COLLEGE of AMERICAN PATHOLOGISTS

ARCHIVES
of Pathology & Laboratory Medicine

EARLY ONLINE RELEASE

Note: This article was posted on the *Archives* Web site as an Early Online Release. Early Online Release articles have been peer reviewed, copyedited, and reviewed by the authors. Additional changes or corrections may appear in these articles when they appear in a future print issue of the *Archives*. Early Online Release articles are citable by using the Digital Object Identifier (DOI), a unique number given to every article. The DOI will typically appear at the end of the abstract.

The DOI for this manuscript is doi: 10.5858/arpa.2018-0404-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 Carcinomas of the Nasal Cavity and Paranasal Sinuses

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

Alessandro Franchi, MD; Justin A. Bishop, MD; Hedley Coleman, MD; Uta Flucke, MD; Lisa F. Licitra, MD; José Luis Llorente Pendás, MD; Edward B. Stelow, MD; Mary Toner, MD; Ilan Weinreb, MD; Bruce M. Wenig, MD; Lester D. R. Thompson, MD

• The International Collaboration on Cancer Reporting was established to internationally unify and standardize the pathologic reporting of cancers based on collected evidence, as well as to allow systematic multi-institutional intercountry data collection to guide cancer care in the future. This data set has been developed by the collaborative efforts of an international multidisciplinary panel of experts involved in the care of patients with carcinomas of the nasal cavity and paranasal sinuses (sinonasal tract). The nasal cavity and paranasal sinuses (including frontal, sphenoid, ethmoid, and maxillary sinuses) comprise a very complex anatomic area of the head and neck, affected by a sometimes bewildering array of neoplasms. Management of malignancies in this anatomic region involves complex surgery because of the anatomic confines and close proximity to many vital structures. Given a multidisciplinary approach, the standardized reporting of the carcinomas that develop in this anatomic region include both required (core) and recommended (noncore) elements in pathology reporting in order to be able to identify critical prognostic factors, often requiring clinical and radiologic correlation. A summary of the International Collaboration on Cancer Reporting guidelines and clinical relevant elements, along with additional explanatory notes, are provided, based on evidentiary support from the literature, set in the context of practical application.

(*Arch Pathol Lab Med*. doi: 10.5858/arpa.2018-0404-SA)

Sinonasal malignancies are rare and aggressive tumors, with an incidence of less than 1 case per 100 000 population annually, representing 3% to 5% of all head and neck cancers.[1–3] They occur predominately in adult male patients and present with nonspecific symptoms that are often indistinguishable from inflammatory diseases. Thus, the diagnosis is often delayed with the tumor in locally advanced stage. In comparison with other malignancies of the head and neck, an elevated fraction of sinonasal carcinomas can be attributed to occupational exposures, including wood and leather dusts for intestinal-type adenocarcinoma or to several chemical substances (glues, formaldehyde, chrome, nickel, and compounds used in the textile industry) for squamous cell carcinoma. Sinonasal neuroendocrine carcinoma may also arise in the setting of previous high-dose radiotherapy. Finally, human papillomavirus (HPV) is emerging as an important etiologic factor in a subset of sinonasal carcinomas.

A comprehensive pathologic report is essential for cancer diagnosis, staging, prognostication, and optimal therapeutic decision-making. Moreover, standardized procedures enable reliable data collection, cohort stratification, and research, especially in rare cancers.

To these aims, a standardized data set ensures that histopathology reports include all relevant information and present it in a concise and consistent format that conforms to international standards. The International Collaboration

Accepted for publication September 27, 2018.

From the Department of Translational Research, University of Pisa, Pisa, Italy (Dr Franchi); the Department of Pathology, University of Texas Southwestern Medical Center, Dallas (Dr Bishop); the Institute of Clinical Pathology and Medical Research, Westmead Hospital, Sydney, Australia (Dr Coleman); the Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands (Dr Flucke); the Head and Neck Medical Oncology Department, Fondazione International Collaboration on Cancer Reporting Istituto Nazionale dei Tumori, and University of Milan, Milan, Italy (Dr Licitra); the Department of Otolaryngology, Instituto Universitario de Oncología del Principado de Asturias, Centro de Investigación Biomédica en Red de Cancer, Hospital Universitario Central de Asturias, Oviedo, Spain (Dr Llorente Pendás); the Department of Pathology, University of Virginia, Charlottesville (Dr Stelow); St James and Dublin Dental Hospitals and Trinity College, Sir Patrick Dunne Research Laboratory, and St James Hospital, Dublin, Ireland (Dr Toner); the Department of Pathology, University Health Network, Toronto, Ontario, Canada (Dr Weinreb); the Department of Anatomic Pathology, Moffitt Cancer Center, Tampa, Florida (Dr Wenig); and the Department of Pathology, Southern California Permanente Medical Group, Woodland Hills Medical Center, Woodland Hills (Dr Thompson).

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Lester D. R. Thompson, MD, Department of Pathology, Southern California Permanente Medical Group, Woodland Hills Medical Center, 5601 De Soto Avenue, Woodland Hills, CA 91365 (email: Lester.D.Thompson@kp.org).

on Cancer Reporting (ICCR) was established in 2011 through a collaboration between the College of American Pathologists, the Canadian Association of Pathologists-Association Canadienne des Pathologists 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. Furthermore, for this data set, members of the authoring panel were chosen from the additional sponsoring organizations: 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. The ICCR aims to produce globally standardized, evidence-based reporting data sets for various organ systems by harnessing international experience and expertise.

The sinonasal tract has a very complex anatomy, with numerous vital structures housed within a relatively confined and limited space. Familiarity with the anatomy, in addition to the diagnoses of the neoplasms of this region, are important for staging and prognostic purposes. Thus, the international collaborative effort achieved by the ICCR is critical for the reporting of carcinomas of the sinonasal tract to ensure international uniformity in pathologic examination and to facilitate multi-institutional and cross-regional data collection for improved patient management. The ICCR data sets include core and noncore elements. The core elements are required, considered essential for the clinical management and prognosis or staging of the neoplasms. The noncore elements are recommended as good clinical practice but may not be clinically validated or used in management decisions at this time. The ICCR data set includes the minimum reporting requirements for the reporting of resection and biopsy specimens of mucosal epithelial malignancies of the nasal cavities and paranasal sinuses.[6–9] There is significant variation in the strength of the evidence available for these tumors, with most data derived from retrospective case series because of the rare nature of primary neoplasms. Sinonasal melanomas, sarcomas, and hematolymphoid tumors are excluded. Further, this process was conducted to incorporate the fourth series of the World Health Organization (WHO) *Classification of Head and Neck Tumours* and the 8th edition of the Union for International Cancer Control cancer staging system.[4]

DATA SET ELEMENTS

Core (Required) Elements

Neoadjuvant Therapy.—Patients with locally advanced sinonasal carcinomas may be treated with preoperative chemotherapy or concurrent chemoradiotherapy protocols that may result in a significant improvement in survival in selected patients.[5–9] Such treatments may significantly alter the gross and microscopic appearance of the tumor and result in difficulties in tumor typing and grading. Although quantification of the extent of response is currently considered not relevant for clinical purposes, specimens should be extensively sampled, and changes presumably induced by treatment should be reported. Type of (chemo) therapy, number of cycles, interval between last cycle of chemotherapy, and local regional treatment initiation can also be annotated if available.

Operative Procedure.—Different options are currently available for the surgical treatment of sinonasal malignancies, which may be chosen according to histopathology, extent of the lesion, and experience of the surgeon. Surgical approaches include craniofacial resections (open or endoscopic), endoscopic endonasal resections, and combined approaches.[10–12] This results in a wide range of surgical specimens submitted for histopathologic analysis (Figure 1).

Specimens Submitted.—Specimens from endoscopic surgery typically consist of fragmented material that should be properly labeled at the time of surgery, including a description of the anatomic site and type of tissue submitted (tumor, margin, or other). Because of the inherent orientation difficulty in samples, separately submitted margins, properly identified and labeled, are encouraged. Surgical resection specimens consist most often of the maxillary bone and adjacent anatomic structures removed according to the extent of the primary tumor (Figure 2).[13]

Tumor Site.—The sinonasal tract consists of the nasal cavity and the paired paranasal sinuses (maxillary, ethmoid, frontal, and sphenoid). The nasal cavity can be further subdivided into the nasal septum, floor, lateral wall, and vestibule. Among sinonasal tract carcinomas, the most common site of tumor origin is the maxillary sinus, followed by the nasal cavity and ethmoid sinus. It is rare for carcinomas to arise from the frontal or sphenoid sinuses.[14–18]

The precise tumor site within the sinonasal tract is important to record. This is not always easy to determine, because some exophytic tumors may almost entirely fill the nasal fossa without any infiltration, and only involve a relatively limited portion of the mucosa (Figure 3). Second, there is prognostic importance to the tumor location. For example, carcinomas primary to the nasal cavity have been shown to have an improved prognosis compared with carcinomas primary to the paranasal sinuses, likely because nasal carcinomas give rise to symptoms (eg, nasal obstruction or epistaxis) and reach clinical attention earlier in the disease course. Among maxillary sinus carcinomas, those arising from the anterior-inferior portion have a better prognosis than those arising from the superior-posterior portion, likely because the latter group more easily involves the skull base and/or orbit.[19,20] Interestingly, primary maxillary carcinomas have a behavior different from carcinomas originating in the oral cavity and secondarily involving the maxilla. Further, there are separate staging systems for the 2 major anatomic sites: maxillary sinus and nasal cavity and/or ethmoid sinus.[4] Finally, certain carcinomas are closely associated with specific sinonasal subsites. For example, intestinal-type adenocarcinomas and neuroendocrine carcinomas occur most often in the ethmoid sinuses, whereas squamous cell carcinoma occurs most often in the maxillary sinuses.[21–23]

It is recognized that some carcinomas, particularly highly aggressive types like sinonasal undifferentiated carcinoma or nuclear protein in testis (NUT) carcinoma, usually affect more than 1 subsite. In this case, every affected site should be specified in the report.

Tumor Dimensions.—The maximum diameter of the tumor should ideally be assessed on the unfixed specimen to avoid size underestimation resulting from formalin fixation–induced shrinkage. Care should be taken not to overestimate tumor size by including areas of adjacent nonneoplastic tissue. The gross assessment of tumor size should be

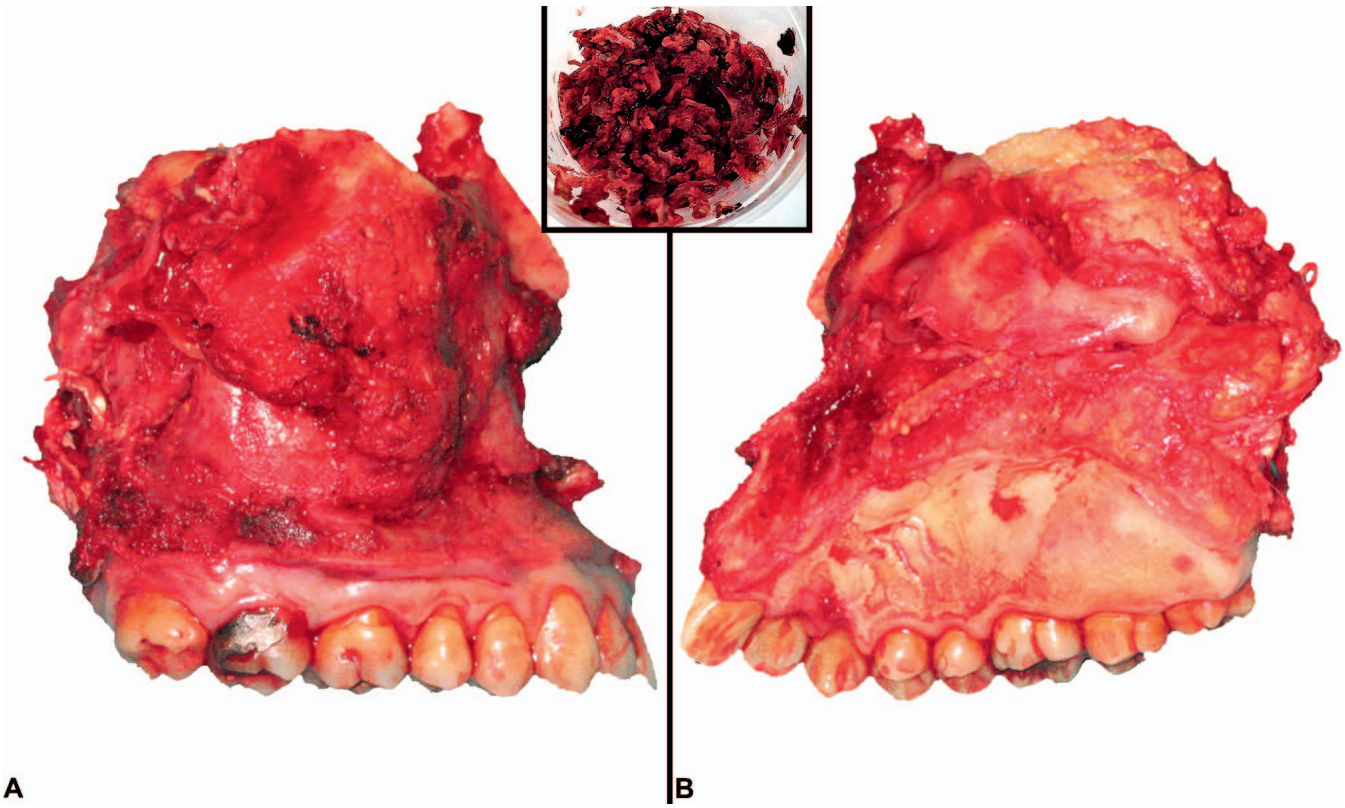


Figure 1. *Resection specimens of sinonasal carcinomas. Specimen from a hemimaxillectomy (A, lateral view; B, medial view) and fragmented material from an endoscopic procedure (inset).*

confirmed microscopically, and in cases where nonneoplastic tissue has been mistakenly incorporated into the tumor measurement, tumor size should be adjusted accordingly. If tumor dimensions are estimated only microscopically, then "at least" should be added to indicate that the measurement is an underestimation resulting from fixation and tissue processing. The option "cannot be assessed" may be used when the tumor is submitted in fragments, as in endoscopic resections. In these cases, radiographic imaging may also be considered to determine tumor dimensions.

Histologic Tumor Type.—All sinonasal tract carcinomas should be given a type based on the most recent edition of the WHO's *Classification of Head and Neck Tumours*,[24] currently from the 4th edition (Table 1). Importantly, because of an effort to reduce duplication and only including an entity once in the book, not every histologic sinonasal tract tumor is described.

The sinonasal tract gives rise to a very large and diverse group of carcinomas, which may arise from the surface epithelium or the underlying seromucinous glands. Squamous cell carcinoma is, by far, the most common sinonasal malignancy, and it is subdivided primarily into keratinizing and nonkeratinizing subtypes (Figure 4, A). Additional subtypes (eg, spindle cell, basaloid, adenosquamous) are rare but should be noted if present. Uncommon carcinoma variants (such as sinonasal undifferentiated carcinoma, NUT carcinoma) are also included, whereas adenocarcinomas are separated into salivary gland types, intestinal types (Figure 5), and nonintestinal types, among other less common variants. Correct classification results in appropriate treatment, correlated with overall patient outcome. These classifications will take additional importance as targeted, molecular-based therapies become more widespread.[25–27]

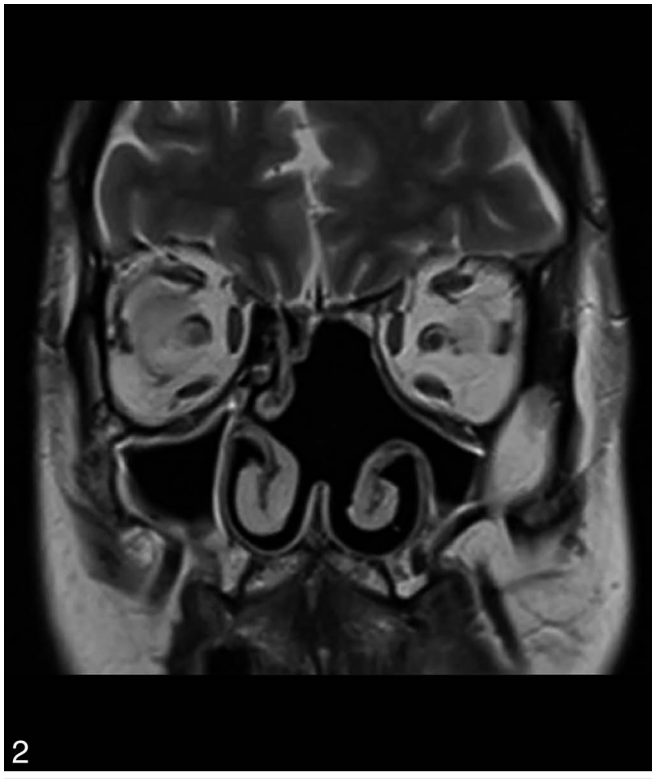
Histologic Tumor Grade.—A 3-tiered grading system based on degree of differentiation is used for squamous cell carcinoma, and it is also applied to some sinonasal adenocarcinomas, as well selected salivary gland neoplasms (eg, adenoid cystic carcinoma, mucoepidermoid carcinoma,

Table 1. World Health Organization Classification of Sinonasal Tract Carcinomas[a]

Descriptor	ICD-O Codes
Keratinizing squamous cell carcinoma	8071/3
Nonkeratinizing squamous cell carcinoma	8072/3
Spindle cell squamous cell carcinoma	8074/3
Lymphoepithelial carcinoma	8082/3
Sinonasal undifferentiated carcinoma	8020/3
NUT carcinoma	8023/3
Neuroendocrine carcinomas	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Adenocarcinomas	
Intestinal-type adenocarcinoma	8144/3
Non–intestinal-type adenocarcinoma	8140/3

Abbreviations: ICD-O, International Classification of Diseases for Oncology; NUT, nuclear protein in testis.

[a] Reproduced with permission from World Health Organization/International Agency for Research on Cancer (IARC).[24] The morphology codes are from the ICD-O. Behavior is coded /3 for malignant tumors.



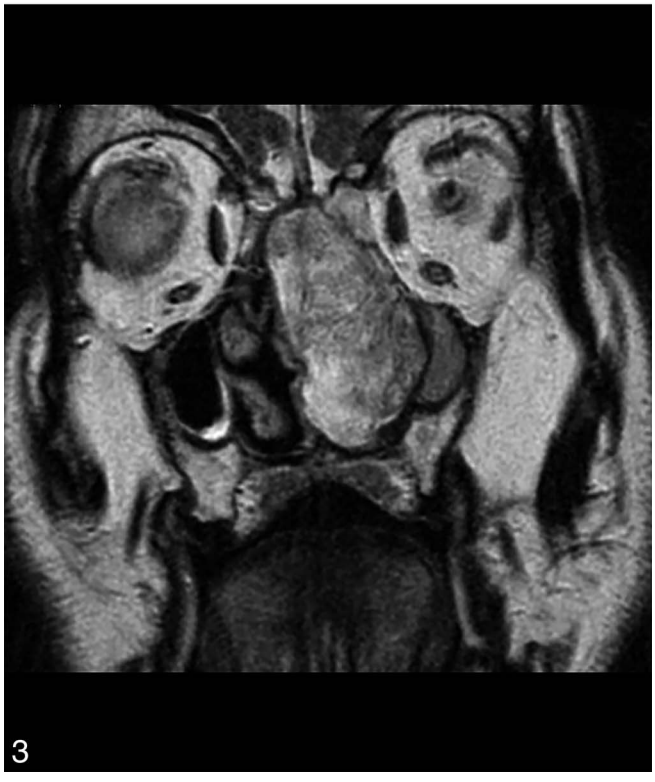


Figure 2. *T2-weighted magnetic resonance imaging image showing a postoperative status of a sinonasal adenocarcinoma without any residual tumor.*

Figure 3. *T2-weighted magnetic resonance imaging image showing an exophytic adenocarcinoma filling almost entirely the nasal fossa but exclusively implanted in the olfactory area.*

etc). Undifferentiated tumors should be considered high grade. Minor salivary gland neoplasms have grading systems unique to selected tumors,[28,29] whereas other adenocarcinomas are assigned a grade based on necrosis and mitotic activity.[30,31] Nearly all sinonasal tract neuroendocrine carcinomas are high grade.[32]

Bone/Cartilage Invasion.—Bone invasion is a frequent finding in sinonasal carcinomas. Both bone erosion and destruction are reported, but sometimes findings from radiographic studies may need to be incorporated into this evaluation, because limited biopsies may not include enough material to yield a meaningful interpretation. In resections, it is strongly recommended that histologic sections be taken from the areas of maximum bone involvement (after appropriate decalcification).

Perineural Invasion.—The frequency of perineural invasion (including named nerves) in sinonasal carcinomas is lower than it is in other head and neck sites, and it varies according to the histologic subtype, identified most frequently in adenoid cystic, sinonasal undifferentiated, squamous cell, and NUT carcinomas, respectively.[33,34] In sinonasal carcinomas, perineural invasion is associated with a high rate of positive margins, with maxillary origin, and with previous surgical treatment, but it is not an independent prognostic factor.[33]

Lymphovascular Invasion.—Lymphovascular invasion includes neoplastic cells within an endothelial-lined space, either lymphatic or venous, and it must be distinguished from retraction artifacts. Immunohistochemical staining for an endothelial marker may help in this distinction in selected cases. Lymphovascular invasion is reported in up to 60% of sinonasal squamous cell carcinomas, but its clinical significance remains elusive.[33]

Margin Status.—Complete tumor resection with negative surgical margins poses a significant challenge in sinonasal carcinomas, given the proximity to critical anatomic structures. The presence of residual microscopic disease has been reported with high frequency in cases managed both by open and by endoscopic surgical techniques.[35,36] In a large series of sinonasal squamous cell carcinomas treated with surgery, 16% had microscopic residual disease and 13% had macroscopic positive resection margins.[37] A negative surgical margin is associated with improved overall survival in retrospective studies for both open and endoscopic approaches.[37,38]

Ideally, the resection specimen should be oriented by the surgeon, including sutures or other annotations, best achieved by direct communication between the surgeon and pathologist, supplemented with specimen photography before and after sectioning. Failing this, the margins should be labeled by the surgeon and/or illustrated with a diagram. Specimens from endoscopic tumor resections should also be labeled and oriented, if possible. If the margins are sent separately, for frozen section or otherwise, identification of their site in relation to the resection specimen should be clarified by the surgeon. The surgical margins—mucosal, soft tissue, bone, and deep—should be thoroughly sampled, because additional therapy is often predicated on margin status. Because of limited data, a clear margin ranges from 3 to 7 mm, with 5 mm generally associated with a better prognosis,[39–43] although recurrence is seen in up to 25% of patients with a clear margin.[41,42] Depending on stage and other factors, a narrower margin may be adequate.[44,45] When the complex anatomy is taken into consideration, a "pushing" border into the periorbital tissues may not

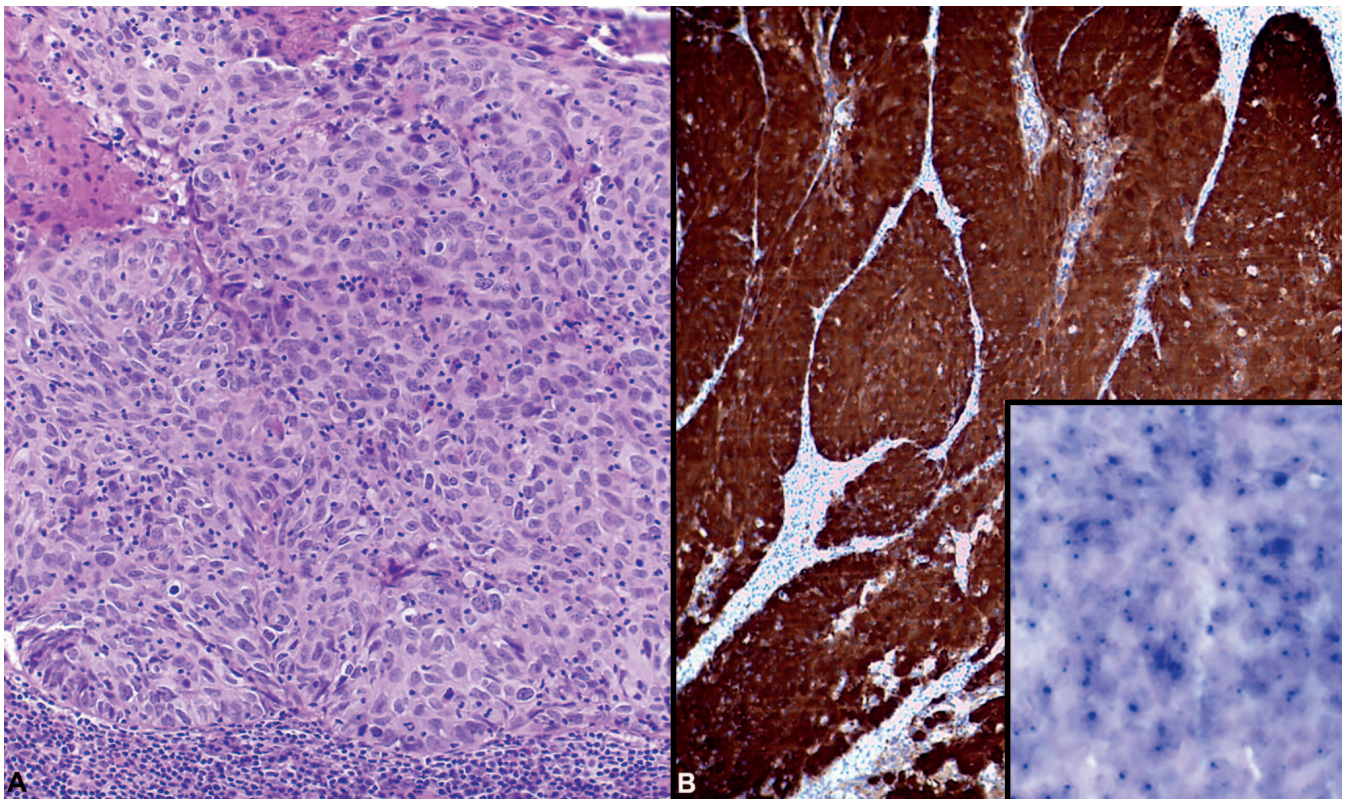


Figure 4. *Nonkeratinizing squamous cell carcinoma. The tumor consists of nonkeratinizing atypical squamoid cells, with peripheral palisading of tumor cell nuclei (A). These tumors are frequently human papillomavirus (HPV) related, and thus positive for both p16 (B) and high-risk HPV by DNA in situ hybridization (inset) (hematoxylin-eosin, original magnification ×300 [A]; original magnifications ×150 [B] and ×400 [inset]).*

require orbital exenteration to achieve a 5 mm margin, if it is a low-grade neoplasm (Figure 6). Thus, margin status is one parameter of many used in treatment and prognostication.[46–48] Most studies also consider carcinoma in situ/high-grade dysplasia as a positive margin.[40] The presence of dysplasia at the margin is associated with a significant risk of local recurrence[49] and development of a second primary.[50] Thus, this information, including distance to the margin from invasive and in situ/dysplasia, is reported.

Pathologic Staging.—Staging of sinonasal cancer remains a difficult task because of the complexity of the anatomic site and the heterogeneity of the tumor types. Nevertheless, an accurate staging is essential for treatment and prognosis implications.[51] The data set is based on the T category of the 8th edition of the Union for International Cancer Control staging system, which is identical to that of the previous edition (Table 2). Tumors located in the maxillary sinus are separated from those arising in the nasal cavity and ethmoid sinus. The pT stage is based on the involved anatomic sites, as well as invasion of the bone, orbit, dura, and other structures. Most sinonasal carcinomas present in advanced T category (T3 and T4). It is worth noting that a number of studies have reported significant discrepancies between clinical and pathological T categorization.[52,53] In particular, imaging is not sufficiently accurate in the assessment of invasion of the orbit, the skull base, frontal, or sphenoid sinuses.[52] Thus, careful histopathologic assessment is essential for a correct staging of sinonasal carcinomas. Finally, when neck lymph node dissections are included as part of the surgical specimen, a separate, linked data set for *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours* has to be completed.[70]

Noncore (Recommended) Elements

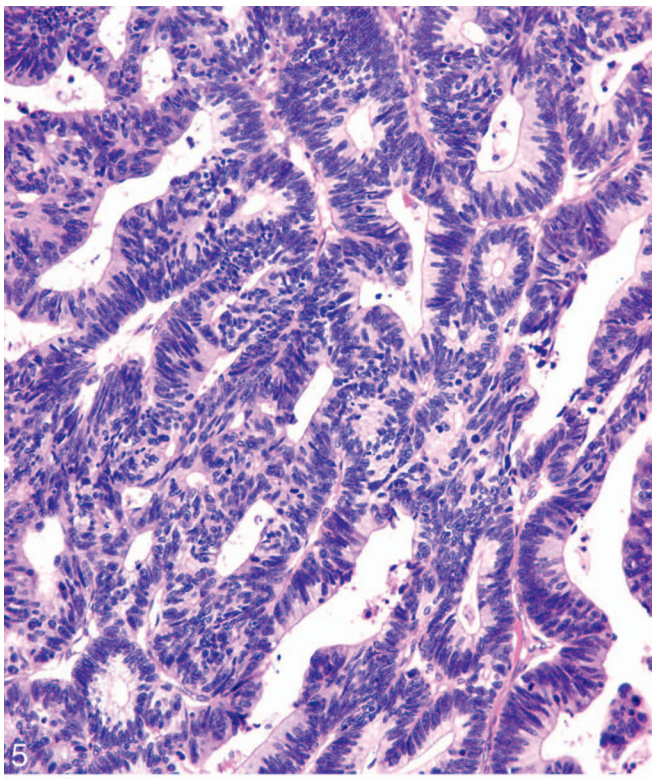
Tumor Focality.—Sinonasal carcinomas may present with multiple synchronous lesions located in different anatomic subsites.[36] Similar to other data sets for reporting carcinomas of the head and neck, multiple, different histologic primaries are separately reported. The term "multifocal" may be used for microscopic foci of in situ or invasive carcinoma adjacent to the primary.

Coexistent Pathology.—A number of histopathologic findings may be associated with sinonasal tract carcinomas. The presence of squamous dysplasia/carcinoma in situ can be used as evidence for histologic classification of the tumor. This is especially true with spindle cell carcinoma or other variants of squamous cell carcinoma that arise from and are often associated with overlying squamous dysplasia/carcinoma in situ.[54]

It is well recognized that a subset of sinonasal squamous cell carcinomas, and less frequently other histologic types, originate from preexisting sinonasal papillomas (formerly Schneiderian papilloma). These tumors represent a group of sinonasal carcinomas characterized by specific genetic alterations and oncogenic mechanisms.[55–57]

Finally, foci of intestinal metaplasia of the adjacent sinonasal respiratory epithelium can be detected in about 25% of intestinal-type adenocarcinomas.[58,59]

Ancillary Studies.—Ancillary studies are variably needed for the diagnosis of specific entities at this site. For example, NUT carcinoma is recognized by the presence of



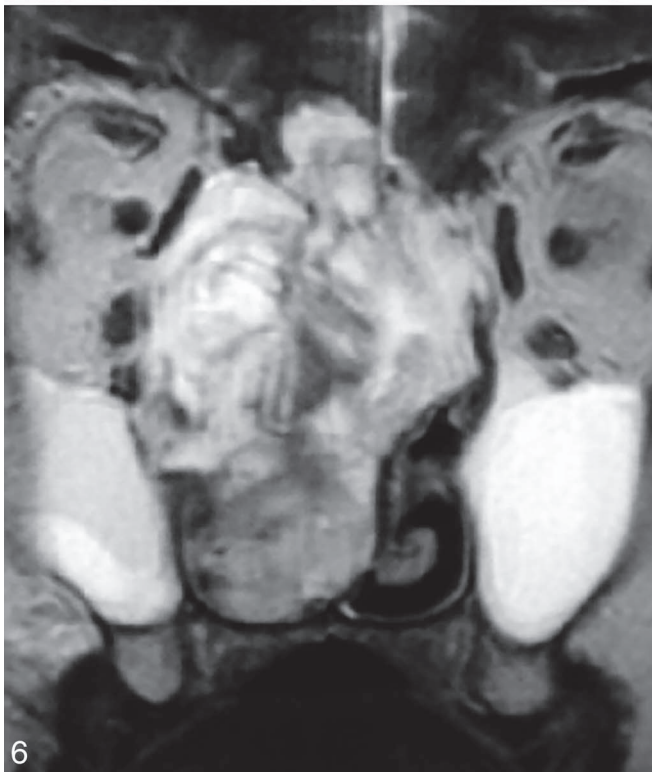


Figure 5. *Sinonasal intestinal-type adenocarcinoma arising in a woodworker. Histologically, the tumor is identical to a colonic adenocarcinoma (hematoxylin-eosin, original magnification ×300).*

Figure 6. *T2-weighted magnetic resonance imaging image showing a sinonasal adenocarcinoma pushing but not infiltrating the orbit. However, there is infiltration of the dura mater into the anterior cranial fossa.*

Table 2. Union for International Cancer Control (UICC) TNM 8th Edition Pathologic Staging of Nasal Cavity and Paranasal Sinuses[a]

pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Carcinoma in situ
Maxillary sinus	
pT1	Tumor limited to the mucosa with no erosion or destruction of bone
pT2	Tumor causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
pT3	Tumor invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, or ethmoid sinuses
pT4	Moderately advanced or very advanced local disease
pT4a	Tumor invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
pT4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus
Nasal cavity and ethmoid sinus	
pT1	Tumor restricted to one subsite of nasal cavity or ethmoid sinus, with or without bony invasion
pT2	Tumor involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion
pT3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
pT4	Moderately advanced or very advanced local disease
pT4a	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
pT4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

[a] Reproduced with permission from the UICC in Brierley et al[4]: Brierley JD, Gospodarowicz MK, Wittekind C. *UICC TNM Classification of Malignant Tumours*. 8th ed. Chichester, UK: Wiley-Blackwell; 2017.

nuclear protein in testis (*NUTM1*) gene rearrangement or positivity with the C52 monoclonal antibody against NUT protein.[60] The diagnosis of HPV-related multiphenotypic sinonasal carcinoma requires HPV-specific testing as part of the tumor definition (Figure 4, B),[61] whereas for the diagnosis of *SMARCB1* (INI1)–deficient carcinoma, loss of nuclear immunohistochemical staining for INI1 is required.[62,63]

In poorly differentiated malignancies, immunohistochemical markers can be used to assign a tumor to a specific category. Useful markers of squamous differentiation are p40, p63, and cytokeratin 5/6, whereas markers of intestinal differentiation, such as cytokeratin 20 and CDX2, help in the diagnosis of intestinal-type adenocarcinoma. Neuroendo-

crine carcinomas can be diagnosed with the support of positive reactivity with at least 1 neuroendocrine marker.

A subset of sinonasal carcinomas appear to be related to high-risk HPV, including nonkeratinizing squamous cell carcinoma, basaloid squamous cell carcinoma, papillary squamous cell carcinoma, adenosquamous carcinoma, and conventional keratinizing squamous cell carcinoma.[64–68] However, the clinical significance of these findings is still debated, and HPV testing is currently considered investigational in this context.

CONCLUSIONS

In summary, the contents of the ICCR data set for reporting carcinomas of the nasal cavity and paranasal sinuses were reviewed. In such a highly heterogeneous group of rare tumors, an internationally agreed-upon pathology data set is important to facilitate data collection and comparison, ensuring that all clinically relevant information is included.

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 their exceptional organizational and editing contributions. The views expressed are those of the authors solely.

References

1. Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. *Head Neck*. 2012;34(6):877–885.

2. Dutta R, Dubal PM, Svider PF, Liu JK, Baredes S, Eloy JA. Sinonasal malignancies: a population-based analysis of site-specific incidence and survival. *Laryngoscope*. 2015;125(11):2491–2497.

3. Van Dijk BA, Gatta G, Capocaccia R, Pierannunzio D, Strojan P, Licitra L; RARECARE Working Group. Rare cancers of the head and neck area in Europe. *Eur J Cancer*. 2012;48(6):783–796.

4. Brierley JD, Gospodarowicz MK, Wittekind C, eds. *UICC TNM Classification of Malignant Tumours*. 8th ed. Chichester, UK: Wiley-Blackwell; 2017.

5. Nibu K, Sugasawa M, Asai M, et al. Results of multimodality therapy for squamous cell carcinoma of maxillary sinus. *Cancer*. 2002;94(5):1476–1482.

6. Samant S, Robbins KT, Vang M, Wan J, Robertson J. Intra-arterial cisplatin and concomitant radiation therapy followed by surgery for advanced paranasal sinus cancer. *Arch Otolaryngol Head Neck Surg*. 2004;130(8):948–955.

7. Madison ML 2nd, Sorenson JM, Samant S, Robertson JH. The treatment of advanced sinonasal malignancies with pre-operative intra-arterial cisplatin and concurrent radiation. *J Neurooncol*. 2005;72(1):67–75.

8. Licitra L, Suardi S, Bossi P, et al. Prediction of TP53 status for primary cisplatin, fluorouracil, and leucovorin chemotherapy in ethmoid sinus intestinal-type adenocarcinoma. *J Clin Oncol*. 2004;22(24):4901–4906.

9. Bossi P, Saba NF, Vermorken JB, et al. The role of systemic therapy in the management of sinonasal cancer: a critical review. *Cancer Treat Rev*. 2015;41(10):836–843.

10. Meccariello G, Deganello A, Choussy O, et al. Endoscopic nasal versus open approach for the management of sinonasal adenocarcinoma: a pooled-analysis of 1826 patients. *Head Neck*. 2016;38(suppl 1):E2267–E2274.

11. Roxbury CR, Ishii M, Richmon JD, Blitz AM, Reh DD, Gallia GL. Endonasal endoscopic surgery in the management of sinonasal and anterior skull base malignancies. *Head Neck Pathol*. 2016;10(1):13–22.

12. Llorente JL, Lopez F, Suarez C, Hermsen MA. Sinonasal carcinoma: clinical, pathological, genetic and therapeutic advances. *Nat Rev Clin Oncol*. 2014;11(8):460–472.

13. Slootweg PJ. Complex head and neck specimens and neck dissections: how to handle them. *J Clin Pathol*. 2005;58(3):243–248.

14. Ansa B, Goodman M, Ward K, et al. Paranasal sinus squamous cell carcinoma incidence and survival based on Surveillance, Epidemiology, and End Results data, 1973 to 2009. *Cancer*. 2013;119(14):2602–2610.

15. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. *Clin Otolaryngol Allied Sci*. 1979;4(6):431–456.

16. Sanghvi S, Khan MN, Patel NR, Yeldandi S, Baredes S, Eloy JA. Epidemiology of sinonasal squamous cell carcinoma: a comprehensive analysis of 4994 patients. *Laryngoscope*. 2014;124(1):76–83.

17. Takahashi Y, Bell D, Agarwal G, et al. Comprehensive assessment of prognostic markers for sinonasal squamous cell carcinoma. *Head Neck*. 2014;36(8):1094–1102.

18. Smith SP, Russell JL, Chen NW, Kuo YF, Resto VA. Sinonasal carcinoma: racial and ethnic disparities in survival–a review of 4714 patients. *Otolaryngol Head Neck Surg*. 2015;153(4):551–560.

19. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress?: a series of 220 patients and a systematic review. *Cancer*. 2001;92(12):3012–3029.

20. Thorup C, Sebbesen L, Dano H, et al. Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995-2004. *Acta Oncol*. 2010;49(3):389–394.

21. Klintenberg C, Olofsson J, Hellquist H, Sokjer H. Adenocarcinoma of the ethmoid sinuses: a review of 28 cases with special reference to wood dust exposure. *Cancer*. 1984;54(3):482–488.

22. Mitchell EH, Diaz A, Yilmaz T, et al. Multimodality treatment for sinonasal neuroendocrine carcinoma. *Head Neck*. 2012;34(10):1372–1376.

23. Smith SR, Som P, Fahmy A, Lawson W, Sacks S, Brandwein M. A clinicopathological study of sinonasal neuroendocrine carcinoma and sinonasal undifferentiated carcinoma. *Laryngoscope*. 2000;110(10, pt 1):1617–1622.

24. El Naggar A, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: IARC; 2017.

25. Stathis A, Zucca E, Bekradda M, et al. Clinical response of carcinomas harboring the BRD4-NUT oncoprotein to the targeted bromodomain inhibitor OTX015/MK-8628. *Cancer Discov*. 2016;6(5):492–500.

26. Franchi A, Innocenti DR, Palomba A, et al. Low prevalence of K-RAS, EGF-R and BRAF mutations in sinonasal adenocarcinomas: implications for anti-EGFR treatments. *Pathol Oncol Res*. 2014;20(3):571–579.

27. Hoeben A, van de Winkel L, Hoebers F, et al. Intestinal-type sinonasal adenocarcinomas: the road to molecular diagnosis and personalized treatment. *Head Neck*. 2016;38(10):1564–1570.

28. Seethala RR. Histologic grading and prognostic biomarkers in salivary gland carcinomas. *Adv Anat Pathol*. 2011;18(1):29–45.

29. Heffner DK, Hyams VJ, Hauck KW, Lingeman C. Low-grade adenocarcinoma of the nasal cavity and paranasal sinuses. *Cancer*. 1982;50(2):312–322.

30. Stelow EB, Brandwein-Gensler M, Franchi A, Nicolai P, Wenig BM. Non-intestinal-type adenocarcinoma. In: El Nagar A, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: IARC; 2017.

31. Stelow EB, Franchi A, Wenig BM. Intestinal-type adenocarcinoma. In: El Nagar A, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: IARC; 2017.

32. Turri-Zanoni M, Maragliano R, Battaglia P, et al. The clinicopathological spectrum of olfactory neuroblastoma and sinonasal neuroendocrine neoplasms: refinements in diagnostic criteria and impact of multimodal treatments on survival. *Oral Oncol*. 2017;74:21–29.

33. Gil Z, Carlson DL, Gupta A, et al. Patterns and incidence of neural invasion in patients with cancers of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg*. 2009;135(2):173–179.

34. Hanna E, Vural E, Prokopakis E, Carrau R, Snyderman C, Weissman J. The sensitivity and specificity of high-resolution imaging in evaluating perineural spread of adenoid cystic carcinoma to the skull base. *Arch Otolaryngol Head Neck Surg*. 2007;133(6):541–545.

35. Batra PS, Luong A, Kanowitz SJ, et al. Outcomes of minimally invasive endoscopic resection of anterior skull base neoplasms. *Laryngoscope*. 2010;120(1):9–16.

36. Cantu G, Solero CL, Mariani L, et al. Intestinal type adenocarcinoma of the ethmoid sinus in wood and leather workers: a retrospective study of 153 cases. *Head Neck*. 2011;33(4):535–542.

37. Cracchiolo JR, Patel K, Migliacci JC, et al. Factors associated with a primary surgical approach for sinonasal squamous cell carcinoma. *J Surg Oncol*. 2017;117(4):756–764.

38. Ganly I, Patel SG, Singh B, et al. Craniofacial resection for malignant paranasal sinus tumors: report of an International Collaborative Study. *Head Neck*. 2005;27(7):575–584.

39. Hinni ML, Ferlito A, Brandwein-Gensler MS, et al. Surgical margins in head and neck cancer: a contemporary review. *Head Neck*. 2013;35(9):1362–1370.

40. Anderson CR, Sisson K, Moncrieff M. A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. *Oral Oncol*. 2015;51(5):464–469.

41. Brandwein-Gensler M, Teixeira MS, Lewis CM, et al. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol*. 2005;29(2):167–178.

42. Liao CT, Chang JT, Wang HM, et al. Analysis of risk factors of predictive local tumor control in oral cavity cancer. *Ann Surg Oncol*. 2008;15(3):915–922.

43. Dik EA, Willems SM, Ipenburg NA, Adriaansens SO, Rosenberg AJ, van Es RJ. Resection of early oral squamous cell carcinoma with positive or close margins: relevance of adjuvant treatment in relation to local recurrence: margins of 3 mm as safe as 5 mm. *Oral Oncol*. 2014;50(6):611–615.

44. Ch'ng S, Corbett-Burns S, Stanton N, et al. Close margin alone does not warrant postoperative adjuvant radiotherapy in oral squamous cell carcinoma. *Cancer*. 2013;119(13):2427–2437.

45. Alicandri-Ciufelli M, Bonali M, Piccinini A, et al. Surgical margins in head and neck squamous cell carcinoma: what is 'close'? *Eur Arch Otorhinolaryngol*. 2013;270(10):2603–2609.

46. Bradley PJ, MacLennan K, Brakenhoff RH, Leemans CR. Status of primary tumour surgical margins in squamous head and neck cancer: prognostic implications. *Curr Opin Otolaryngol Head Neck Surg*. 2007;15(2):74–81.

47. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. *Int J Oral Maxillofac Surg*. 2003;32(1):30–34.

48. Dillon JK, Brown CB, McDonald TM, et al. How does the close surgical margin impact recurrence and survival when treating oral squamous cell carcinoma? *J Oral Maxillofac Surg*. 2015;73(6):1182–1188.

49. Jerjes W, Upile T, Petrie A, et al. Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients. *Head Neck Oncol*. 2010;2:9.

50. Slootweg PJ, Hordijk GJ, Schade Y, van Es RJ, Koole R. Treatment failure and margin status in head and neck cancer: a critical view on the potential value of molecular pathology. *Oral Oncol*. 2002;38(5):500–503.

51. Kreppel M, Amir Manawi NN, Scheer M, et al. Prognostic quality of the Union Internationale Contre le Cancer/American Joint Committee on Cancer TNM classification, 7th edition, for cancer of the maxillary sinus. *Head Neck*. 2015;37(3):400–406.

52. Mortuaire G, Camous D, Vandenhende-Szymanski C, Dubrulle F, Chevalier D. Local extension staging of sinonasal tumours: retrospective comparison between CT/MRI assessment and pathological findings. *Clin Otolaryngol*. 2017; 42(5):988–993.

53. Lee DJ, Lee MJ, Kwon KH, Chung EJ, Yoon DY, Rho YS. Discrepancy between preoperative MRI evaluation and intraoperative or postoperative pathological findings for the extent of local invasion in maxillary squamous cell carcinoma. *Int J Oral Maxillofac Surg*. 2014;43(6):674–679.

54. Thompson LD, Wieneke JA, Miettinen M, Heffner DK. Spindle cell (sarcomatoid) carcinomas of the larynx: a clinicopathologic study of 187 cases. *Am J Surg Pathol*. 2002;26(2):153–170.

55. Udager AM, McHugh JB, Goudsmit CM, et al. Human papillomavirus (HPV) and somatic EGFR mutations are essential, mutually exclusive oncogenic mechanisms for inverted sinonasal papillomas and associated sinonasal squamous cell carcinomas. *Ann Oncol*. 2017;29(2):466–471.

56. Udager AM, McHugh JB, Betz BL, et al. Activating KRAS mutations are characteristic of oncocytic sinonasal papilloma and associated sinonasal squamous cell carcinoma. *J Pathol*. 2016;239(4):394–398.

57. Udager AM, Rolland DCM, McHugh JB, et al. High-frequency targetable EGFR mutations in sinonasal squamous cell carcinomas arising from inverted sinonasal papilloma. *Cancer Res*. 2015;75(13):2600–2606.

58. Vivanco B, Llorente JL, Perez-Escuredo J, Alvarez Marcos C, Fresno MF, Hermsen MA. Benign lesions in mucosa adjacent to intestinal-type sinonasal adenocarcinoma. *Pathol Res Int*. 2011;2011:230147.

59. Franchi A, Palomba A, Miligi L, et al. Intestinal metaplasia of the sinonasal mucosa adjacent to intestinal-type adenocarcinoma: a morphologic, immunohistochemical, and molecular study. *Virchows Arch*. 2015;466(2):161–168.

60. Haack H, Johnson LA, Fry CJ, et al. Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. *Am J Surg Pathol*. 2009;33(7):984–991.

61. Bishop JA, Andreasen S, Hang JF, et al. HPV-related multiphenotypic sinonasal carcinoma: an expanded series of 49 cases of the tumor formerly known as HPV-related carcinoma with adenoid cystic carcinoma-like features. *Am J Surg Pathol*. 2017;41(12):1690–1701.

62. Agaimy A, Rau TT, Hartmann A, Stoehr R. *SMARCB1* (INI1)-negative rhabdoid carcinomas of the gastrointestinal tract: clinicopathologic and molecular study of a highly aggressive variant with literature review. *Am J Surg Pathol*. 2014;38(7):910–920.

63. Bishop JA, Antonescu CR, Westra WH. *SMARCB1* (INI-1)-deficient carcinomas of the sinonasal tract. *Am J Surg Pathol*. 2014;38(9):1282–1289.

64. El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. *Am J Surg Pathol*. 2005;29(10): 1367–1372.

65. Larque AB, Hakim S, Ordi J, et al. High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas. *Mod Pathol*. 2014;27(3):343–351.

66. Bishop JA, Guo TW, Smith DF, et al. Human papillomavirus-related carcinomas of the sinonasal tract. *Am J Surg Pathol*. 2013;37(2):185–192.

67. Laco J, Sieglova K, Vosmikova H, et al. The presence of high-risk human papillomavirus (HPV) E6/E7 mRNA transcripts in a subset of sinonasal carcinomas is evidence of involvement of HPV in its etiopathogenesis. *Virchows Arch*. 2015;467(4):405–415.

68. Lewis JS, Jr. Sinonasal squamous cell carcinoma: a review with emphasis on emerging histologic subtypes and the role of human papillomavirus. *Head Neck Pathol*. 2016;10(1):60–67.

69. Franchi A, Bishop JA, Coleman H, et al. *Carcinomas of the Nasal Cavity and Paranasal Sinuses, Histopathology Reporting Guide*. 1st edition. Sydney, Australia: International Collaboration on Cancer Reporting; 2018.

70. 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.