Nasopharyngeal Carcinoma

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Outline

- Case presentation
- Differential diagnoses
- Nasopharyngeal carcinoma
  - Background information
  - Diagnosis
  - Treatment

Case presentation

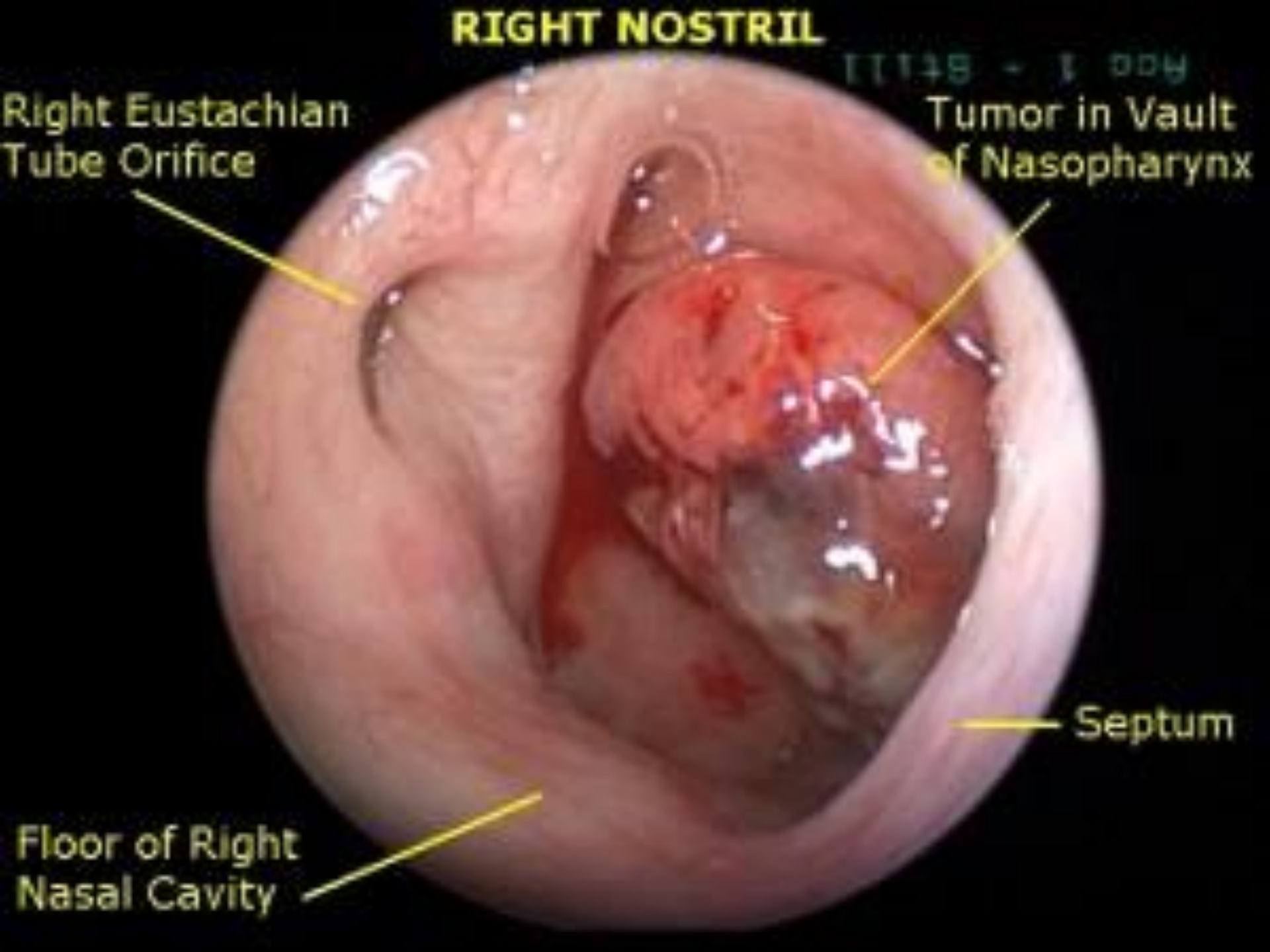
69-year-old man with hearing loss

History & ROS

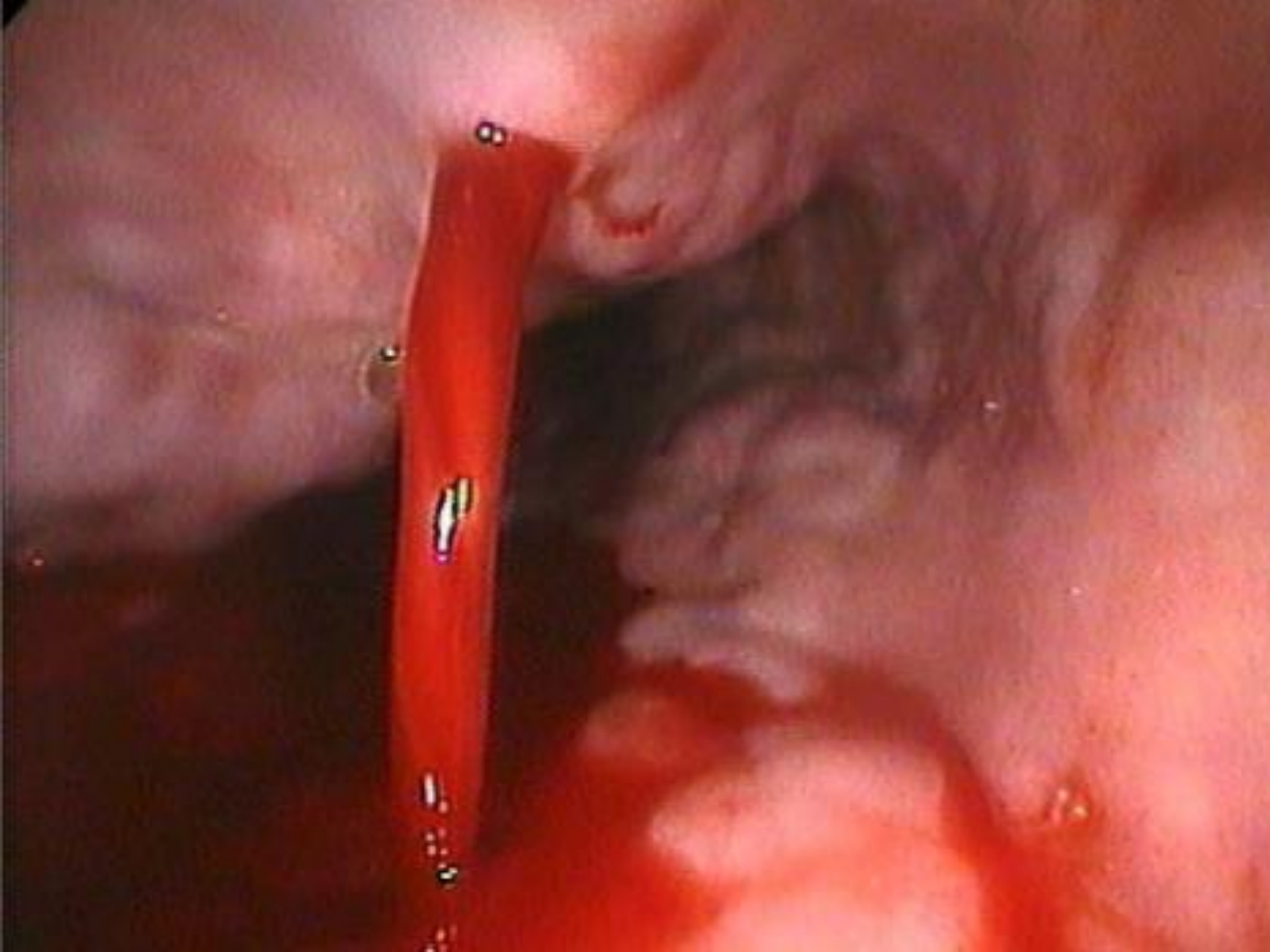
- Progress right sided hearing loss x several months
- Occasional pain and tinnitus
- Occasional blood tinged sputum

Physical exam

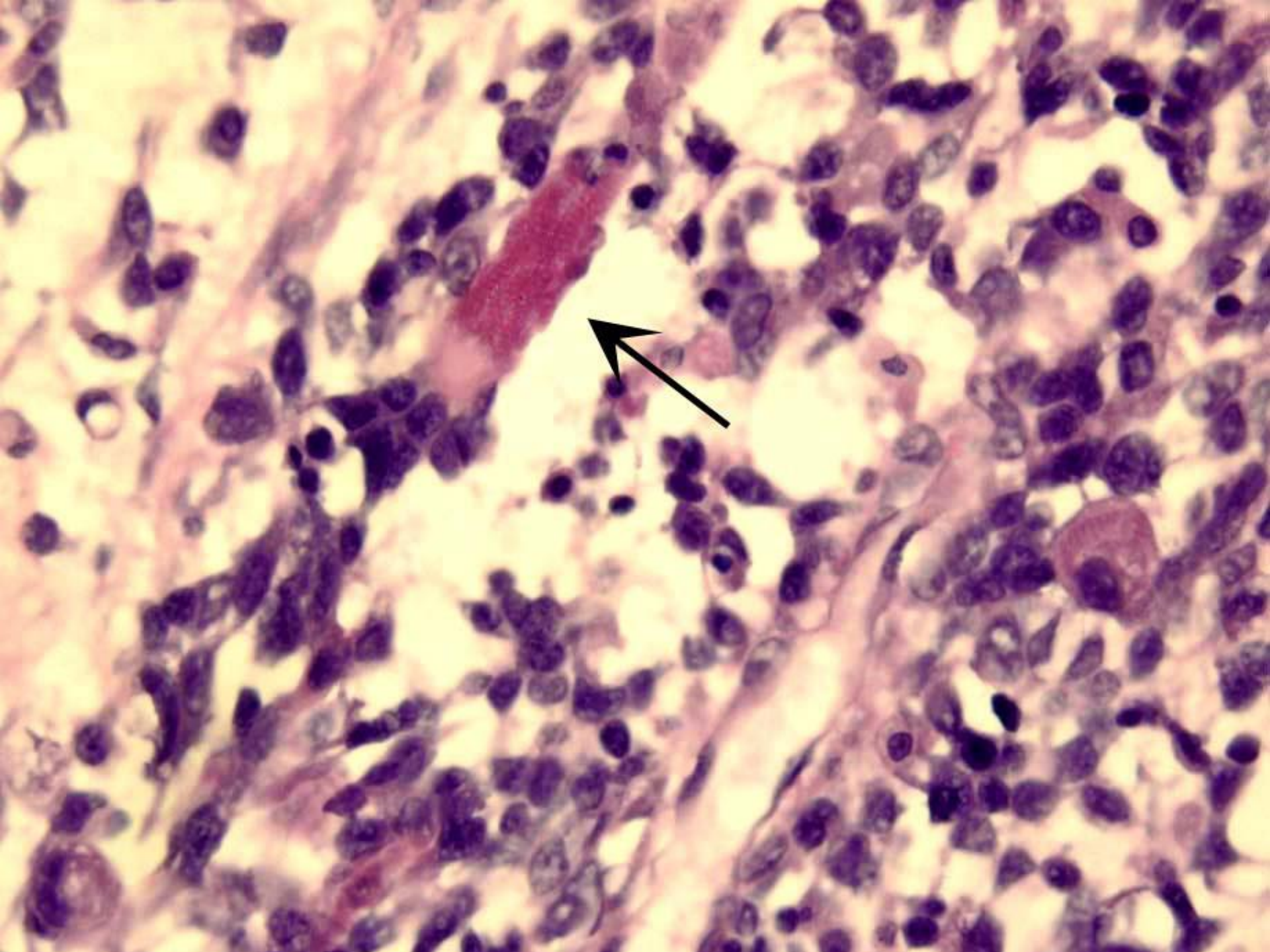
- Right serous otitis with CHL
- Unable to tolerate mirror exam
- Otherwise normal exam


RIGHT NOSTRIL
Right Eustachian Tube Orifice
Tumor in Vault of Nasopharynx
Septum
Floor of Right Nasal Cavity

19 year old



9 year old



Benign and Malignant Tumors of the Nasopharynx

Benign Tumors
- Developmental
  - Thornwaldt's cyst
  - Hairy polyp
  - Teratomas (varied origin)
- Ectodermal Papilloma
  - Adenomatous polyps
- Mesodermal
  - Juvenile angiofibroma
  - Fibromyxomatous polyps
  - Choanal polyps
  - Osteomas
  - Fibrous dysplasia
  - Craniopharyngioma
  - Solitary fibrous tumor
  - Desmoid fibromatosis
  - Schwannoma
- Benign Salivary Gland Tumors
  - Pleomorphic adenoma
  - Monomorphic adenoma

Malignant Tumors

Epithelial
- Nasopharyngeal cancer (NPC)
- Undifferentiated carcinoma
- SCCA

Embryonal
- Chordoma

Lymphoma

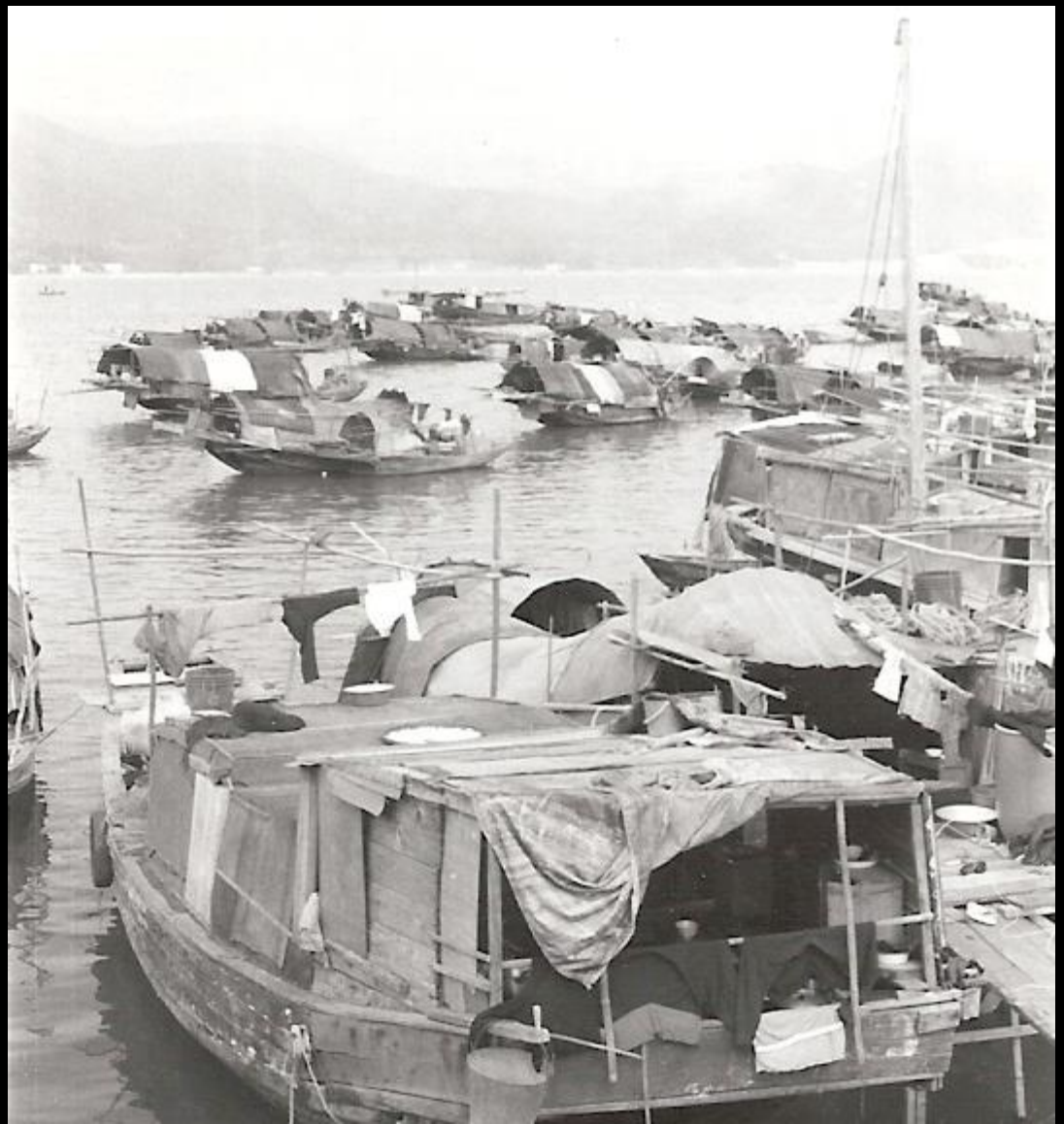
Mesodermal
- Hemangiopericytoma
- Malignant fibrous histiocytoma
- Rhabdomyosarcoma

Malignant Salivary Gland Tumors
- Adenoid cystic carcinoma
- Mucoepidermoid carcinoma
- Acinic cell carcinoma
- Adenocarcinoma

Metastatic Tumors
- Adenocarcinoma
- Papillary carcinoma

Nasopharyngeal Carcinoma

“On water people”



Incidence

- Common in certain ethnic groups, highest incidence in southern China, Hong Kong, and southeast Asia
- In North America, highest incidences are seen in the 1st generation Chinese [1]
- Subsequent-generation have a lower incidence, although still higher than the other ethnic groups
- 8x risk of NPC in 1st degree relative [2]
- Suggest the possibility of a genetic link or a shared habit such as dietary intake

1. Sun LM, Epplein M, Li CI, et al: Trends in the incidence rates of nasopharyngeal carcinoma in Chinese Americans living in the Los Angeles County and the San Francisco metropolitan area, 1992-2002. *Am J Epidemiol* 2005; 162:1174-1178.

2. Ung A, Chen CJ, Levine PH, et al: Familial and sporadic cases of nasopharyngeal carcinoma in Taiwan. *Anticancer Res* 1999; 19:661-665.

Etiology

- Genetic
  - HLA A2, Bw46, B 17, Bw58, DR3, and DR9 [1]
  - Deletions in chromosomes 3, 9 & 11 [2]
- Environmental factors
  - Salted fish, nitrosamines, chemical fumes, wood dust
  - Diet lack of fruits and vegetables
  - EBV

1. Simons MJ, Wee GB, Chan SH, et al: Probable identification of an HL-A second-locus antigen associated with a high risk of nasopharyngeal carcinoma. *Lancet* 1975; 1:142-143.

2. Huang DP, Lo KW, Choi PH, et al: Loss of heterozygosity on the short arm of chromosome 3 in nasopharyngeal carcinoma. *Cancer Genet Cytogenet* 1991; 54:91-99.

Hirayama T: Descriptive and analytical epidemiology of nasopharyngeal cancer. *IARC Sci Publ* 1978; 20:167-189.

EBV

- Herpes virus
- Vast majority of the population in the world have been infected with EBV
- Most people express elevated IgM and IgG to nuclear core early antigen or the viral capsid antigen
- Pts w/ NPC express elevated **IgA** VCA and Ea [1]
- Sensitivity and specificity of these two antibodies are high – potential screening tool for high-risk patients [2]

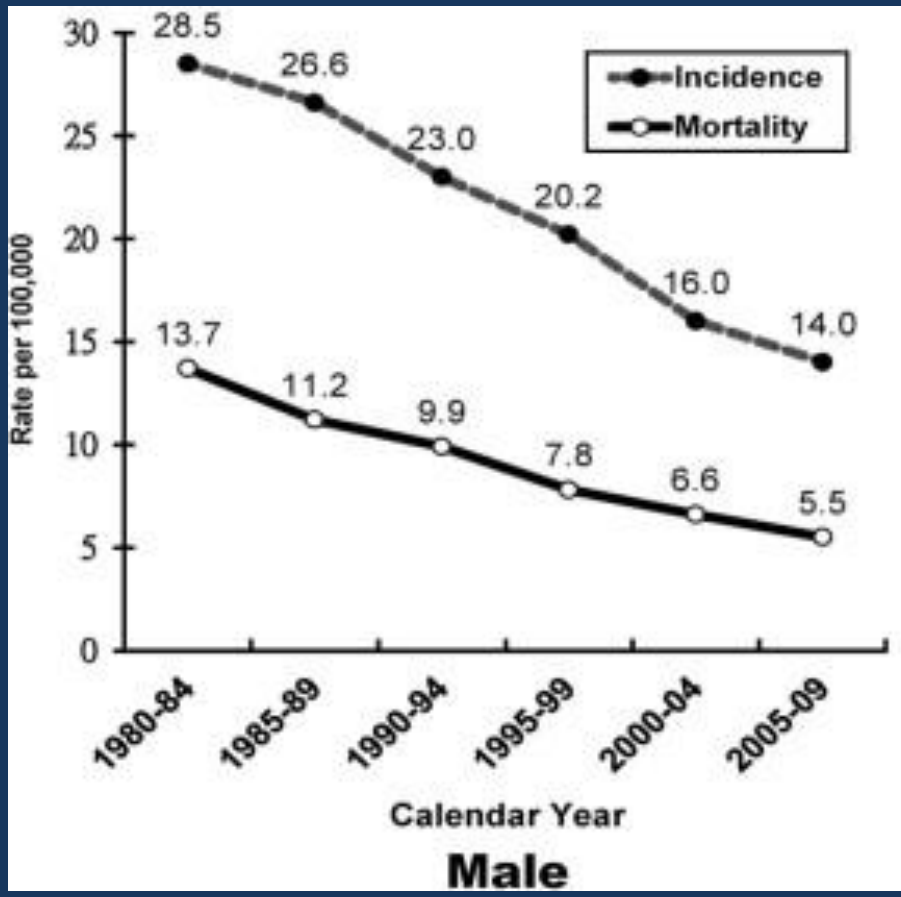
1. Henle G, Henle W: Epstein-Barr virus-specific IgA serum antibodies as an outstanding feature of nasopharyngeal carcinoma. *Int J Cancer* 1976 Jan 15; 17(1):1-7
2. W.T. Ng, C.W. Choi, M.C. Lee, L.Y. Law, T.K. Yau, A.W. Lee Outcomes of nasopharyngeal carcinoma screening for high risk family members in Hong Kong Fam Cancer, 9 (2010), pp. 221–228

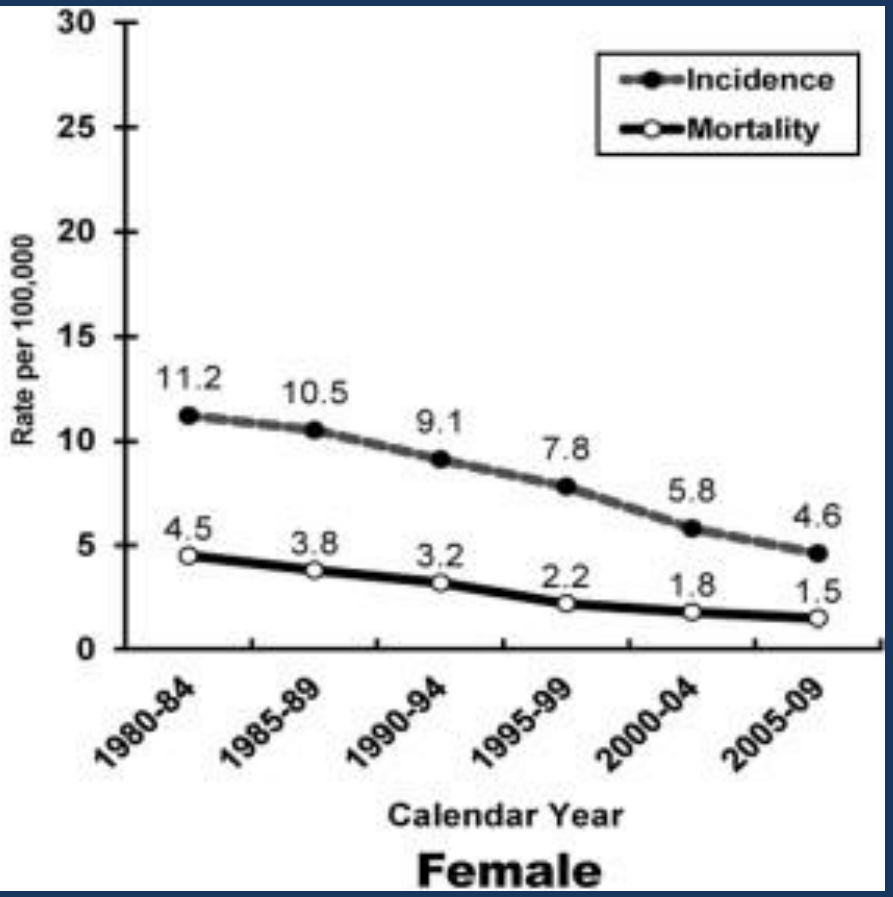
Prognosis

- Majority of patients are diagnosed with advanced disease
- Survival has improved over the past 20 yrs[1]
- Stage I and II NPC patients treated by radiation alone have 5-year overall survival rates of > 80%[2]
- Stage III or IV disease who have had concurrent chemoradiation have a 5-year overall survival rate of about 70%

1. Lee AW, Foo W, Mang O, et al: Changing epidemiology of nasopharyngeal carcinoma in Hong Kong over a 20-year period (1980-1999): an encouraging reduction in both incidence and mortality. *Int J Cancer* 2003; 103:680-685.

Incidence and Morality of NPC in HK





Lee AW, Ng WT, Chan YH, Sze H, Chan C, Lam TH. The battle against nasopharyngeal cancer.Radiother Oncol. 2012 Sep;104(3):272-8. doi: 10.1016/j.radonc.2012.08.001. Epub 2012 Aug 30.

Symptoms

- Cervical lymphadenopathy (most common presentation)
- Blood-stained saliva or sputum (2nd most common)
- Deafness (OME)
- Nasal obstruction
- Unilateral tinnitus
- Persistent headaches (intracranial extension or clival erosion)
- Cranial nerve palsies (10%)

Cummings

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- The cranial nerve most frequently affected by nasopharyngeal carcinoma:
  - 6th
  - 5th
  - 12th
  - 9th and 10th

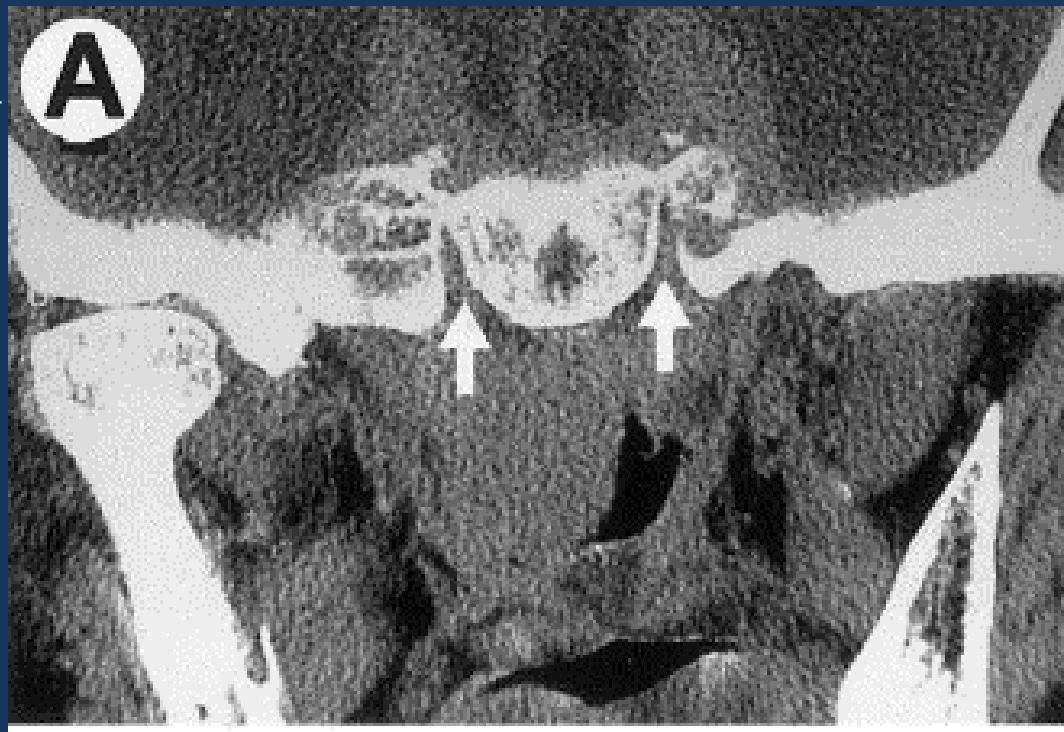
Cummings

Sixth nerve palsy is caused by cephalad extension of nasopharyngeal carcinoma through:

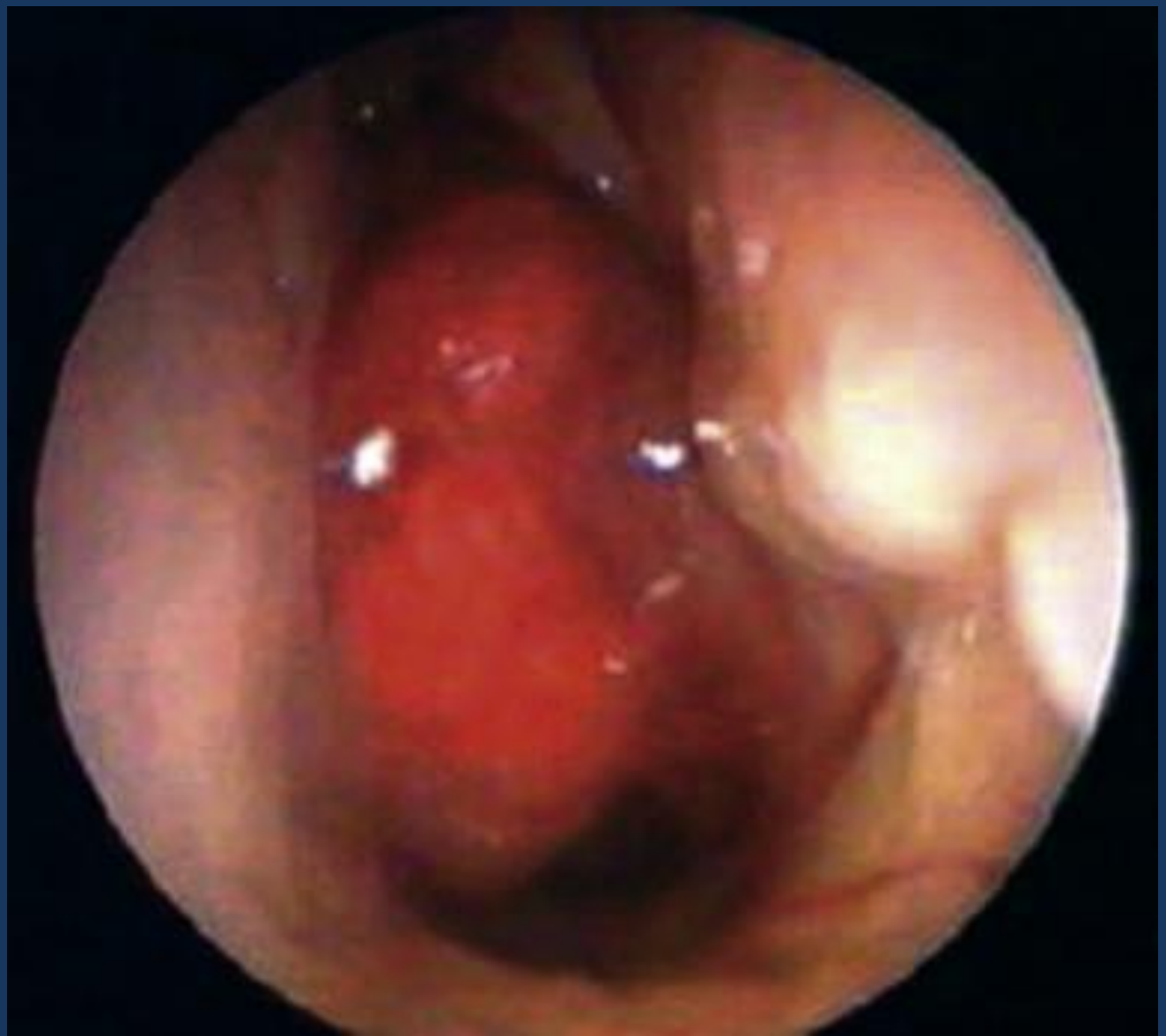
A. Foramen lacerum

B. Foramen ovale

C. Foramen rotundum



Physical exam



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Classification

World Health Organization (WHO) Classification of Nasopharyngeal Carcinoma	
Type 1 (I)	Squamous cell carcinoma
Type 2a (II)	Keratinizing undifferentiated carcinoma
Type 2b (III)	Nonkeratinizing undifferentiated carcinoma

Types 1, 2a, and 2b correspond to WHO types I, II, and III, respectively, and are used interchangeably.

Cummings

- The vast majority of patients with NPC—at least 90%—in the endemic region have the histologic pattern termed
  a. Type 2b (III) nonkeratinizing undifferentiated carcinoma
  b. Type 1 (I) squamous cell carcinoma
  c. Type 2a (II) keratinizing undifferentiated carcinoma

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Workup

- CT scan had been for many years the essential staging investigation for assessing the primary tumor, as well as regional disease. The soft tissue of the nasopharynx is shown well and CT is particularly useful in delineating clival and skull base erosion.
- MRI has been used increasingly in many centers.
  - Superior definition afforded by MRI in detecting soft tissue changes and intracranial involvement.
  - Higher sensitivity

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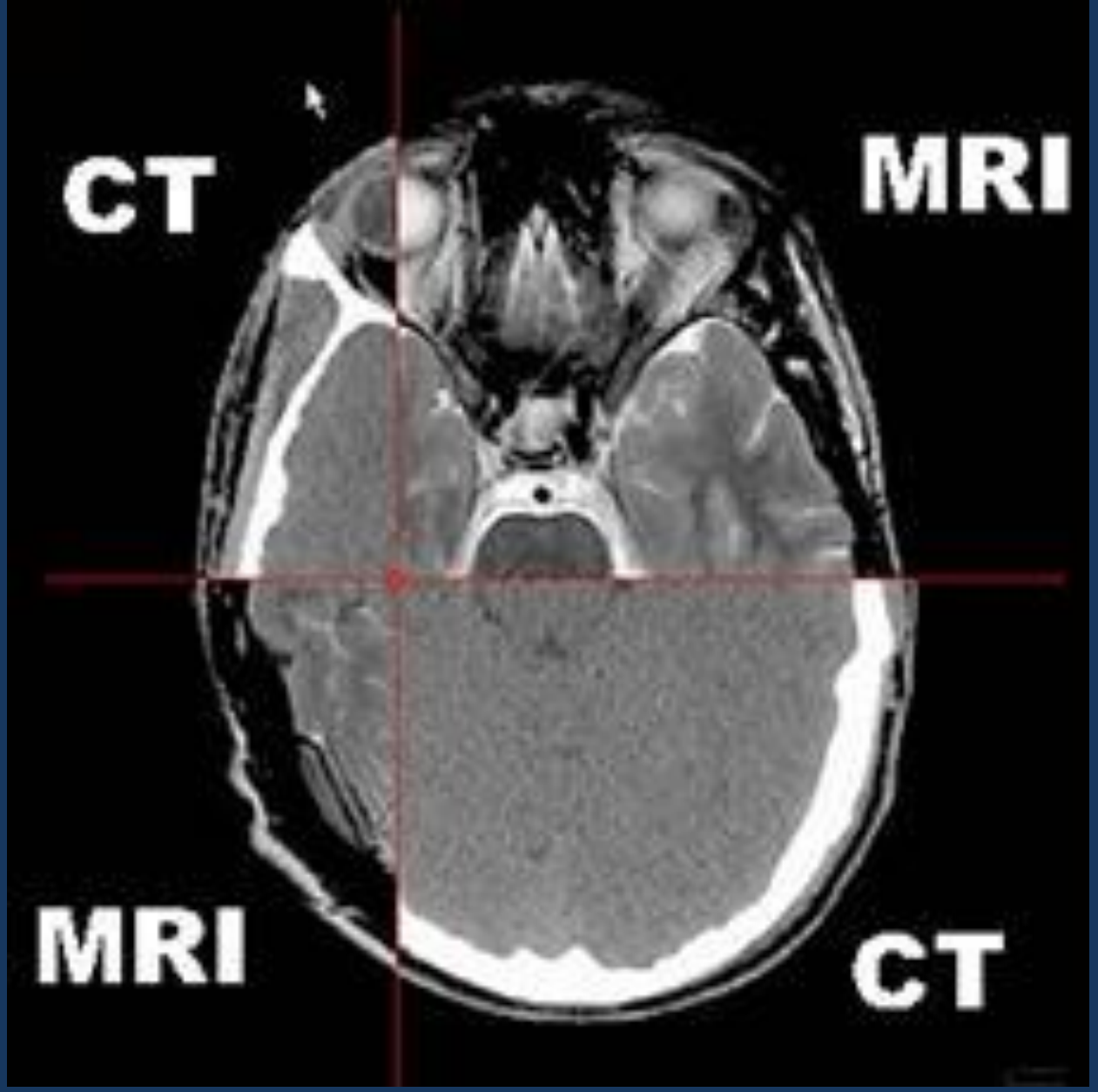

http://radonc.ucsd.edu/patient-info/Pages/what-to-expect.aspx

Workup

- Chest radiograph
- Ultrasound of liver
- Bone scans
- Alternatively, CT of lungs and liver

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The most common distant site of metastasis in NPC is

a. Skeleton
b. Liver
c. Lung
d. Brain

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Workup

- Audiogram and tympanogram
- EBV serology titers
  - IgA Viral Capsid Antigen (sensitive)
  - IgA Early Antigen (specific)

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The 2002 UICC TNM Staging of Nasopharyngeal Carcinoma

T Classification

Tx	Primary tumor unable to be assessed
T0	No evidence of tumor
T1	Confined to nasopharynx
T2a	Extends to nasal cavity, oropharynx
T2b	Tumor extends to parapharyngeal space
T3	Tumor involves sinuses, orbit, skull base, hypopharynx
T4	Intracranial or infratemporal involvement

N Classification

N0	No nodal involvement
N1	Ipsilateral lymph nodes < 6 cm
N2	Bilateral lymph nodes < 6 cm
N3	Lymph node > 6 cm; supraclavicular node

M Classification

M0	No distant metastasis
M1	Distant metastasis (includes mediastinal nodes)

Stage Classification

Stage I	T1N0M0
Stage II	T1N1M0, T2N0M0, T2N1M0
Stage III	T3N0-2M0, T1-2N2M0
Stage IVa	T4, any NM0
Stage IVb	any TN3M0
Stage IVc	any T, any N, M1

Treatment

- Stage I and II NPC – radiation only
- Stage III and stage IV – concurrent chemotherapy and radiation
- Stage IV NPC with locally advanced disease – neoadjuvant cisplatin followed by chemoradiation

Chan AT, Ma BB, Lo YM, et al: Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: therapeutic monitoring with plasma Epstein-Barr virus DNA. *J Clin Oncol* 2004; 22:3053-3060.

Radiation

- 60 to 70 Gy in the nasopharynx and both necks
- Side effects:
  - Mucositis
  - Xerostomia
  - Sinusitis
  - Custing
  - Bloody nasal discharge
  - +/- OE
  - Trismus
  - CN palsies

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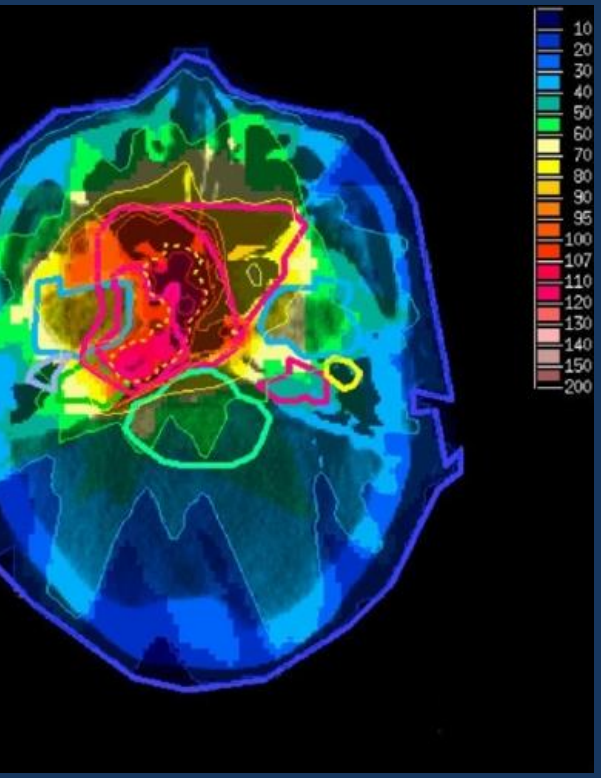
The most common cranial nerve to be affected postradiation, other than the cochlear-vestibular nerve, is:

- CN 12
- CN 1
- CN 2
- CN 3


3D

Intensity-Modulated Radiation Therapy



- Better recovery of salivary flow and better quality of life than those irradiated by 2-D RT [1]
- Whole saliva flow recovered partially to 40% of baseline [2]
- A general trend of deterioration in most quality of life scales was observed after IMRT, followed by gradual recovery [2]
- Persistent oral-related symptoms were found 2 years after treatment [2]

1. M.K. Kam, S.F. Leung, B. Zee et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients J Clin Oncol, 25 (2007), pp. 4873–4879

2. E.H. Pow, D.L. Kwong, J.S.T. Sham, V.H. Lee, S.C. Ng Can intensity-modulated radiotherapy preserve oral health-related quality of life of nasopharyngeal carcinoma patients?Int J Radiat Oncol Biol Phys, 83 (2012), pp. e213–e221

Intensity-Modulated Radiation Therapy

- Serious complications:
  - Temporal lobe necrosis, incidence was as high as 12–14% following concurrent CRT to a total dose of 68–70.2 Gy [1]
  - Massive bleeding due to damage of the internal carotid artery, was reported following dose escalation to 76 Gy at 2.17 Gy/fraction [2,3]
  - Therapeutic margin for NPC is extremely narrow

1. R.L. Bakst, N. Lee, D.G. Pfister et al. Hypofractionated dose-painting intensity modulated radiation therapy with chemotherapy for nasopharyngeal carcinoma: a prospective trial Int J Radiat Oncol Biol Phys, 80 (2011), pp. 148–153D.
2. L. Kwong, J.S. Sham, L.H. Leung et al. Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma Int J Radiat Oncol Biol Phys, 64 (2006), pp. 374–381
3. S. Lin, J. Pan, L. Han et al. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series Int J Radiat Oncol Biol Phys, 75 (2009), pp. 1071–1078

Treatment

- Intergroup-0099 Study (1998):
  - Cisplatin & conventional-fractionated RT followed by adjuvant chemotherapy with cisplatin plus 5 FU
  - Improvement in both event-free survival and overall survival

M. Al-Sarraf, M. LeBlanc, P.G. Giri et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099 J Clin Oncol, 16 (1998), pp. 1310–1317

Treatment

- Meta-analysis by Baujat et al. (2006)
  - Concurrent chemotherapy - most potent
  - Induction chemotherapy - reduce the risk of locoregional and distant failures resulting in improved EFS, but no benefit in overall survival
  - Adjuvant chemotherapy - no significant benefit in any endpoints.

B. Baujat, H. Audry, J. Bourhis et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients Int J Radiat Oncol Biol Phys, 64 (2006), pp. 47–56

Treatment limitations

Traditional regimen:

Cisplatin + RT

Cisplatin + 5 FU

- Only around 60% received all three scheduled cycles of adjuvant chemotherapy[1]
- The number of adjuvant cycles given had a significant impact on distant control [2]

1. M. Al-Sarraf, M. LeBlanc, P.G. Giri et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099 J Clin Oncol, 16 (1998), pp. 1310–1317

2. A.W.M. Lee, Y. Tung, R.K.C. Ngan et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 TrialsEur J Cancer, 47 (2011), pp. 656–666

Treatment

- Indications for surgical treatment of NPC are currently for local and regional recurrences

Treatment

- Indications for surgical treatment of NPC are currently for local and regional recurrences

  …and radiation complications

Surgery

- 5% to 10% of all newly diagnosed NPC patients will develop local recurrences
- 50% surgical salvageable (success depends on T)
- Contraindications
  - Carotid encasement
  - Intracranial invasion
  - Distant metastasis

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Surgical Approach

- 10 cm from the nasal vestibule to the nasopharynx
- Operating through a narrow and deep window
- Proximity of internal carotid artery
- Possible intracranial extension
- Operating in a previously radiated or chemoradiated field

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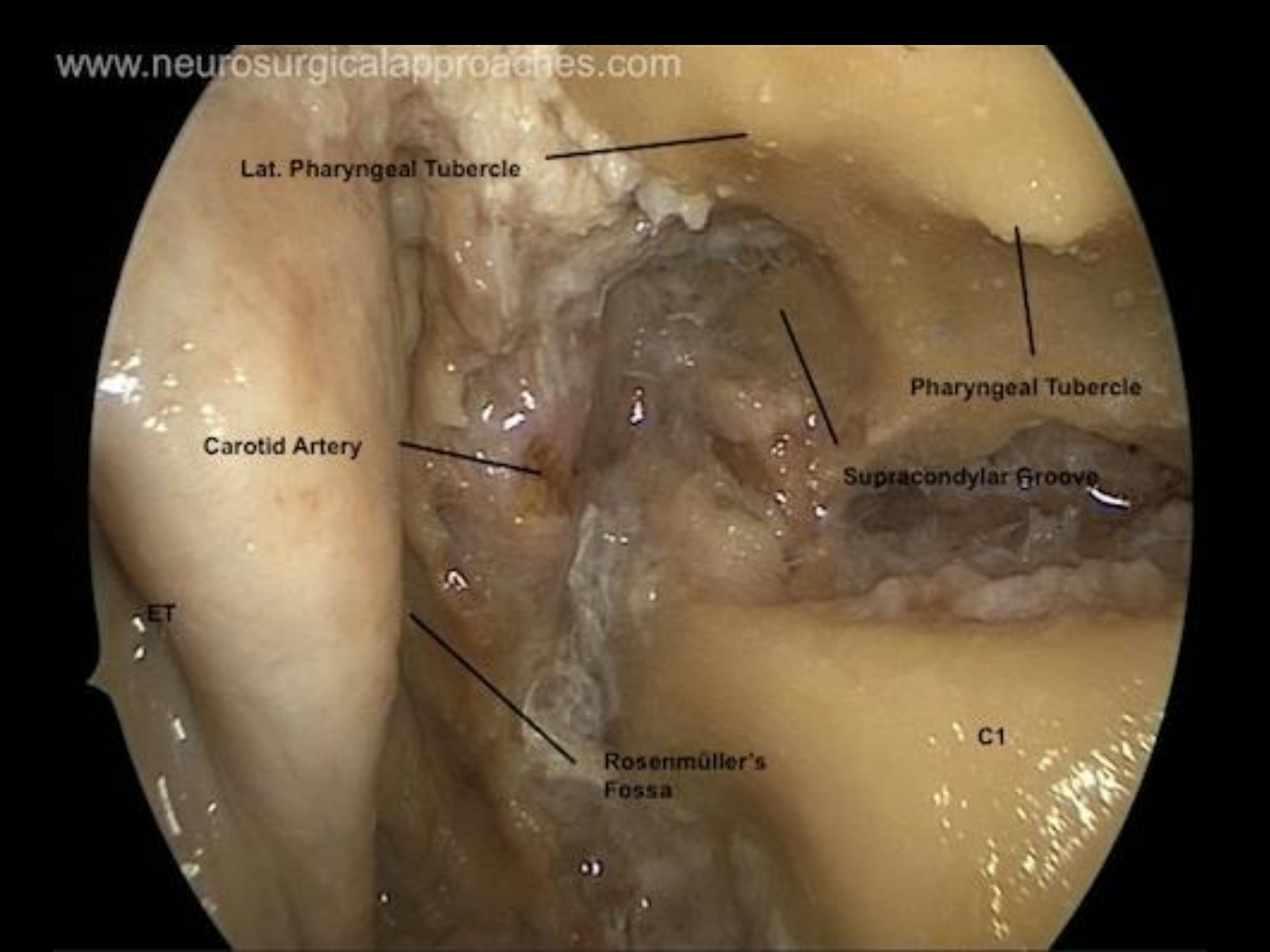
http://neurocirugia.com/neurosurgicalapproaches/doku.php?id=endoscopic_endonasal_odontoidectomy



Sugrical approach

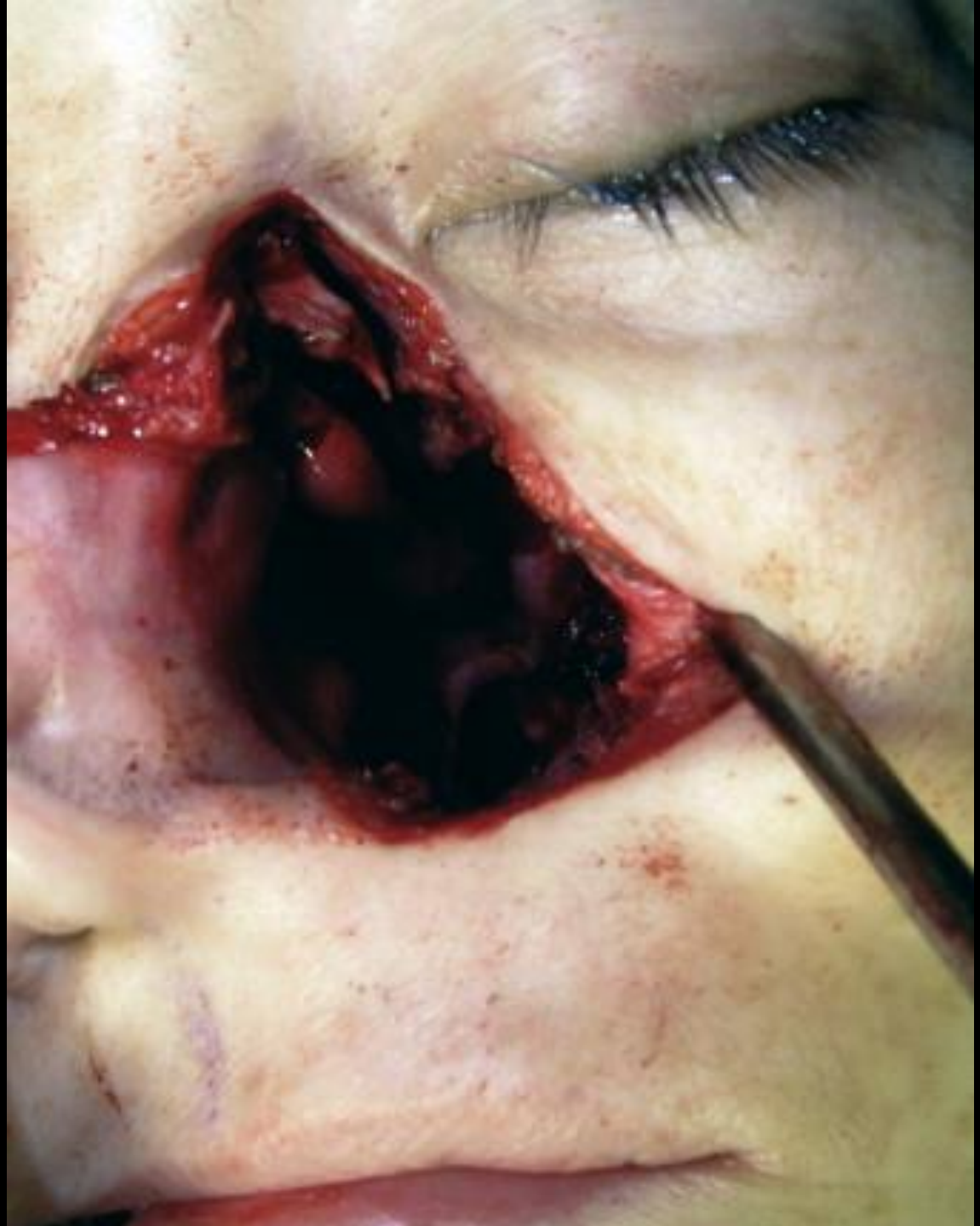
- Endoscopic
- Lateral Rhinotomy and Medial Maxillectomy Approach
- Maxillary Swing

Endoscopic

- Small recurrences
  - Centrally placed on the posterior wall of the nasopharynx
  - Relative contraindications: involvement of pterygopalatine fossa, the soft palate
- Adequate resection the roof of the nasopharynx and drilling down the vomer
- Resection of the posterior nasal septum
- +/- Resection of medial maxillary wall
- Resect down to the prevertebral muscles

Lateral Rhinotomy and Medial Maxillectomy Approach

- Tumors limited to the nasopharynx or with extension out to the pterygopalatine fossa.
- Lateral rhinotomy
- Medial wall of the maxilla resection
- Nasolacrimal duct is marsupialized
- Inferior half of the middle turbinate resection
- Posterior nasal septum resection
- The surgical access is adequate but not as wide as the view afforded by the maxillary swing approach.
- Does not require palatal split.
- Trismus is uncommon



Cummings

Maxillary Swing

- Described by Wei in 1991
- Weber-Ferguson incision to expose the maxilla
- Osteotomies to rotate the maxilla laterally (skin and subcutaneous tissues continue to provide the blood supply to the maxilla because it is not dissected off the anterior wall of the bone
- Medial maxillary wall is removed
- Excellent access to the pterygopalatine space.
- Potential complication of palatal fistulas from palatal split

Wei WI, Lam KH, Sham JS: New approach to the nasopharynx: the maxillary swing approach. *Head Neck* 1991; 13:200-207.

Chan JY, Chow VL, Wong ST, Wei WI. Surgical salvage for recurrent retropharyngeal lymph node metastasis in nasopharyngeal carcinoma. Head Neck. 2013 Mar 6. doi: 10.1002/hed.23214.

‘‘Thoroughness was not attainable at the bottom of a deep pit, surgery merely added to anemia of cancerous cachexia’’

- Dr. C. Jackson
JAMA 1901

THE END

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Prognosis

- Stage I and II NPC patients treated by radiation alone have 5-year overall survival rates of > 80%[2]
- Stage III or IV disease who have had concurrent chemoradiation have a 5-year overall survival rate of about 70%

Chan AT, Leung SF, Ngan RK, et al: Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2005; 97:536-539.