Challenges in Histologic Diagnosis of Nonchordomatous Lesions of the Clivus

Julia Kristin, MD; Jörg H. Schipper, MD; Muhammad Jalkhi, MD; Thomas Zahnert, MD; Martin Wagenmann, MD

**IMPORTANCE** Nonchordomatous clival lesions are rare and represent a wide range of different benign and malignant pathologies. For an accurate and specific final diagnosis, biopsy procedures and/or resections followed by histologic examination are mandatory.

**OBJECTIVE** To illustrate the challenges in obtaining a final histologic diagnosis in patients with various types of clival lesions.

**DESIGN, SETTING, AND PARTICIPANTS** We performed a retrospective analysis of medical records of 24 patients who underwent endonasal endoscopic biopsy of the clivus between February 1, 2005, and June 1, 2013, in 2 medical university hospitals. Analysis was conducted between January 1 and August 15, 2014.

**INTERVENTIONS** All patients underwent endoscopic biopsy of the clivus.

**MAIN OUTCOMES AND MEASURES** The number of biopsies performed to establish a diagnosis in clival lesions and the problems encountered when analyzing the radiologic findings and histologic results.

**RESULTS** In 14 of 24 patients (58%), a conclusive histologic diagnosis of the nonchordomatous clival lesion could be determined. Despite up to 3 endonasal endoscopic biopsies, the histologic result could not be clearly specified in the remaining 10 patients (42%). No major complications occurred. Treatment based on the testing results included endonasal endoscopic surgery, radiotherapy or radiochemotherapy, and/or follow-up examination.

**CONCLUSIONS AND RELEVANCE** Challenges can occur in the radiologic evaluation and pathologic differentiation of diverse bone lesions with overlapping morphologic features as well as in the differentiation between neoplastic, reactive, inflammatory, and metabolic bone lesions and developmental disorders. Despite more than 1 biopsy, histologic classification will not always lead to a definitive diagnosis. In such cases, an interdisciplinary team should decide whether additional biopsies should be performed or whether clinical, endoscopic, and radiologic controls are sufficient.
Clival lesions are rare and represent a wide range of different benign and malignant pathologies. The most common tumors in the clival region are chordomas, with an overall incidence of 0.2 to 0.5 per 100,000 persons per year. As part of the skull base, the clivus extends from the floor of the sphenoid sinus to the foramen magnum. In rare cases, the sphenoid sinus can pneumatize the whole clivus and terminate at the anterior margin of the foramen magnum. An iatrogenic perforation could be dangerous for the basilar artery or the brainstem lying directly above the clivus. The cavernous sinus is lateral to the sphenoid sinus, with the internal carotid artery running along the lateral wall of the cavernous sinus. The abducens nerve is more lateral but closer to the internal carotid artery. Running superoinferiorly in the lateral wall are the oculomotor nerve, the trochlear nerve, and the maxillary nerve.

High-resolution computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in the differentiation between tumor and inflammation, in the differentiation between benign and malignant neoplasms, and for the exact description of the extension. Nevertheless, for an accurate and specific final diagnosis, biopsy procedures and/or resections followed by histologic examination are mandatory.

The endoscopic endonasal approach provides minimally invasive access to deeply seated pathologies of the clivus. Use of the natural corridors (the nostrils) minimizes trauma for critical neurovascular structures and improves visualization with the ability to look through angled endoscopes. Additional advantages of endonasal techniques compared with conventional open anterior or lateral routes are the decreased length of hospital stay, improved quality of life, and lack of external incisions of otorhinolaryngology and head and neck surgery of the University of the University Hospital between February 1, 2005, and June 1, 2013, at the departments of otorhinolaryngology and head and neck surgery of the University Hospital Düsseldorf and the Carl Gustav Carus University Hospital were identified. All patients had been directly referred for endonasal biopsy of the clivus. Other approaches for biopsy of the clivus were not performed in these 2 centers.

The study was carried out in compliance with the Helsinki declaration and was approved by the relevant ethics committees of the institutions. Patients had provided oral informed consent, and the data were deidentified. Medical records were reviewed for clinical symptoms, preoperative imaging, number of biopsies, histologic results and diagnosis, treatment, and length of hospital stay. Data analysis was conducted between January 1 and August 15, 2014.

Surgery was performed under general anesthesia. Intraoperative, computer-aided surgical navigation (BrainLab, VectorVision ENT; or Navigation Panel, Karl Storz GmbH & Co KG) was used in all cases. We used 0°, 30°, 45°, and 70° endoscopes (18-cm length, 4-mm diameter; Karl Storz GmbH & Co KG), high-density monitors, and video recording for visualization.

Depending on the location of the lesion, the surgical procedure ranged from a “simple” sphenoidotomy to a resection of the posterior septum and resection of the complete anterior wall of the sphenoids. We always drilled back the bone to reach the correct location to obtain a representative biopsy. Intraoperative bleeding was common and was controlled by several applications of epinephrine-soaked swabs, bipolar coagulation, use of a diamond drill, or application of a warm saline solution. For more intensive bleeding, we used oxidized regenerate cellulose (Tabotamp; Ethicon, Johnson and Johnson Medical GmbH). Nevertheless, at the end of the procedure, some patients required nasal packing to control remaining minor bleeding.

All tissue samples were examined by 2 pathologists at the institutes of pathology at both centers, and cases with nonspecific histologic findings were also examined by 2 specialized pathologists at the reference centers. For definitive classification, the pathologic procedures comprised all common techniques for bone tumors, including immunohistochemical and genetic/molecular techniques. Despite these multiple examinations and assessments, it was frequently necessary to repeat the biopsy procedure. The choice of appropriate therapy depended on the histologic result and the patient’s general state of health. The recommended and performed therapy included complete endonasal endoscopic resection of the tumor and/or radiotherapy or radiochemotherapy. In some cases with nonspecific histologic results and no signs of cancer on clinical examination or radiologic imaging, we recommended active surveillance of the patient. Routine follow-up examinations included nasal endoscopy and postoperative imaging.

Results

Patients and Symptoms
A total of 16 patients at the University Hospital Düsseldorf and 8 patients at the Carl Gustav Carus University Hospital were identified. Patients included 13 males (54%) and 11 females (46%) with a mean age of 59.5 years (median, 65; range, 9-83 years). The patients’ preoperative symptoms were headache (11 [46%]), hearing loss (4 [17%]), vertigo (3 [12%]), and hyposmia (2 [8%]). Propensity to fall, tinnitus, earache, anterior and posterior wall pain, and anosmia were found in 10 [41%], 8 [31%], 7 [27%], and 7 [27%] patients, respectively. Aneurysm, infection, or trauma were excluded in all cases, and the ONS was not “sagittal cistern.”

# Methods

In a 2-center, retrospective medical record analysis, all patients who underwent endonasal endoscopic biopsy of the clivus between February 1, 2005, and June 1, 2013, at the departments of otorhinolaryngology and head and neck surgery of the University Hospital Düsseldorf and the Carl Gustav Carus University Hospital were identified. All patients had been directly referred for endonasal biopsy of the clivus. Other approaches for biopsy of the clivus were not performed in these 2 centers.

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posterior rhinorrhea, nasal blockage, ptosis, exophthalmos, double vision, reduced vision, dysphagia, and trigeminal neuralgia each occurred only once (each 4%). There were 4 incidental findings (17%): nasal polyps, depression, and dystonia were discovered on radiologic imaging, and a bladder tumor was detected during general staging.

**Imaging**
Preoperative imaging included high-resolution CT scans of the head in all 24 cases (100%) and additional MRI in 20 cases (83%). The additional MRI suggested a specific diagnosis in 3 cases (adenocarcinoma, lymphoepithelial carcinoma, and a cyst; [15%]). The general radiologic diagnosis was in agreement with the pathologic diagnosis in 4 cases: twice when the MRI showed a strong suspicion for a malignant neoplasm (adenocarcinoma and lymphoepithelial carcinoma), once for the mucocele noted in the CT image, and once for fibrous dysplasia noted in the CT image. The suggested diagnosis based on radiologic findings was discordant with the pathologic diagnosis in the following cases:

1. The CT image indicated clivus chordoma or metastasis of a malignant melanoma; the histologic result was osteomyelitis.
2. The CT image indicated chondroma; the histologic result was fibrous dysplasia.
3. The MRI indicated adenocarcinoma; the histologic result was chondromyxoid fibroma.
4. The MRI indicated suspicion for recurrence of lymphoepithelial carcinoma; the histologic result showed no recurrence.

All other MRI and CT reports described findings such as destruction of the bone, osteolysis, calcifications, abnormal signal, and contrast enhancement but did not offer a specific diagnosis.

**Histologic Results**
The histologic results (Table) showed a mixture of diverse entities, including benign, malignant, and unspecific findings. The list of findings included mucocele, fibrous dysplasia, intraepithelial dysplasia, osteomyelitis, chondromyxoid fibroma, neuroendocrine neoplasm without exact classification, chondromatous tumor without evidence of a benign or malignant process, and cancer, such as metastasis of adenocarcinoma, non-Hodgkin lymphoma, and lymphoepithelial carcinoma. Moreover, different nonspecific results were found, such as polypoid tissue, reactive inflammatory tissue, chronic inflammation, lymphatic hyperplasia, lymphoepithelial tissue, fibrotic fascia, lymphopholicular hyperplasia, and a fibrotic lipomatous lesion with dystrophic calcification.

In 14 of 24 patients (58%), a definitive histologic diagnosis of the clival lesion was reached (Figure). In 4 of these 24 cases (17%) (chondromyxoid fibroma, fibrous dysplasia, chondromatous tumor, and neuroendocrine neoplasia), the diagnosis was determined by additional review by other pathologists (the reference center). In 14 cases (58%), the clivus was biopsied only once; in another 8 cases (33%), a second biopsy was performed; and in 2 additional cases (8%), the clivus was biopsied 3 times owing to insufficient histologic results.

In 9 of 14 patients (64%), a diagnosis was made after 1 biopsy. In 5 of the 14 patients (36%), no specific diagnosis could be determined. Of these 5 patients, 3 individuals (60%) refused a second biopsy and opted for active surveillance, 1 patient (20%) did not return for follow-up, and 1 patient (20%) was free of symptoms (the histologic test result was not specific; the MRI showed a cyst, but the patient’s preoperative headache had resolved).

In 5 of 8 patients (62%), a diagnosis was made after 2 biopsies. In 3 of the 8 patients (38%) undergoing 2 biopsies, no specific diagnosis could be determined. Of these 3 patients, 1 patient (33%) died of pneumonia in another hospital center. For the remaining 2 patients (67%), we had no strong suspicion for cancer after the second biopsy, and we opted for active surveillance and endoscopic monitoring. In 2 patients, we could not determine a diagnosis after 3 biopsies and ultimately decided for active surveillance and endoscopic monitoring. A final diagnosis could not be reached in 10 of 24 cases (42%) despite 1 or 2 additional biopsies.

The 14 patients with definitive diagnoses received treatment in accordance with their diseases. We recommended active surveillance procedures with MRI and/or CT for patients with fibrous dysplasia, osteomyelitis, and chondromatous tumors. One patient with intraepithelial dysplasia refused another surgical intervention and was also monitored via MRI. The patients with chondromyxoid fibroma, mucocele, and neuroendocrine neoplasm underwent complete endonasal endoscopic resection of their lesions. The patients with non-Hodgkin lymphoma, lymphoepithelial carcinoma, and metastasis of adenocarcinoma received radiotherapy or radiochemotherapy.

<table>
<thead>
<tr>
<th>Table. Number and Distribution of Histologic Results</th>
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<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Specific results (n = 14)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Fibrous dysplasia</td>
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<tr>
<td>Osteomyelitis</td>
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<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>Lymphoepithelial carcinoma</td>
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<tr>
<td>Intraepithelial dysplasia</td>
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<tr>
<td>Chondromatous tumor</td>
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<tr>
<td>Neuroendocrine neoplasm</td>
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<tr>
<td>Chondromyxoid fibroma</td>
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<tr>
<td>Mucocele</td>
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<tr>
<td>Non-specific results (n = 10)</td>
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<tr>
<td>Polypoid tissue</td>
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<tr>
<td>Reactive inflammatory tissue</td>
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<tr>
<td>Chronic inflammation</td>
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<tr>
<td>Lymphatic hyperplasia</td>
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<tr>
<td>Lymphoepithelial tissue</td>
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<tr>
<td>Fibrotic fascia</td>
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<tr>
<td>Lymphopholicular hyperplasia</td>
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<tr>
<td>Fibrotic lipomatous lesion with dystrophic calcification</td>
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</tbody>
</table>
### Surgical Procedures
Complications occurred rarely. Significant intraoperative bleeding developed twice. In both cases, we performed nasal packing and immediately referred the patient to the department of neuroradiology to undergo carotid angiography; no injury to the internal carotid artery was found in either patient. Postoperative relevant bleeding occurred once, necessitating coagulation of the sphenopalatine artery.

One case of cerebrospinal fluid leak was suspected postoperatively. Computed tomographic scanning including intrathecal contrast medium injection and a β-trace test of the subarachnoid contrast medium injection did not reveal cerebrospinal fluid leaks, and none of our patients showed injuries to the optic nerve or other cranial nerves.

### General Data and Follow-up
The mean length of hospital stay was 5.7 days (median, 4; range, 3-23 days). The hospital stays of 13 and 23 days in 2 patients were the result of poor general health conditions independent of the clival lesions.

Follow-up occurred between 6 months and 6 years (median, 1.5 years). The last date of follow-up was June 2014 in our outpatient department for 2 patients; additional follow-up for these 2 patients is planned in 2015. To our knowledge, no patient had shown progress of the clival lesion on endoscopic monitoring or active surveillance during follow-up. The patients who were unavailable for follow-up missed their appointments in our outpatient department and most likely returned to their family physicians or their ear, nose, and throat practice specialists. Only 1 patient never returned for follow-up after surgery.

### Discussion
In accordance with the literature, our results demonstrate that the endoscopic endonasal approach for biopsy of lesions of the clivus is safe and has few adverse effects. There were no injuries to the internal carotid artery and no cerebrospinal fluid leaks, and none of our patients showed injuries to the optic nerve or other cranial nerves. The advantages of this endoscopic technique are the use of natural corridors, minimized trauma to neurovascular structures, and improved visualization by the use of angled endoscopes. The additional use of surgical navigation systems supports surgeons in orienting amid deeply seated and anatomically complex regions, which increases safety; this approach is viewed as a requirement for endoscopic skull base surgery by many authors.

Intraoperative navigation was used in all our cases, and it is mandatory in our opinion. The endoscopic technique enables postoperative control of the operative site, especially the region of the clivus. Therefore, endonasal endoscopic follow-up control is easily feasible and repeatable and thus generally recommended.

For preoperative assessment of the clival lesion, planning the surgery, and intraoperative navigation, all our patients underwent high-resolution CT scanning, and an additional 83% underwent MRI scanning. Preoperative CT determines the widely varied extent of the final pneumatization of the sphenoid sinus as well as the pneumatization of the pterygoid and clinoid processes. Kazkayasi et al12 showed that there is a statistically significant correlation between pterygoid pneumatization and protrusions of the vidian canal and

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**Figure. Number of Biopsies, Diagnoses, and Further Treatment**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>With 1 biopsy</th>
<th>With 2 biopsies</th>
<th>With 3 biopsies</th>
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<tbody>
<tr>
<td>Diagnosis made</td>
<td>9</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Intraepithelial dysplasia</td>
<td>1</td>
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<tr>
<td>Intraepithelial dysplasia</td>
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<td>Osteomyelitis</td>
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<tr>
<td>Chondromyxoid fibroma</td>
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<tr>
<td>Adenocarcinoma</td>
<td>1</td>
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<tr>
<td>Lymphoepithelial carcinoma</td>
<td>3</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Fibrous dysplasia</td>
<td>1</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Sphenoiditis</td>
<td>1</td>
<td></td>
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<tr>
<td>Neurofibroma</td>
<td>1</td>
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<tr>
<td>Neuroendocrine neoplasma</td>
<td>2</td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>1</td>
<td></td>
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<tr>
<td>Chondromyxoid fibroma</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Procedure</th>
<th>1 biopsy</th>
<th>2 biopsies</th>
<th>3 biopsies</th>
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<tbody>
<tr>
<td>Endoscopic control</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Surgery with radiotherapy</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Radiotherapy</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Radiochemotherapy</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Imaging control</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Antibiotic therapy with imaging control</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No specific diagnosis</td>
<td>9</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

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**Diagnosis made**

- Intraepithelial dysplasia
- Intraepithelial dysplasia
- Osteomyelitis
- Chondromyxoid fibroma
- Adenocarcinoma
- Lymphoepithelial carcinoma
- Non-Hodgkin lymphoma
- Fibrous dysplasia
- Non-Hodgkin lymphoma
- Sphenoiditis
- Neurofibroma
- Neuroendocrine neoplasma
- Adenocarcinoma
- Chondromyxoid fibroma
- Other

**Therapy/follow-up**

- Surgery
- Surgery with radiotherapy
- Radiotherapy
- Radiochemotherapy
- Imaging control
- Antibiotic therapy with imaging control
- Endoscopic control
- No specific diagnosis
- No specific diagnosis
- No specific diagnosis
- No follow-up owing to patient delay
- No symptoms
- Refused second biopsy
- Imaging control
- Endoscopic control
- Imaging control
- Endoscopic control
- Endoscopic control
- Died
- Endoscopic control
- Endoscopic control

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**Description of the resulting distribution of the diverse entities, therapy, and follow-up.**
the foramen rotundum into the sinus cavity. Pneumatization of the anterior clinoid process is correlated with protrusion or a complete intrasinus course of the optic canal. Imaging demonstrates the exact localization and extension of the tumor, including its relationship to vulnerable structures.

Moreover, CT is the best option for evaluating cortical bone and for demonstrating the detailed anatomy of the cortical margins of the clivus. However, CT lacks sensitivity in evaluating bone marrow space involvement until significant marrow infiltration and subsequent trabecular bone loss has occurred. Because of its superior contrast resolution, MRI is more sensitive in assessing bone marrow signal abnormalities in the skull base and in discriminating soft tissue. Magnetic resonance imaging gives additional information about dural infiltration and the intracerebral origin of the tumor. In our patients, imaging is an important supporting element; however, as shown in the results, a final diagnosis cannot be sufficiently achieved with MRI or CT alone without histologic biopsy. As seen in our results, rare nonchordomatous lesions are radiologically difficult to specify, and the suspected radiologic diagnosis and histologic results often differ in these special cases.

In our group, the radiologic and histologic diagnoses were in agreement on one patient with adenocarcinoma. In another patient, the radiologic findings were suspicious for adenocarcinoma, but the histologic diagnosis was chondromyxoid fibroma. The CT findings in skull base metastasis are variable. The findings may demonstrate lytic destruction of trabecular or cortical bone. On MRI, there is a loss of normal marrow signal on precontrast T1-weighted sequences associated with heterogeneous T2 signal abnormalities and enhancement on the postcontrast T1-weighted scan. Associated extraosseous soft-tissue tumor generally demonstrates contiguous growth and can extend intracranially or extracranially. Chondromyxoid fibromas have been reported to be isointense on T1-weighted images and hyperintense on T2-weighted images. Contrast enhancement can be dishomogeneous or mostly homogeneous.

For fibrous dysplasia, the radiologic and histologic diagnoses in our patients were in agreement in one case and discordant in the other. These lesions can be small and focal, multifocal, or large and can involve multiple contiguous bones of the skull base. On CT scanning, fibrous dysplasia lesions may have a ground glass appearance (56%), a homogeneously dense pattern (23%), cystic characteristics (21%), or a mixed pattern. This disease is a potential diagnostic pitfall that can easily be confused with neoplastic disease on MRI. Low signal on both T1- and T2-weighted images improves the radiologist’s confidence in making a correct diagnosis.

A radiologic diagnosis of osteomyelitis often requires high-resolution CT with bone algorithm and MRI. Osteomyelitis results in T1 hypointensity, T2 hyperintensity, and postcontrast enhancement in the affected bone marrow space. Infection of the clivus invariably leads to abnormal signal and enhancement of the preclival musculature and the adjacent soft tissues. Given the extraosseous involvement and the aggressive appearance on MRI and CT scanning, osteomyelitis can be difficult to distinguish from invasive neoplasms of the central skull base. Our radiologists faced similar problems. In one patient, they stated preoperatively that the differential diagnosis included clivus chordoma and metastasis of a malignant melanoma; the histologic result was osteomyelitis.

Our group recommends CT for every patient as part of the basic preoperative examination. Whenever possible, additional MRI should be conducted for discrimination of the soft tissue and for evaluation of suspected dural infiltration or an intracerebral origin of the tumor. There was no clival chordoma in our group of patients, which is the most common tumor in this region. Clival chordomas are a visual diagnosis for radiologists with a differential diagnosis of osteochondroma and echodochysis physaliphora. Owing to frequent intracranial growth, patients with chordomas are usually referred to neurosurgical departments. This strategy probably explains why no patients with these diagnoses were referred to our ear, nose, and throat departments.

Generally, postoperative surveillance imaging is recommended for all tumors. In our opinion, exceptions can include patients with benign entities and easily performable endoscopic monitoring.

A diagnosis of bone tumor often has serious consequences in terms of surgical and adjuvant treatment. The histologic entities of clival lesions reported in the literature include clival chordoma, meningioma, adenoid- cystic carcinoma, sinonasal undifferentiated carcinoma, hemangiopericytoma, enterogenous cyst, epidermoid and metastasis, cholesterol granulomas, and others. Excluding lymphoma and myeloma, malignant primary bone tumors account for only 0.2% of all cancers in adults.

Our data showed no final histologic result in 10 of 24 cases (42%) despite repeated biopsies by experienced head and neck and skull base surgeons. These difficulties did not occur because biopsy samples were too small, which was confirmed by the examining pathologists. The pathologic differentiation of diverse bone lesions with overlapping morphologic features and the differentiation between neoplastic, reactive, inflammatory, and metabolic bone lesions or developmental disorders can be challenging. Kindblom noted that the primary problems that pathologists face in diagnosing primary bone tumors are the lack of sufficient diagnostic experience owing to lesion rarity and a lack of interdisciplinary teamwork. For diagnostic techniques, fresh and unfixed bone tumor specimens can enable multiple histologic procedures. Histochemistry, immunohistochemistry, and electron microscopy can be important in cases of metastatic bone disease, lymphohematologic cancers, chordomas, or osteofibrous dysplasia. Cyto genetic and molecular genetic techniques provide additional information to support morphology-based classifications.

All unclassified biopsies should be sent to reference centers for a second opinion. Furthermore, in all of these cases, interdisciplinary discussions between radiologists, pathologists, and surgeons should be held.

Conclusions

Preoperative imaging, knowledge of anatomic landmarks, experience in skull base surgery, and an intraoperative navigation
system are mandatory to perform endoscopic endonasal biopsy of clival lesions. Despite all of these requirements, a final diagnosis cannot always be determined. The radiologic differential diagnosis can be difficult because these lesions may appear very similar. The histologic assignment of clival lesions can be challenging for pathologists owing to their rarity and the presence of diverse bone lesions with overlapping morphologic features. All unclassified biopsies should be sent to reference centers for a second opinion. We recommend performing additional endoscopic biopsies of clival lesions until a malignant neoplasm is excluded by the sum of all findings. It is not recommended to perform major surgery instead of undertaking a second or third biopsy. In every case with an unclear diagnosis, the decision on the proceedings should be made by an interdisciplinary team and include performing another biopsy, active surveillance, and/or clinical endoscopic monitoring.

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REFERENCES