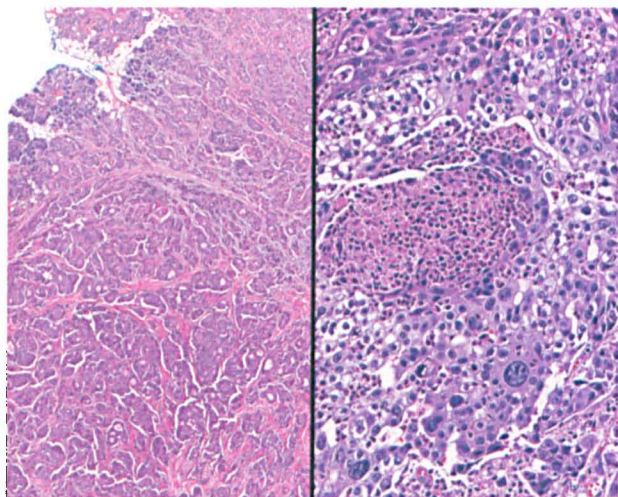
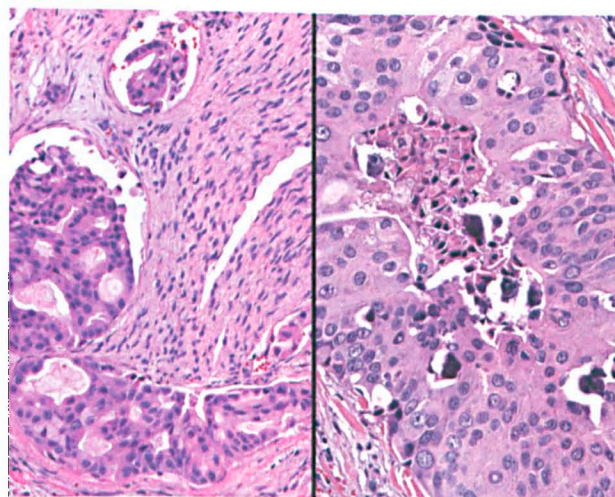


## Salivary duct carcinoma

Lester D.R. Thompson, MD



*Figure 1. Left: Widely invasive tumor exhibits a solid-glandular architecture. Right: High-power view demonstrates a highly pleomorphic population with comedonecrosis.*



*Figure 2. Left: Slide shows peri- and intraneural invasion by a cribriform neoplasm. Right: Central comedonecrosis is seen within a duct space. There is moderate nuclear pleomorphism.*

Salivary duct carcinoma is a high-grade adenocarcinoma that resembles breast ductal carcinoma. It is believed to be derived from intra- and interlobular excretory ducts. Salivary duct carcinoma may arise de novo or as a relatively common malignant component of a carcinoma ex pleomorphic adenoma. It accounts for about 9% of all malignant salivary gland tumors. Although there is a wide age range at presentation, most patients present in the seventh decade of life; men are affected much more frequently than women (4:1).

The vast majority of cases arise in the parotid gland, where they usually manifest as a rapidly growing mass, often with ulceration and facial nerve palsy. Patients with carcinoma ex pleomorphic adenoma may have a history of a long-standing mass with recent enlargement.

Because lymph node metastasis occurs frequently, aggressive multimodality therapy is required; surgery, radiotherapy, and chemotherapy yield the best out-

comes. Administration of trastuzumab may be useful in patients with HER-2/neu-positive tumors. The overall prognosis is poor, as rates of recurrence and metastasis are high and 5-year survival is less than 35%.

The average size of these tumors is 3.5 cm. They are predominantly solid with a generally white, gray, or tan cut surface. Cysts, necrosis, and hemorrhage are frequently seen. Invasion is easily identified (figure 1), although it is more common in de novo tumors than in those that arise from carcinoma ex pleomorphic adenoma. There is significant lymph-vascular and perineural invasion (figure 2), which is often associated with positive resection margins. Stromal fibrosis or infarction and inflammatory infiltration is often conspicuous.

Salivary duct carcinomas are similar to both intraductal and infiltrating ductal carcinomas of the breast. They feature large ducts with solid, papillary,

From the Department of Pathology, Southern California Permanente Medical Group, Woodland Hills Medical Center, Woodland Hills, Calif.

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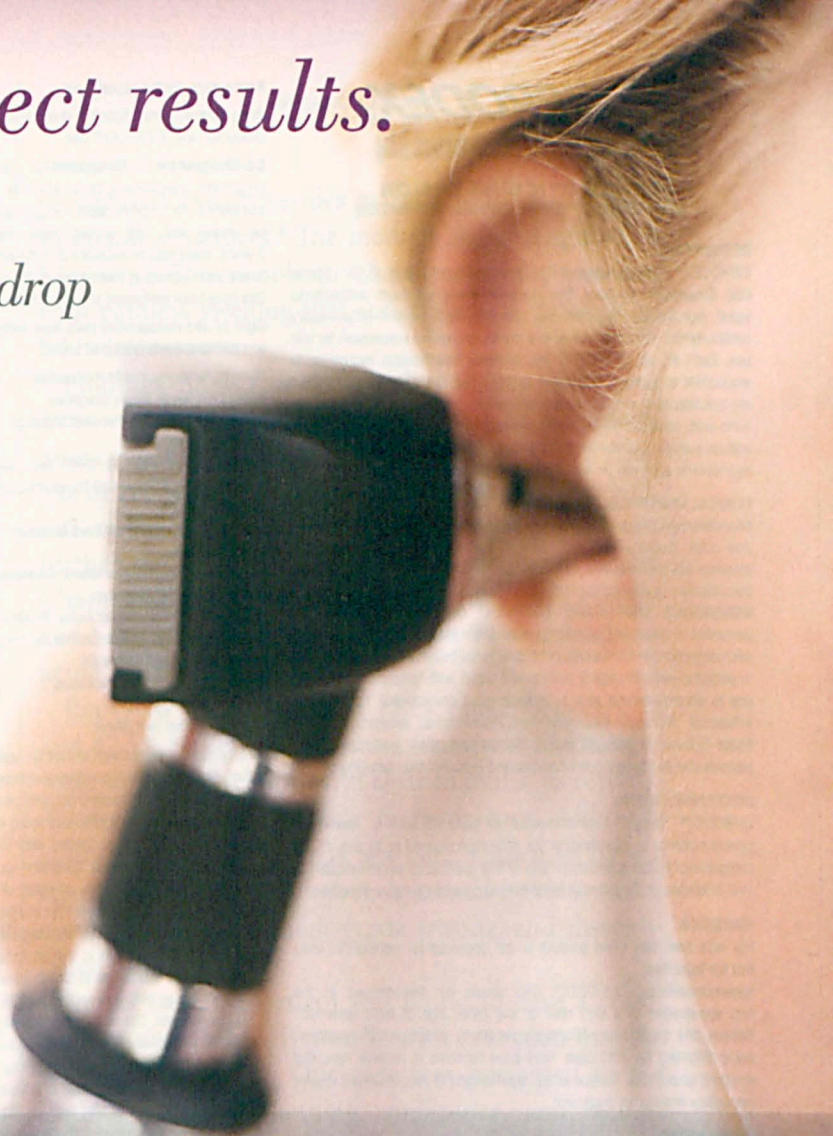
*CIPRODEX® Otic, the #1 otic drop  
among otolaryngologists.<sup>1</sup>*

For acute otitis media (AOM)  
with tympanostomy tubes  
and acute otitis externa (AOE)<sup>2</sup>

- High clinical cure rates<sup>2</sup>
- Proven inflammation control<sup>2,3</sup>
- The power of an anti-inflammatory  
and antibiotic in each drop<sup>2</sup>



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*Easy to afford with 99% commercial lives covered<sup>4</sup>*

**INDICATIONS and USAGE:** CIPRODEX® Otic is indicated in patients 6 months and older for acute otitis externa due to *Staphylococcus aureus* and *Pseudomonas aeruginosa* and for acute otitis media with tympanostomy tubes due to *S. aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *P. aeruginosa*.

#### **IMPORTANT SAFETY INFORMATION:**

**Contraindications:** CIPRODEX® Otic is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components in this medication. Use of this product is contraindicated in viral infections of the external canal including herpes simplex infections.

**Warnings:** CIPRODEX® Otic is approved for otic use only (this product is not approved for ophthalmic use). CIPRODEX® Otic should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment. If the infection is not improved after one week of treatment, cultures should be obtained to guide further treatment.

**Adverse Events:** Most commonly reported adverse reactions in clinical trials in AOE patients: ear pruritus (1.5%), ear debris (0.6%), superimposed ear infection (0.6%), ear congestion (0.4%), ear pain (0.4%) and erythema (0.4%). In AOM patients with tympanostomy tubes: ear discomfort (3.0%), ear pain (2.3%), ear residue (0.5%), irritability (0.5%) and taste perversion (0.5%).

**For additional information please refer to the accompanying brief summary of prescribing information on adjacent page.**

*Why choose  
anything else?*

**CIPRODEX®**  
(ciprofloxacin 0.3% and dexamethasone 0.1%)  
**STERILE OTIC SUSPENSION**

**References:** 1. IMS Health, IMS National Prescription Audit™, October 2010 to September 2011, USC 62320 OTIC ANTINFCT W/GLUCOCORT. 2. CIPRODEX® Otic package insert. 3. Roland PS, Pien FD, Schultz CC, et al. Efficacy and safety of topical ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone for otitis externa. *Curr Med Res Opin.* 2004;20(8):1175-1183. 4. Formulary data provided by Pinsonault Associates, LLC, PathfinderRx, October 2011.

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## STERILE OTIC SUSPENSION BRIEF SUMMARY OF PRESCRIBING INFORMATION

### DESCRIPTION

CIPRODEX® (ciprofloxacin 0.3% and dexamethasone 0.1%) Sterile Otic Suspension contains the synthetic broad-spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, dexamethasone, in a sterile, preserved suspension for otic use. Each mL of CIPRODEX® Otic contains ciprofloxacin hydrochloride (equivalent to 3 mg ciprofloxacin base), 1 mg dexamethasone, and 0.1 mg benzalkonium chloride as a preservative. The inactive ingredients are boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

### CLINICAL PHARMACOLOGY

**Microbiology:** Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

**INDICATIONS AND USAGE:** CIPRODEX® Otic is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below: **Acute Otitis Media** in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*. **Acute Otitis Externa** in pediatric (age 6 months and older), adult and elderly patients due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

### CONTRAINDICATIONS

CIPRODEX® Otic is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components in this medication. Use of this product is contraindicated in viral infections of the external canal including herpes simplex infections.

### WARNINGS

**For otic use only** (This product is not approved for ophthalmic use). **Not for injection**

**Hypersensitivity:** CIPRODEX® Otic should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

### PRECAUTIONS

**General:** As with other antibacterial preparations, use of this product may result in overgrowth of nonsusceptible organisms, including yeast and fungi. If the infection is not improved after one week of treatment, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor. The systemic administration of quinolones, including ciprofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Guinea pigs dosed in the middle ear with CIPRODEX® Otic for one month exhibited no drug-related structural or functional changes of the cochlear hair cells and no lesions in the ossicles. CIPRODEX® Otic was also shown to lack dermal sensitizing potential in the guinea pig when tested according to the method of Buehler. No signs of local irritation were found when CIPRODEX® Otic was applied topically in the rabbit eye.

**Information for Patients:** For otic use only. (This product is not approved for use in the eye.) Warm the bottle in your hand for one to two minutes prior to use and shake well immediately before using. Avoid contaminating the tip with material from the ear, fingers, or other sources. Protect from light. If rash or allergic reaction occurs, discontinue use immediately and contact your physician. It is very important to use the ear drops for as long as the doctor has instructed, even if the symptoms improve. Discard unused portion after therapy is completed. **Acute Otitis Media in pediatric patients with tympanostomy tubes:** Prior to administration of CIPRODEX® Otic in patients (6 months and older) with acute otitis media through tympanostomy tubes, the solution should be warmed by holding the bottle in the hand for one to two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds. Repeat, if necessary, for the opposite ear. **Acute Otitis Externa:** Prior to administration of CIPRODEX® Otic in patients with acute otitis externa, the solution should be warmed by holding the bottle in the hand for one to two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. Repeat,

if necessary, for the opposite ear.

**Drug Interactions:** Specific drug interaction studies have not been conducted with CIPRODEX® Otic.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of CIPRODEX® Otic have been performed to evaluate carcinogenic potential.

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

*Salmonella*/Microsome Test (Negative),

*E. coli* DNA Repair Assay (Negative),

Mouse Lymphoma Cell Forward Mutation Assay (Positive),

Chinese Hamster V79 Cell HGPRT Test (Negative),

Syrian Hamster Embryo Cell Transformation Assay (Negative),

*Saccharomyces cerevisiae* Point Mutation Assay (Negative),

*Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative),

Rat Hepatocyte DNA Repair Assay (Positive).

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay,

Micronucleus Test (Mice),

Dominant Lethal Test (Mice).

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 100 times the maximum recommended clinical dose of otic ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with CIPRODEX® Otic twice per day according to label directions. Long term studies have not been performed to evaluate the carcinogenic potential of topical otic dexamethasone. Dexamethasone has been tested for *in vitro* and *in vivo* genotoxic potential and shown to be positive in the following assays: chromosomal aberrations, sister-chromatid exchange in human lymphocytes and micronuclei and sister-chromatid exchanges in mouse bone marrow. However, the Ames/Salmonella assay, both with and without S9 mix, did not show any increase in His<sup>+</sup> revertants. The effect of dexamethasone on fertility has not been investigated following topical otic application. However, the lowest toxic dose of dexamethasone identified following topical dermal application was 1.802 mg/kg in a 26-week study in male rats and resulted in changes to the testes, epididymis, sperm duct, prostate, seminal vesicle, Cowper's gland and accessory glands. The relevance of this study for short term topical otic use is unknown.

**Pregnancy; Teratogenic Effects; Pregnancy Category C.** Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Animal reproduction studies have not been conducted with CIPRODEX® Otic. No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when CIPRODEX® Otic is used by a pregnant woman.

**Nursing Mothers:** Ciprofloxacin and corticosteroids, as a class, appear in milk following oral administration. Dexamethasone in breast milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical otic administration of ciprofloxacin or dexamethasone could result in sufficient systemic absorption to produce detectable quantities in human milk. Because of the potential for unwanted effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and efficacy of CIPRODEX® Otic have been established in pediatric patients 6 months and older (937 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that would preclude use of this product. No clinically relevant changes in hearing function were observed in 69 pediatric patients (age 4 to 12 years) treated with CIPRODEX® Otic and tested for audiometric parameters.

### ADVERSE REACTIONS

In Phases II and III clinical trials, a total of 937 patients were treated with CIPRODEX® Otic. This included 400 patients with acute otitis media with tympanostomy tubes and 537 patients with acute otitis externa. The reported treatment-related adverse events are listed below:

### Acute Otitis Media in pediatric patients with tympanostomy tubes:

The following treatment-related adverse events occurred in 0.5% or more of the patients with non-intact tympanic membranes.

Adverse Event	Incidence (N=400)
Ear discomfort	3.0%
Ear pain	2.3%
Ear precipitate (residue)	0.5%
Irritability	0.5%
Taste perversion	0.5%

The following treatment-related adverse events were each reported in a single patient: tympanostomy tube blockage; ear pruritus; tinnitus; oral moniliasis; crying; dizziness; and erythema. **Acute Otitis Externa:** The following treatment-related adverse events occurred in 0.4% or more of the patients with intact tympanic membranes.

Adverse Event	Incidence (N=537)
Ear pruritus	1.5%
Ear debris	0.6%
Superimposed ear infection	0.6%
Ear congestion	0.4%
Ear pain	0.4%
Erythema	0.4%

The following treatment-related adverse events were each reported in a single patient: ear discomfort; decreased hearing; and ear disorder (tingling).

### DOSAGE AND ADMINISTRATION

**CIPRODEX® Otic should be shaken well immediately before use. Acute Otitis Media in pediatric patients with tympanostomy tubes:** The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (age 6 months and older) through tympanostomy tubes is: Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days. The suspension should be warmed by holding the bottle in the hand for one to two minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed. **Acute Otitis Externa:** The recommended dosage regimen for the treatment of acute otitis externa is: For patients (age 6 months and older): Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days. The solution should be warmed by holding the bottle in the hand for one to two minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

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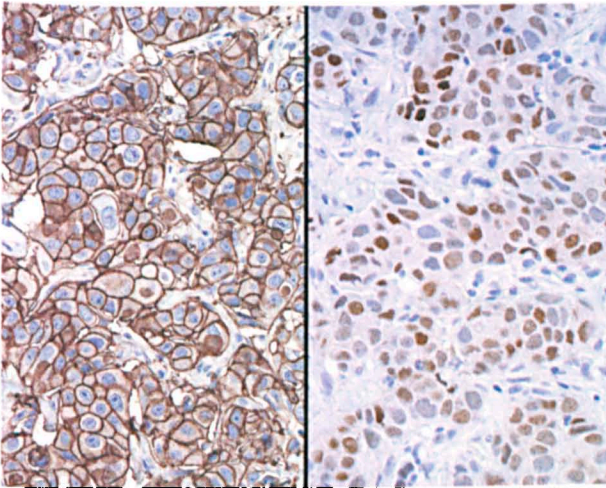


Figure 3. Left: Immunohistochemistry reveals a strong, diffuse, circumferential membranous reaction with HER-2/neu. Right: A strong nuclear reaction with androgen receptor is seen in most tumor nuclei by immunohistochemistry.

and comedonecrosis areas (figure 1). Cribriform and “Roman bridge” configurations are common (figure 2). The tumor cells exhibit remarkable pleomorphism, with pink, granular cytoplasm surrounding irregular nuclei with prominent nucleoli (figure 2). Oncocytic change is common. There are usually many mitoses, including atypical forms. Several variants are recognized, including spindled, sarcomatoid, mucin-rich, micropapillary, and osteoclast-type giant cells.

The neoplastic cells are reactive with several keratins, including CK5/6, EMA, and CEA, while demonstrating a strong and diffuse membranous HER-2/neu immunoreaction and strong nuclear positivity for androgen receptor (figure 3). In general, salivary duct carcinoma must be distinguished from metastatic breast carcinoma, poorly differentiated squamous cell carcinoma, cystadenocarcinoma, and oncocytic carcinoma.

### Suggested reading

- Hoang MP, Callender DL, Sola Gallego JJ, et al. Molecular and biomarker analyses of salivary duct carcinomas: Comparison with mammary duct carcinoma. *Int J Oncol* 2001;19(4):865-71.
- Jaehne M, Roeser K, Jaekel T, et al. Clinical and immunohistologic typing of salivary duct carcinoma: A report of 50 cases. *Cancer* 2005;103(12):2526-33.
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Continued from page 355

malignancy usually resides in the anterior maxilla and sinonasal structures.<sup>4</sup> The median age at diagnosis is 52 years.<sup>1</sup> The neoplasm characteristically presents with painless swelling that sometimes becomes painful in later stages.

Findings on CT include a hypodense soft-tissue mass with scattered chondroid matrix calcifications. These calcifications characteristically appear in a ring-like or arc-whorl pattern; amorphous or absent calcifications are suggestive of a high-grade tumor. MRI may further define the extent of soft-tissue involvement. Characteristic MRI findings are an increased T2 signal and heterogeneous enhancement on T1-weighted imaging with contrast.<sup>5</sup>

Reported 5-year survival rates range between 32 and 87.5%.<sup>2</sup> The most effective treatment modality is wide surgical resection with clear margins, as residual disease is a primary factor in recurrence. Although adjuvant radiotherapy has not been shown to have a significant effect on survival, it is used in cases of incomplete resection, high-grade lesions, and disseminated disease.<sup>2</sup>

In our case, the patient was found to have a chondrosarcoma of the left maxilla with extension into the infratemporal fossa. Our case was presented to the multidisciplinary planning conference, and recommendations were made for maxillectomy and resection of the infratemporal fossa followed by radiotherapy.

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