):687–701.

19. Boni P, Sozzi D, Novelli G, Pagni F, Valente G, Bozzetti A. Primary intraosseous squamous cell carcinoma of the jaws: 6 new cases, experience, and literature comparison. *J Oral Maxillofac Surg*. 2016;74(3):541–546.

20. Kruse AL, Zwahlen RA, Gratz KW. New classification of maxillary ameloblastic carcinoma based on an evidence-based literature review over the last 60 years. *Head Neck Oncol*. 2009;1:31.

21. Carlos-Bregni R, Mosqueda-Taylor A, Meneses-García A. Ameloblastic fibrosarcoma of the mandible: report of two cases and review of the literature. *J Oral Pathol Med*. 2001;30(5):316–320.

22. Noordhoek R, Pizer ME, Laskin DM. Ameloblastic fibrosarcoma of the mandible: treatment, long-term follow-up, and subsequent reconstruction of a case. *J Oral Maxillofac Surg*. 2012;70(12):2930–2935.

23. Gilani SM, Raza A, Al-Khafaji BM. Ameloblastic fibrosarcoma: a rare malignant odontogenic tumor. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2014; 131(1):53–56.

24. Ebert CS Jr, Dubin MG, Hart CF, Chalian AA, Shockley WW. Clear cell odontogenic carcinoma: a comprehensive analysis of treatment strategies. *Head Neck*. 2005;27(6):536–542.

25. Zwetyenga N, Pinsolle J, Rivel J, et al. Primary intraosseous carcinoma of the jaws. *Arch Otolaryngol Head Neck Surg*. 2001;127(7):794–797.

26. Arashiyama T, Kodama Y, Kobayashi T, et al. Ghost cell odontogenic carcinoma arising in the background of a benign calcifying cystic odontogenic tumor of the mandible. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(3): e35–e40.

27. Irie T, Ogawa I, Takata T, et al. Sclerosing odontogenic carcinoma with benign fibro-osseous lesion of the mandible: an extremely rare case report. *Pathol Int*. 2010;60(10):694–700.

28. Saluja TS, Hosalkar R. Reconnoitre ameloblastic carcinoma: a prognostic update. *Oral Oncol*. 2018;77:118–124.

29. Bodner L, Manor E, Shear M, van der Waal I. Primary intraosseous squamous cell carcinoma arising in an odontogenic cyst: a clinicopathologic analysis of 116 reported cases. *J Oral Pathol Med*. 2011;40(10):733–738.

30. Odell E, Baumhoer D, Carlos R, et al. *Malignant Odontogenic Tumours, Histopathology Reporting Guide*. 1st ed. Sydney, Australia: International Collaboration on Cancer Reporting; 2018.

31. Bullock M, Beitler JJ, Carlson DL, et al. *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours: Histopathology Reporting Guide*. 1st ed. Sydney, Australia: International Collaboration on Cancer Reporting; 2018.