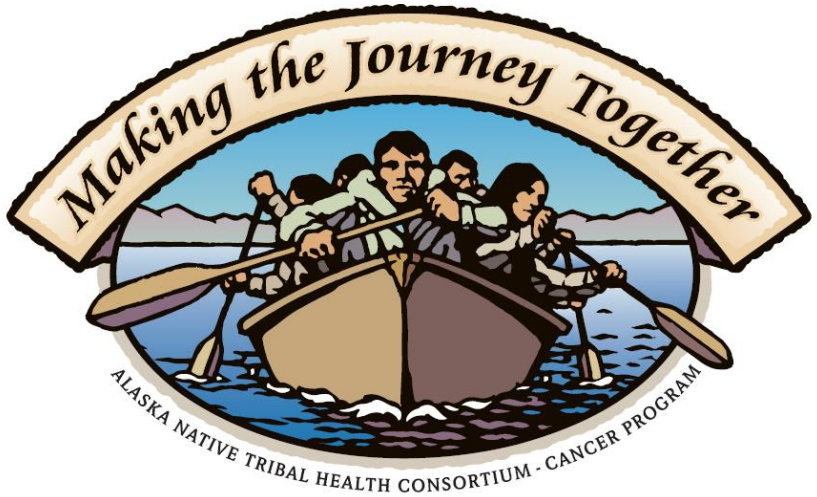
Nasopharyngeal Cancer in Alaska Native People: A Cancer Health Disparity



Matthew J. Olnes, MD, PhD, FACP

Hematology and Medical Oncology

Alaska Native Medical Center

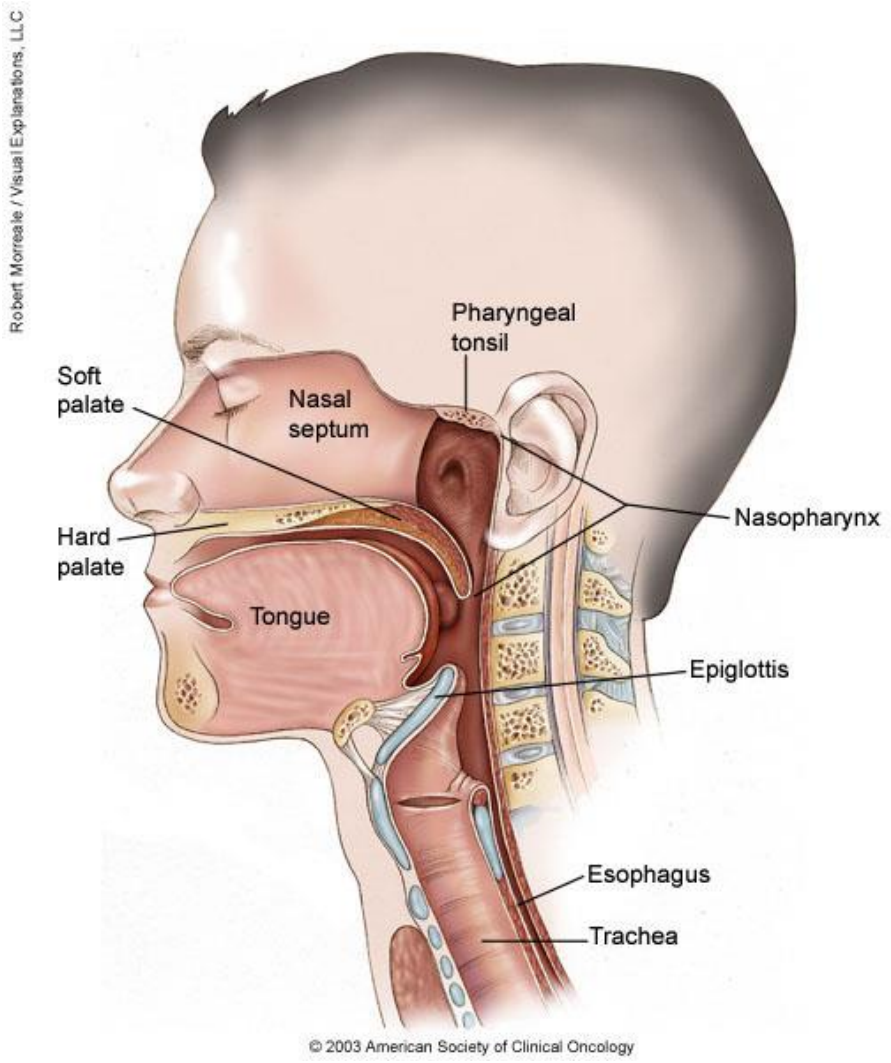
Objectives

- To understand the mortality of NPC in AN people in comparison to other ethnic populations
- To understand the role of chemotherapy in treating NPC and its complications and toxicities
- To understand the role of radiation therapy in treating NPC and its complications and toxicities
- To understand how AN patients with NPC present at the time of diagnosis, and how they respond to treatment

Nasopharyngeal Cancer in Alaska Native People

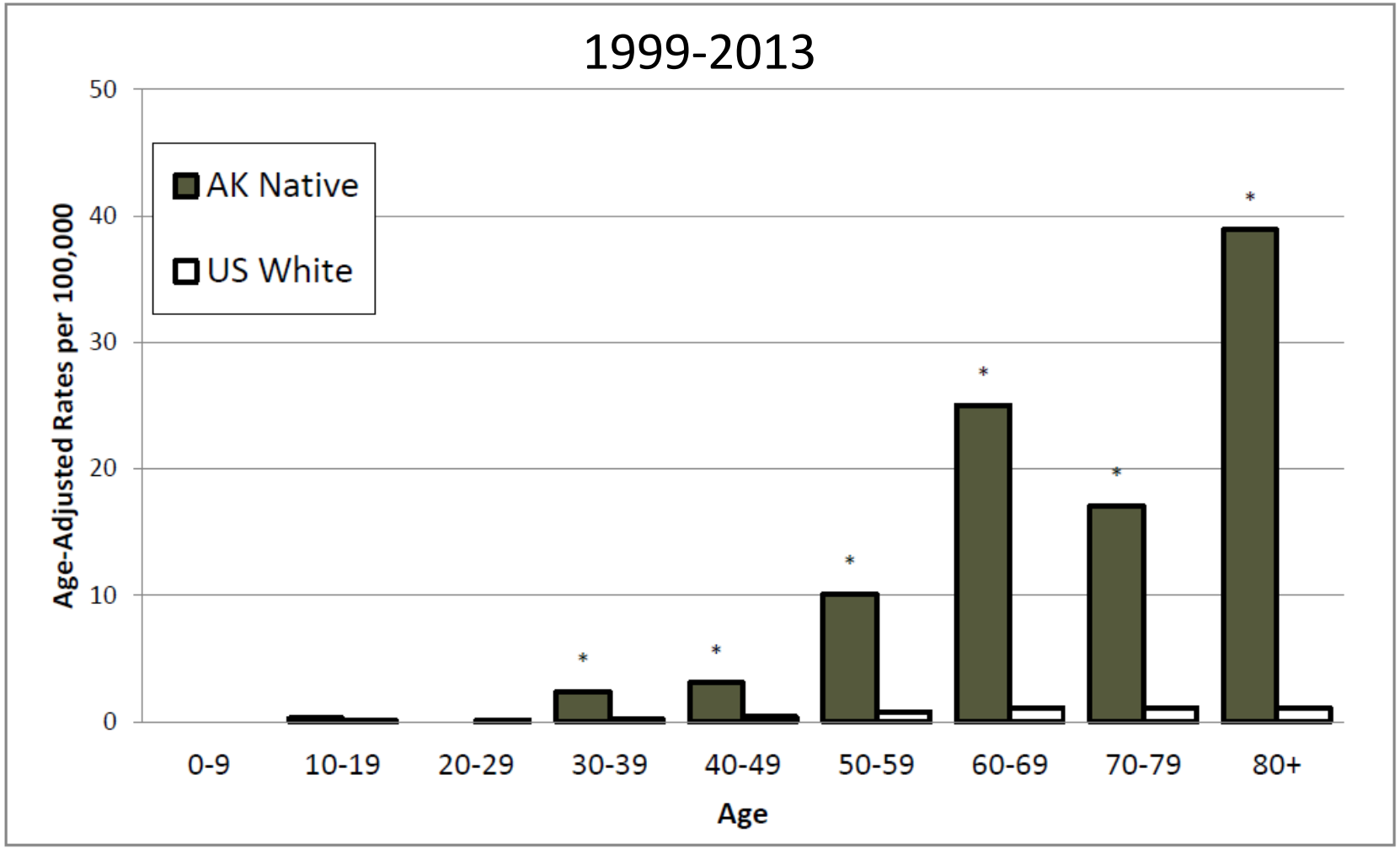
- Nasopharyngeal Cancer (NPC) is a cancer originating in the head and neck

- NPC is the leading cancer disparity among Alaska Native people
  - 17-fold higher incidence than in U.S. white population
  - Mortality rate 21 times higher than in U.S. whites



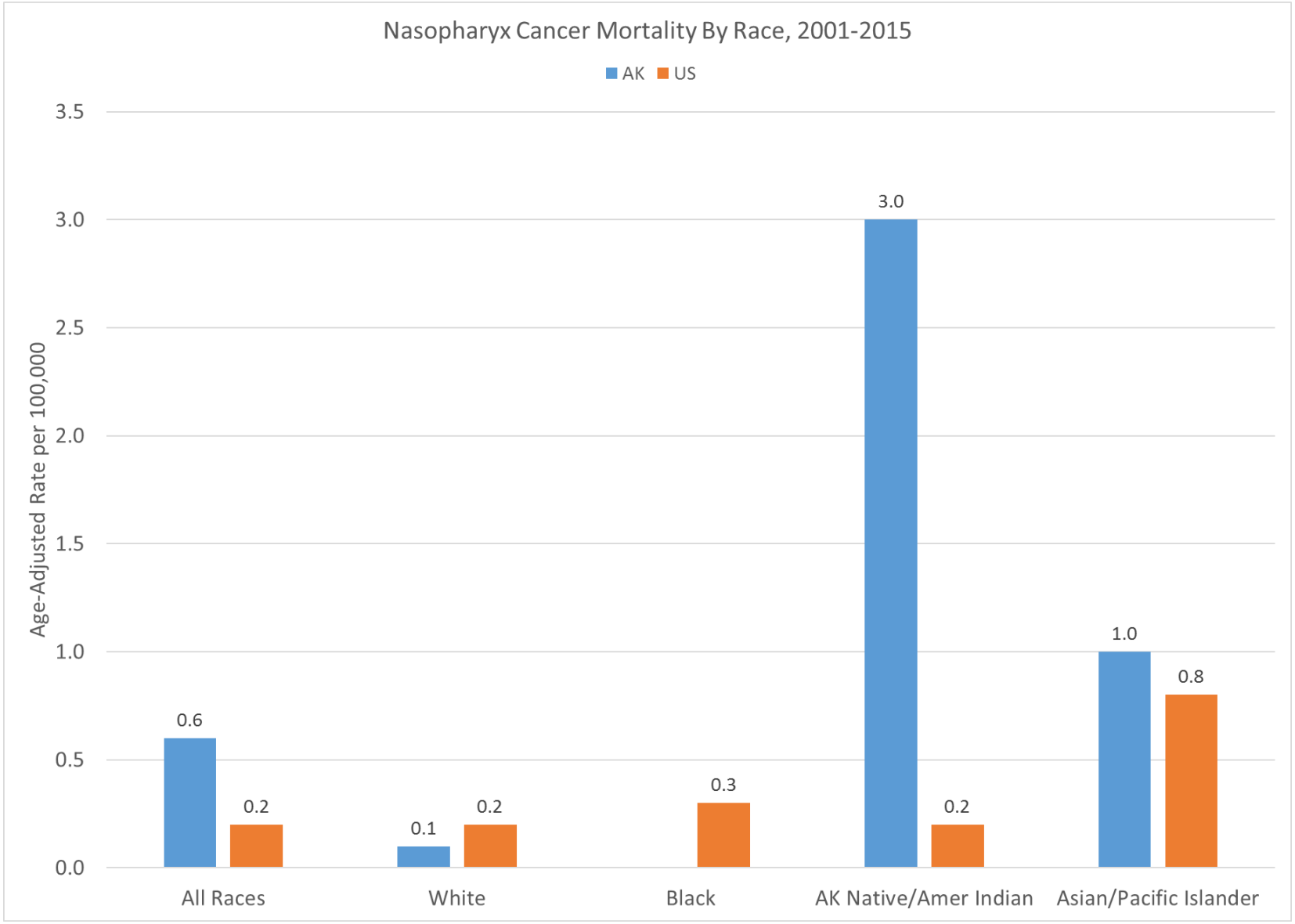
American Society Clin. Oncol.

Age-Specific Incidence Rates of NPC in Alaska Native People



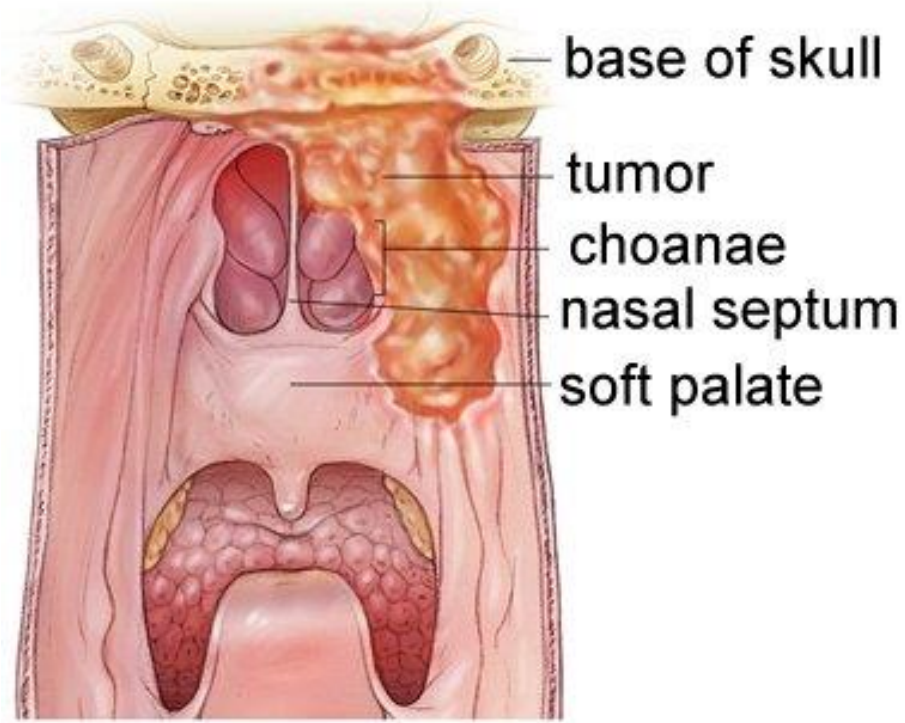
Cancer in Alaska Native People, 45-year report, http://www.anthctoday.org/epicenter/antr/index.html

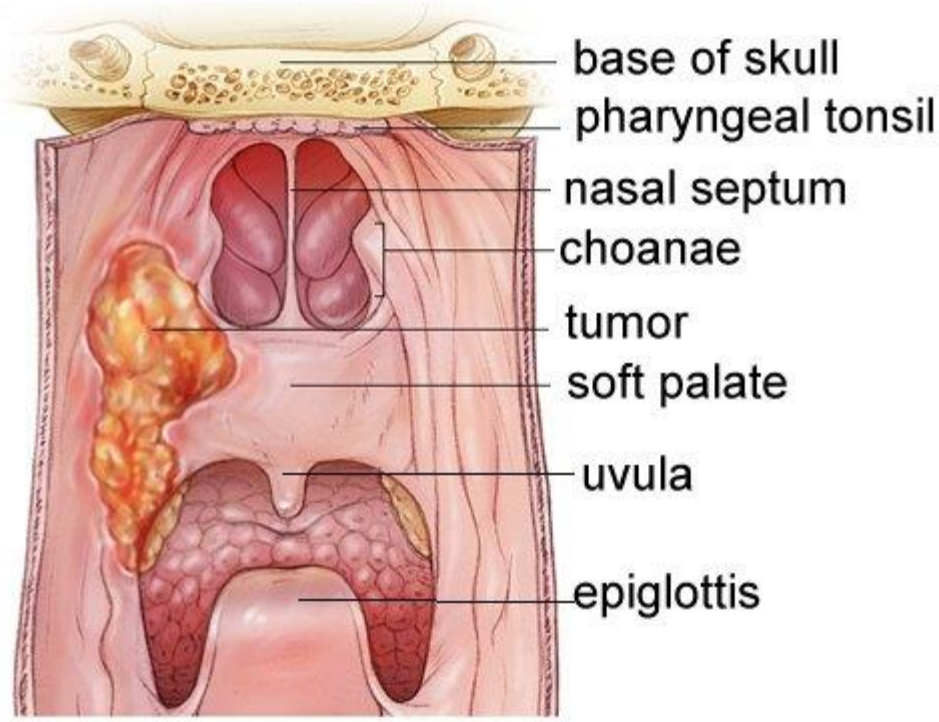
NPC Mortality by Race in U.S.



Alaska Vital Statistics, Division of Public Health, Alaska Department of Health and Social Services, February 2018.

NPC: Anatomic Location

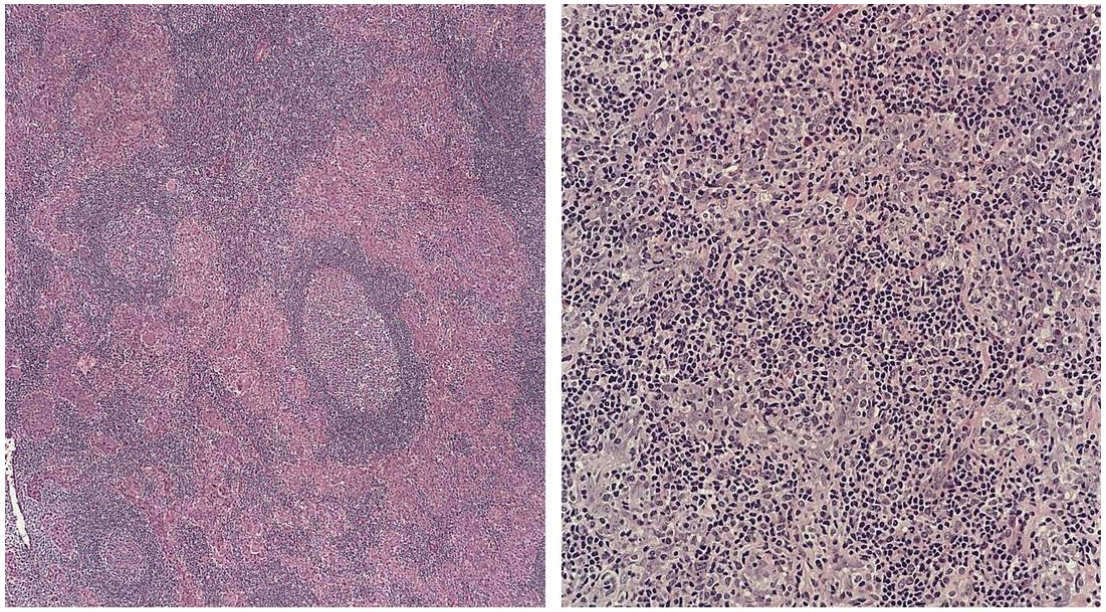




About Cancer, 2013

WHO Classification of NPC

- Type I: keratinizing squamous cell carcinomas
- Type II: non-keratinizing squamous carcinomas
- Type III: undifferentiated carcinoma- high local control rate, higher incidence of distant metastasis
- Types II and III have a stronger relationship with Epstein-Barr virus



METASTATIC UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA IN LYMPH NODE
Examination of the lymph node at medium magnification helps appreciate the cohesive growth pattern.
Left: In this example, the growth (pink staining) occurs predominantly between lymphoid follicles.
Right: The cohesive quality of the tumor can be appreciated as irregular discrete trabeculae.

Pathology Outlines

NPC Staging: Anatomic Stage Groups

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Head and Neck Cancers

NCCN Guidelines Index
Table of Contents
Discussion

Table 2
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Nasopharynx (8th ed., 2017)
(The following types of cancer are not included: Mucosal melanoma, lymphoma, sarcoma of the soft tissue, bone and cartilage.)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Carcinoma *in situ*
T1	Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/ or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)
A grading system is not used for NPCs.

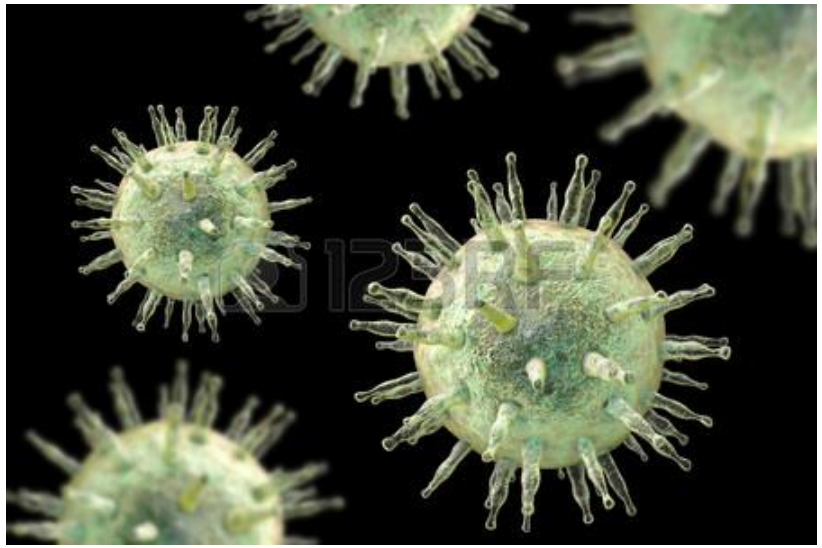
Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T0,T1	N1	M0
	T2	N0,N1	M0
Stage III	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage IVA	T4	N0,N1,N2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

NCCN, 2020

Epstein-Barr Virus and NPC

- Greater than 95% of patients with WHO types II and III have EBV DNA incorporated into the tumor genome
- Helpful as diagnostic tool to distinguish between squamous cell carcinoma (WHO type I)
- Found in both endemic, and non-endemic areas of the world
- Some studies have shown utility in screening for EBV in endemic populations and performing ENT examinations in those who are EBV positive



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 10, 2017 VOL. 377 NO. 6

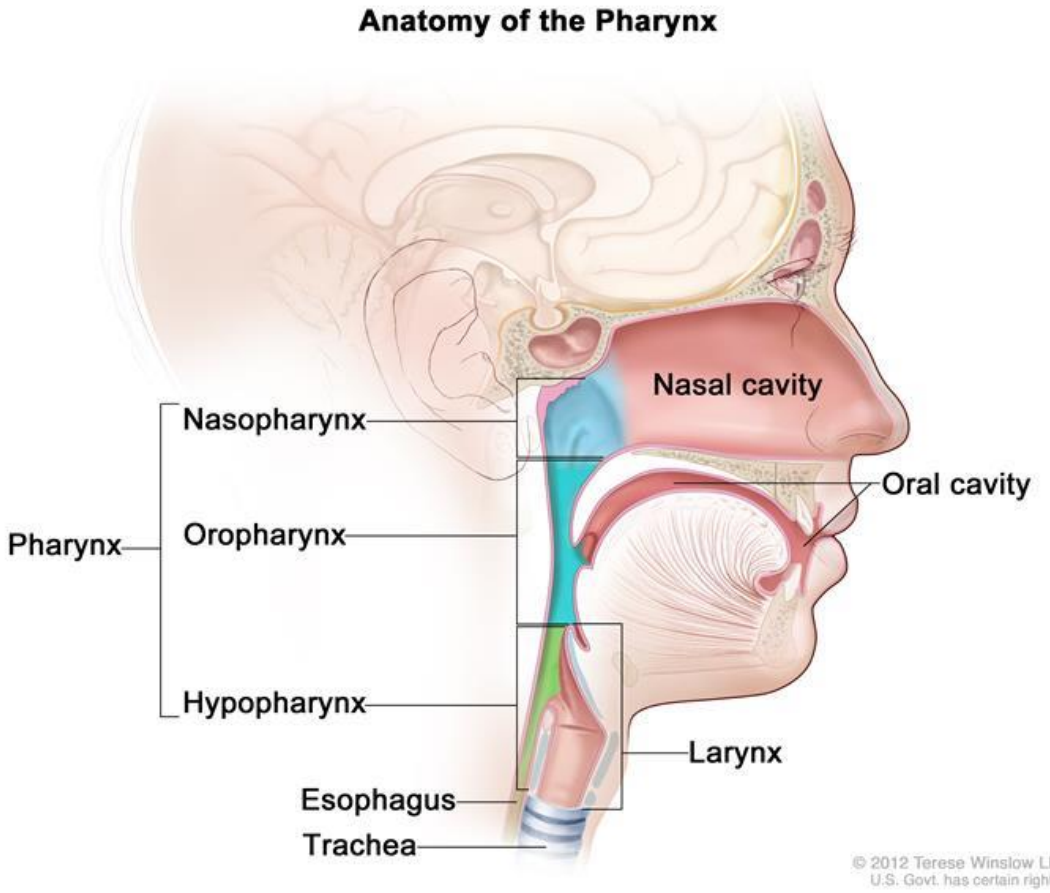
Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

K.C. Allen Chan, F.R.C.P.A., John K.S. Woo, F.R.C.S., Ann King, F.R.C.R., Benny C.Y. Zee, Ph.D., W.K. Jacky Lam, F.R.C.S., Stephen L. Chan, F.R.C.P., Sam W.I. Chu, B.Sc., Constance Mak, B.S.N., Irene O.L. Tse, B.N., Samantha Y.M. Leung, B.N., Gloria Chan, R.N., Edwin P. Hui, F.R.C.P., Brigette B.Y. Ma, M.D., Rossa W.K. Chiu, F.R.C.P.A., Sing-Fai Leung, F.R.C.R.,* Andrew C. van Hasselt, F.R.C.S., Anthony T.C. Chan, F.R.C.P., and Y.M. Dennis Lo, F.R.S.

- 20,000 people screened for EBV DNA in blood
- Those with positive tests were screened one month later
- 309 people (1.5%) had persistently positive EBV DNA levels
- All screened for NPC with fiberoptic endoscopies + MRIs
  - 34 (11%) of people had NPC upon screening
  - 71% of people had stages I or II disease

Initial Clinical Presentation of Nasopharyngeal Carcinoma (NPC)

- A lump in the nose or neck
- A sore throat
- Trouble breathing or speaking
- Nosebleeds
- Trouble hearing
- Pain or ringing in the ear
- Headaches
- Bone pain

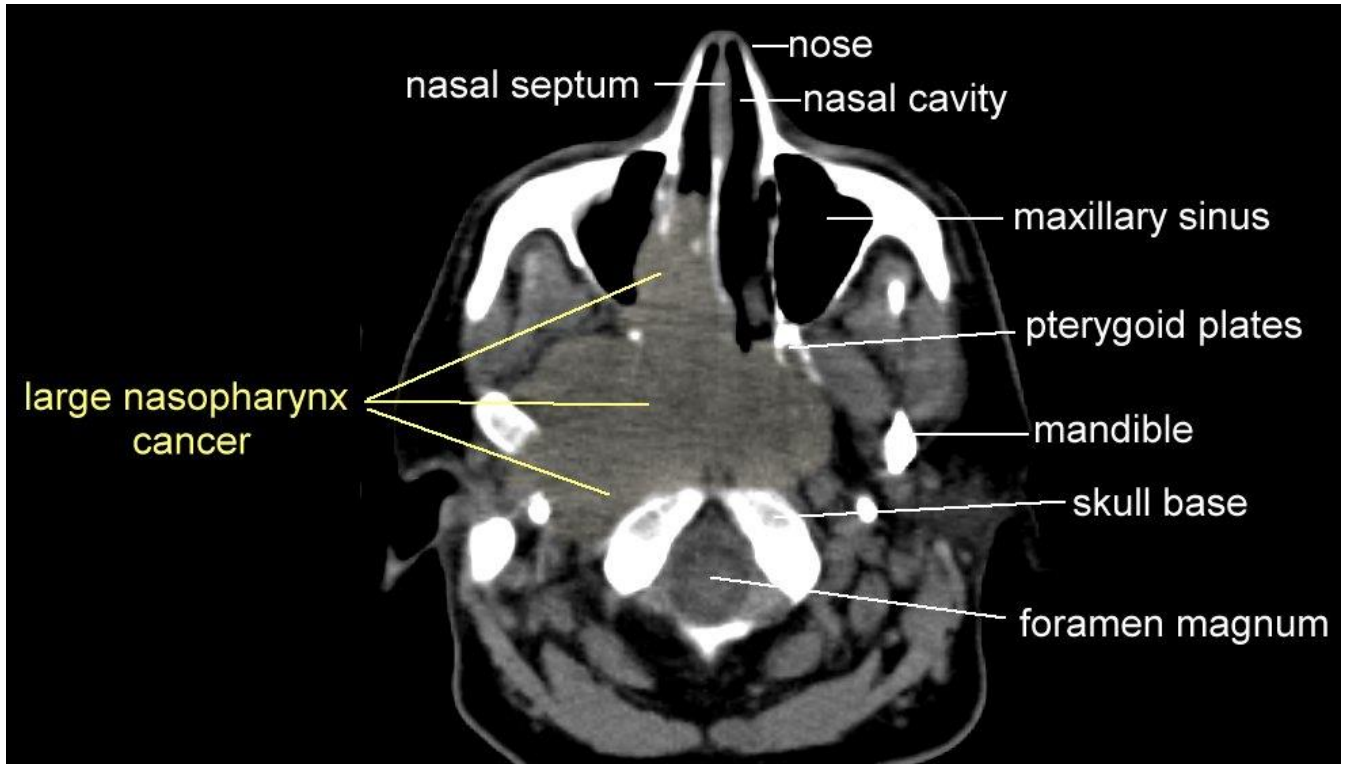


National Cancer Institute

Diagnostic Evaluation of Nasopharyngeal Carcinoma (NPC)

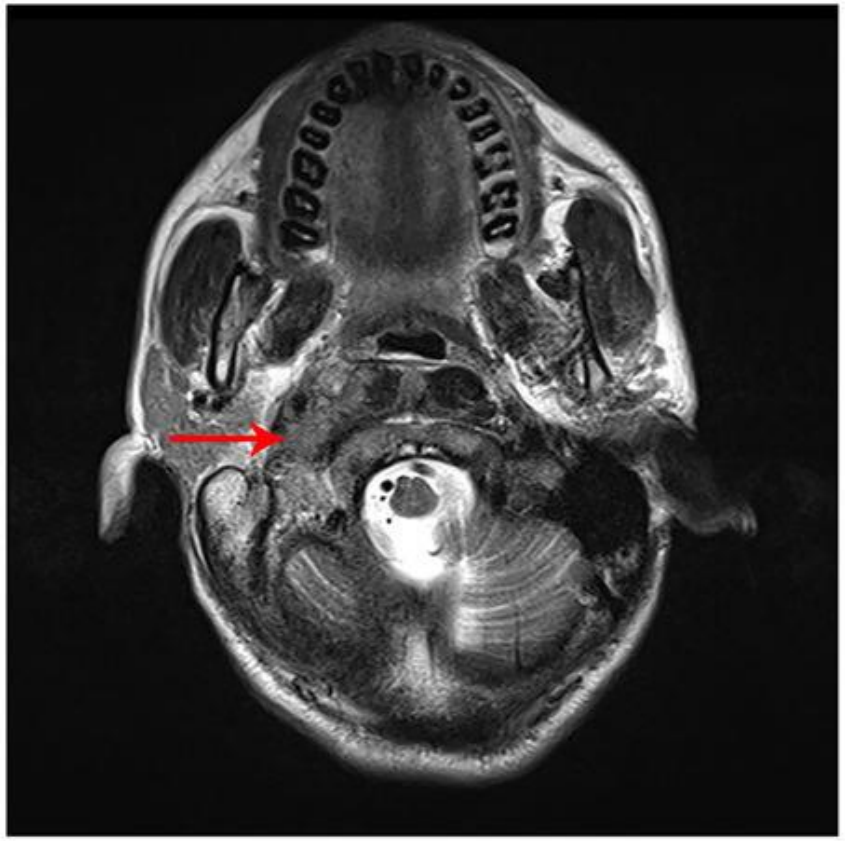
- History and physical examination
  - Any suspicious presenting symptoms?
  - Enlarged lymph nodes or cranial nerve findings?
  - Any weight loss, signs or symptoms of systemic disease?
- Neurologic examination
  - Attention to cranial nerve exam
- Audiology examination
- Imaging: MRI, diagnostic CT, PET/CT
- Biopsy of nasopharynx, upper aerodigestive tract

NPC: CT Imaging

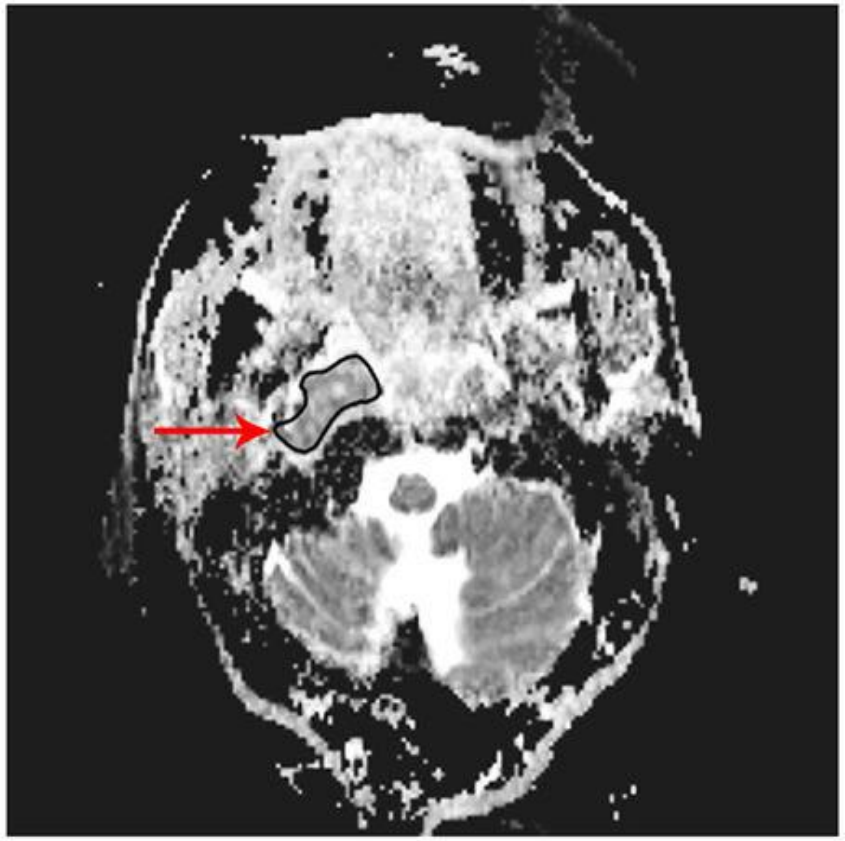


About Cancer, 2013

NPC: MRI Imaging



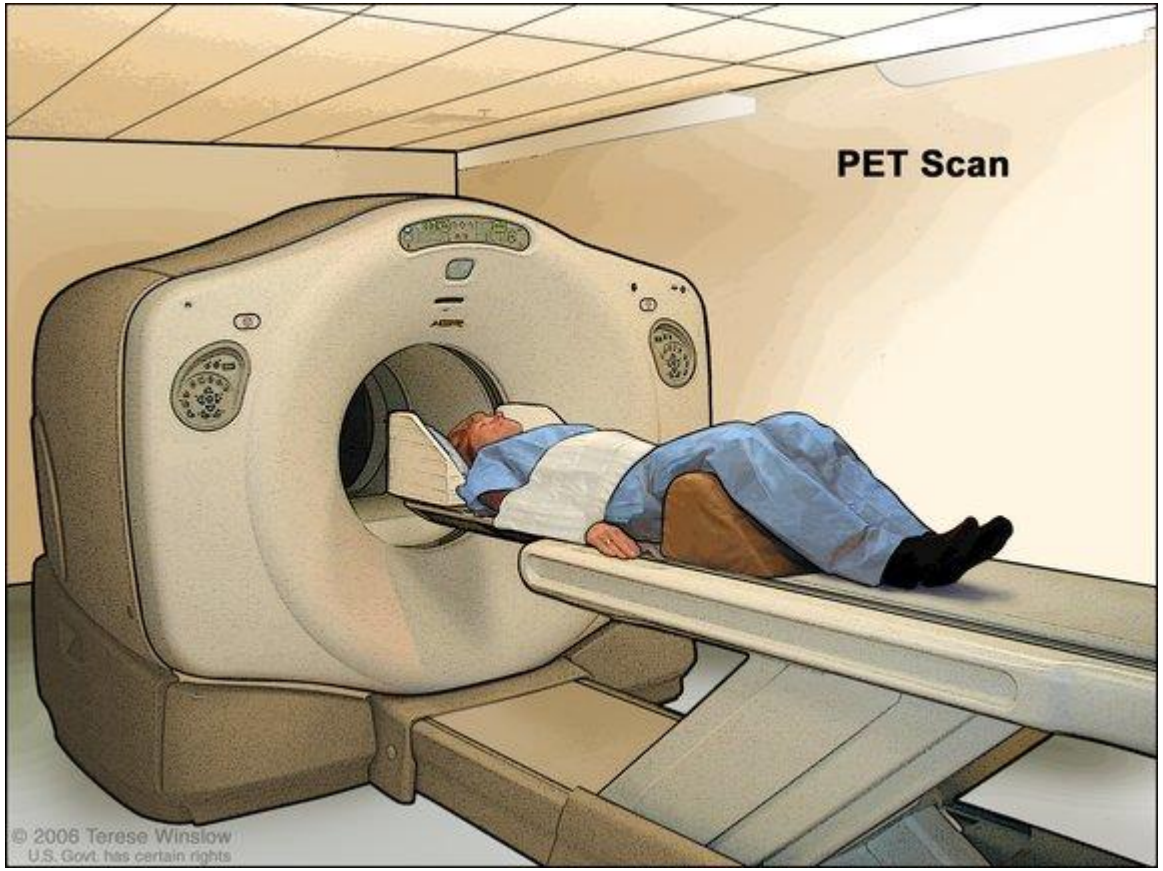
a Axial T2 imaging



b Diffusion weighted imaging

Zhang et al, Sci. Reports, 2015

Positron Emission Tomography CT Imaging



NCI

Establishing a Tissue Diagnosis

Diagnostic Evaluation

Histopathological Evaluation

- Biopsy : first necessary investigation for NPC
- Endoscopic biopsy : Ideally it shuold be carried out during the patient's ist outpatient visit in suspected cases.
- The most common sites are roof of nasopharynx and fossae of Rosenmuller.
- FNA biopsy : should be done in suspicious neck lump.

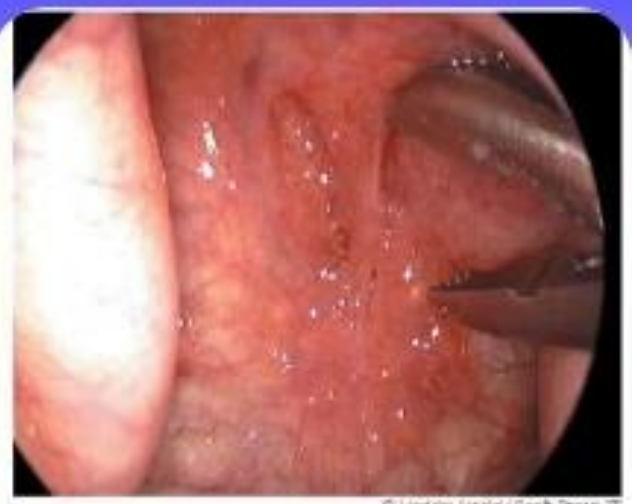


Figure 188.13 Biopsy of a left nasopharyngeal carcinoma under direct visual guide. A 0° rigid nasendoscope was introduced through the right nostril while Takahashi biopsy forceps were passed along the floor of the left nostril (ipsilateral to the side of the tumour). Note the very accurate placement of the biopsy forceps.

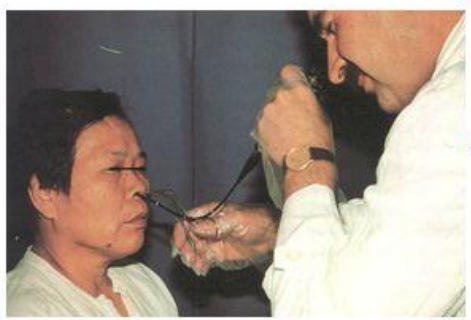
Establishing a Tissue Diagnosis

Nasopharyngeal cancer (NPC)

7th most prevalent cancer in Hong Kong.

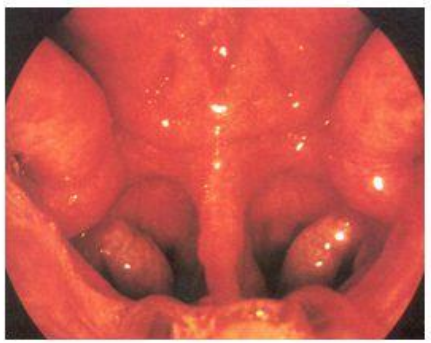
Problems in clinical management of NPC:-

1. Diagnosis at late stage (at stage 3/4)
2. Frequent relapse (>50% for CR patients)

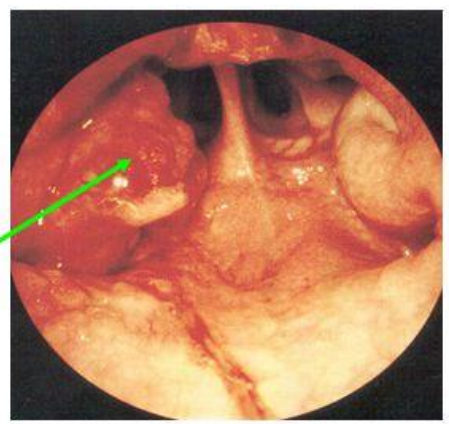


Tumor on the right eustachian cushion

Normal nasopharynx

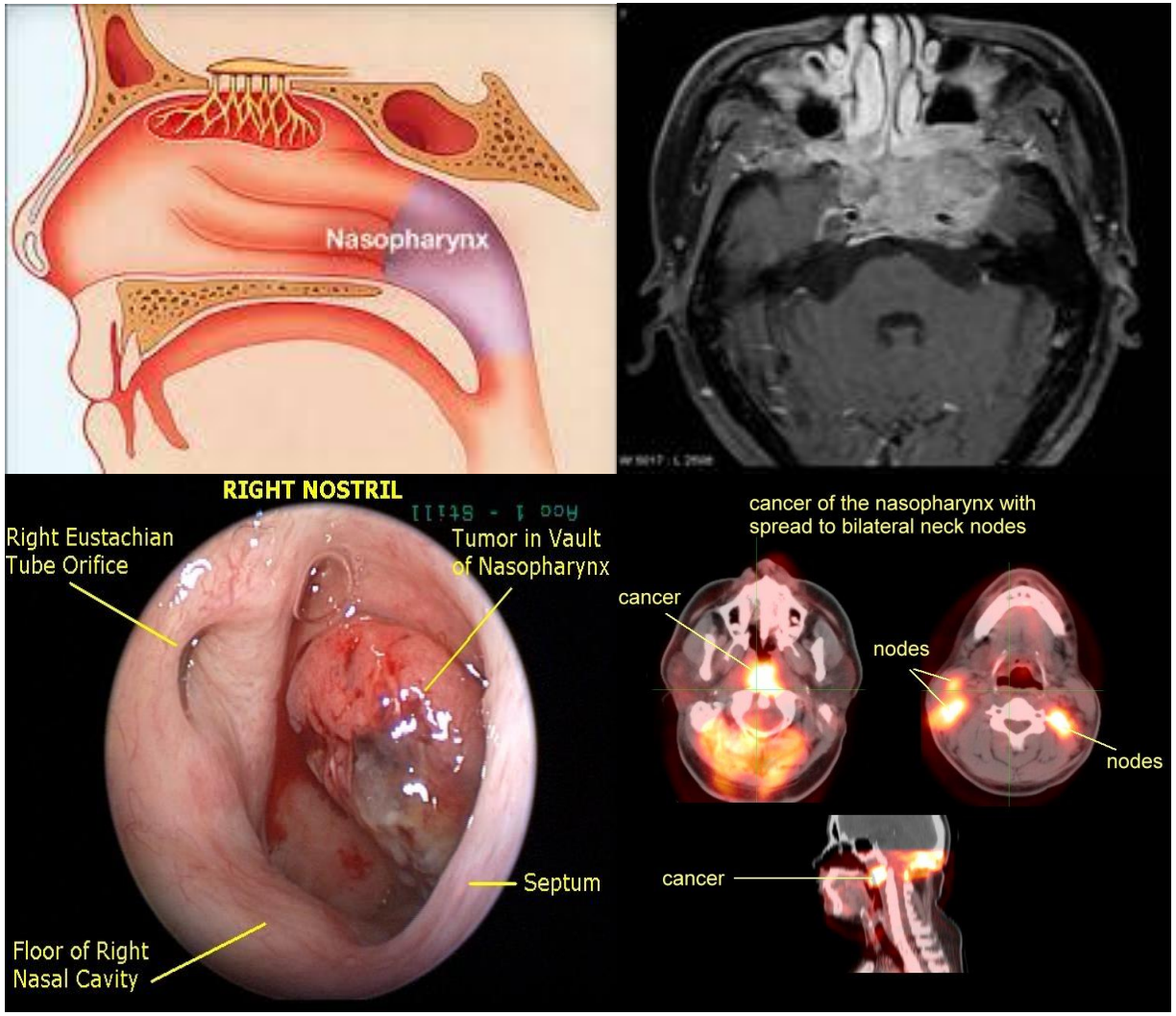


Nasopharynx with tumor



Cho WC. Most common cancers in Asia-Pacific region: nasopharyngeal carcinoma. In: *Cancer report of Asian-Pacific region 2010.* 284-289.

Nasopharynx Cancer – Not a Surgical Disease



- Tumors in the nasopharynx are either extremely dangerous to resect or result in severe functional deficits

- Hence, standard of care treatment involves combination of chemotherapy and radiation
  - Induction chemo, chemo-RT
  - Chemo-RT, adjuvant chemo

NPC: Treatment Response Rates

- Response rates and duration of response depends on stage
  - Stages I-II, good prognosis with overall response rates of 70-95%
  - More advanced disease has a worse prognosis
    - Similarly high initial response rate, but shorter time to relapse
    - Decreased overall survival
  - Most studies report a 3 year disease-free survival rate of 50-70%, and 3 year overall survival rate of 60-90%
  - Most studies (and clinical experience) show lower rates of long term relapse-free survival and overall survival
  - Relapses can be local or with systemic disease, often with bone involvement

Treatment for Progressive or Recurrent Disease

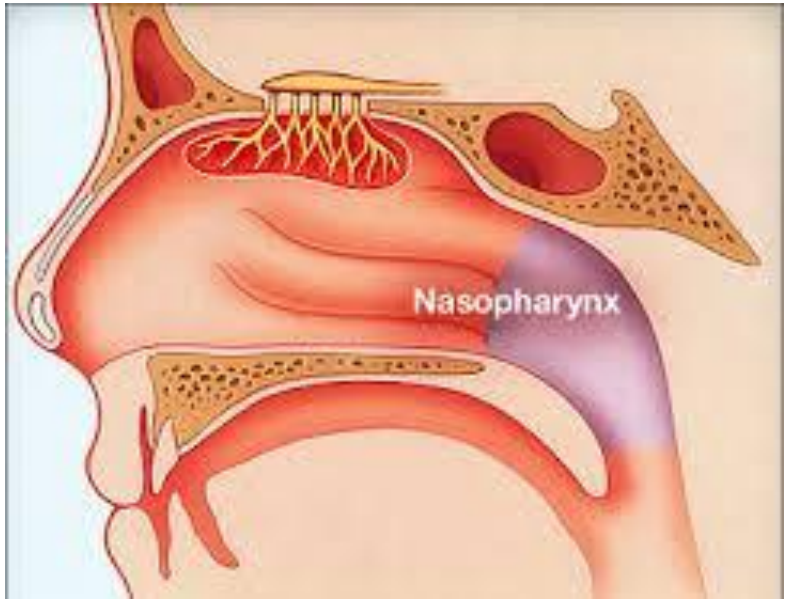
- Intensity-modulated radiation therapy, or internal radiation therapy
- Surgery
- Chemotherapy
- A clinical trial of chemotherapy
- A clinical trial of stereotactic radiation therapy
- *Immune checkpoint inhibitor therapy ?*

Specific Aims

- To create a statewide database of AN patients with NPC derived from:
  - Alaska Native Tumor Registry
  - Alaska Native Medical Center Tumor Registry
  - Electronic Patient Record Reviews
- To systematically describe patterns of care and clinical outcomes of AN NPC patients following radiation and chemotherapy regimens
- To determine whether baseline clinical and pathological features correlate with clinical responses to current NPC treatment regimens

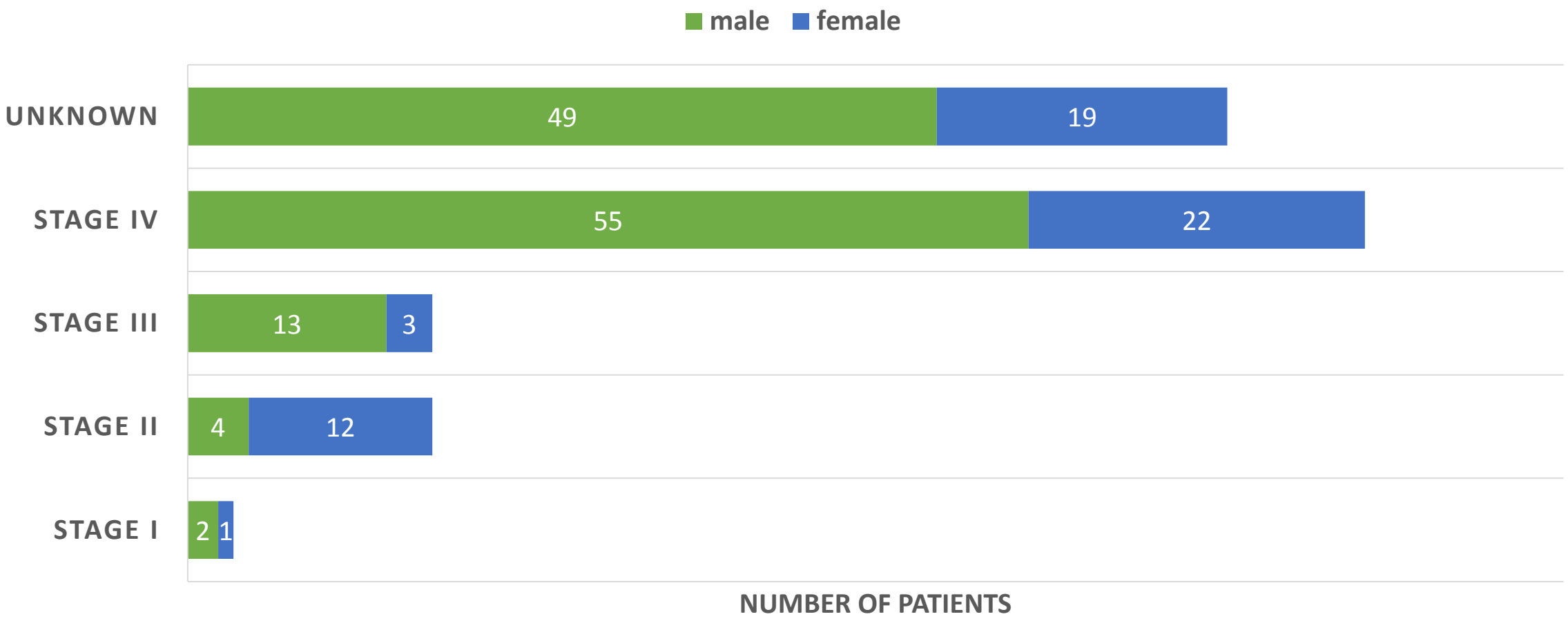
NPC Alaska Native Patient Cohort

- Year Diagnosed: 1975-2015
- 180 Total patients
  - 123 Male (68%)
  - 57 Female (32%)
- Median Age of Diagnosis
  - Male: 59.5 years
  - Female: 60.9 years



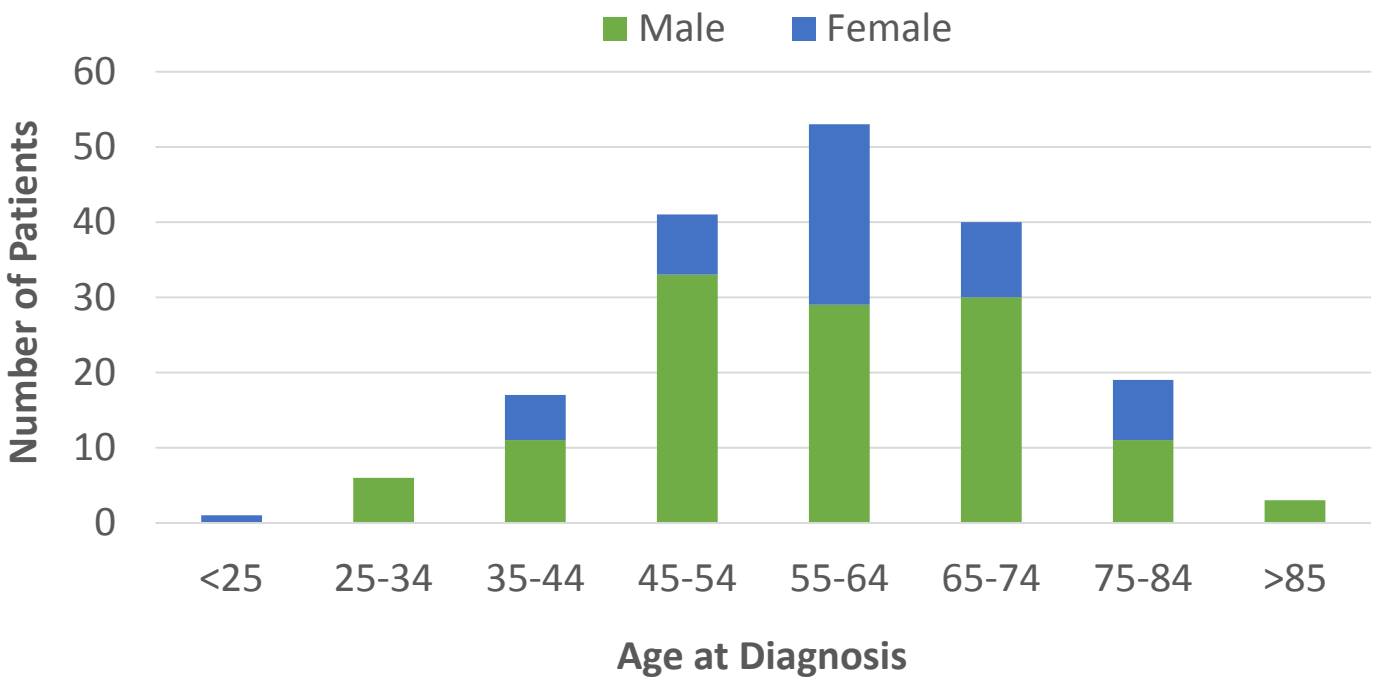
Olnes et al, ASCO 2018

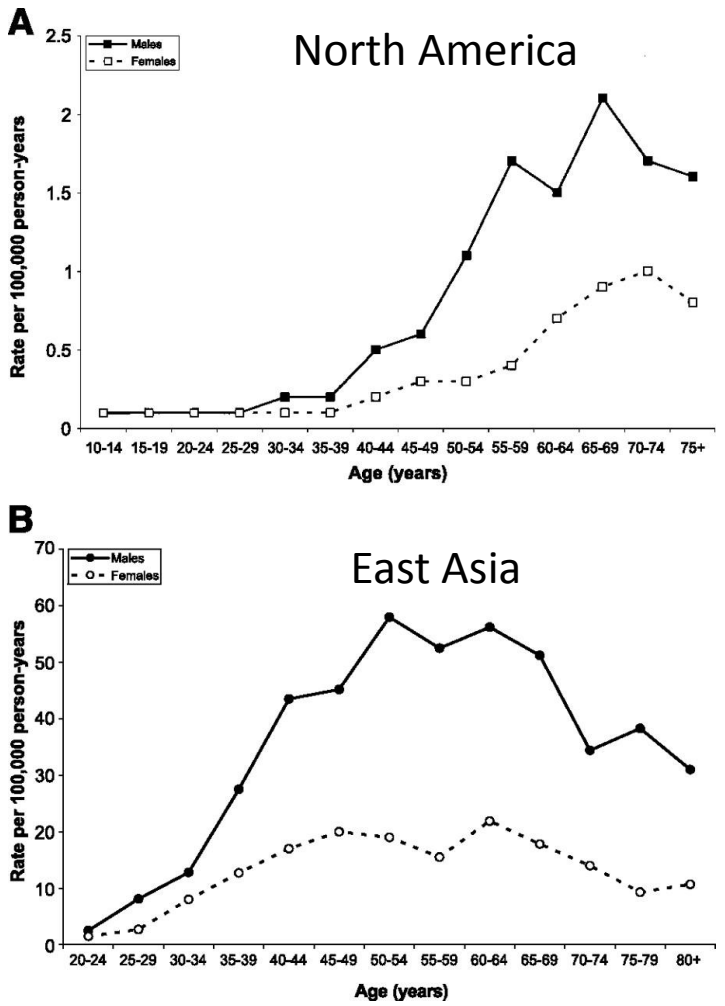
NPC Stage at Diagnosis



Olnes et al, ASCO 2018

Age at Time of Diagnosis

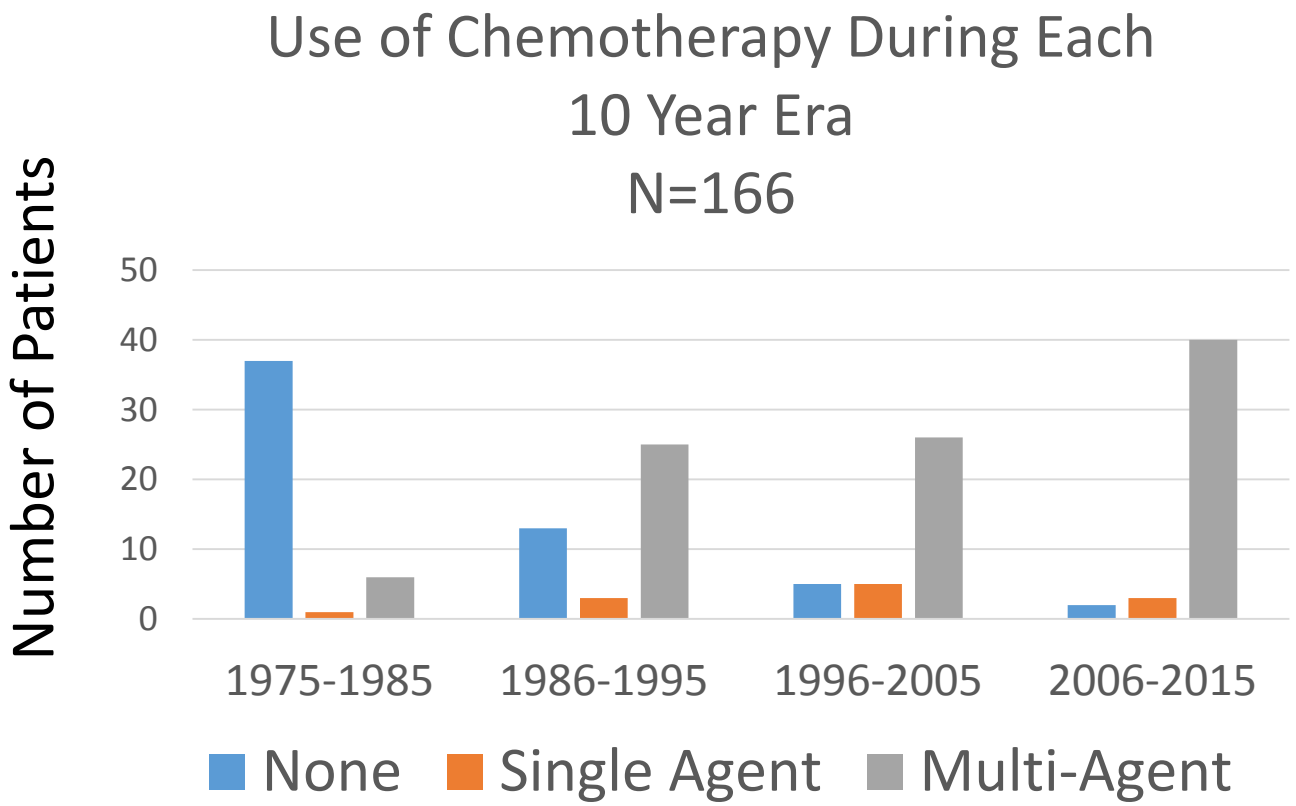




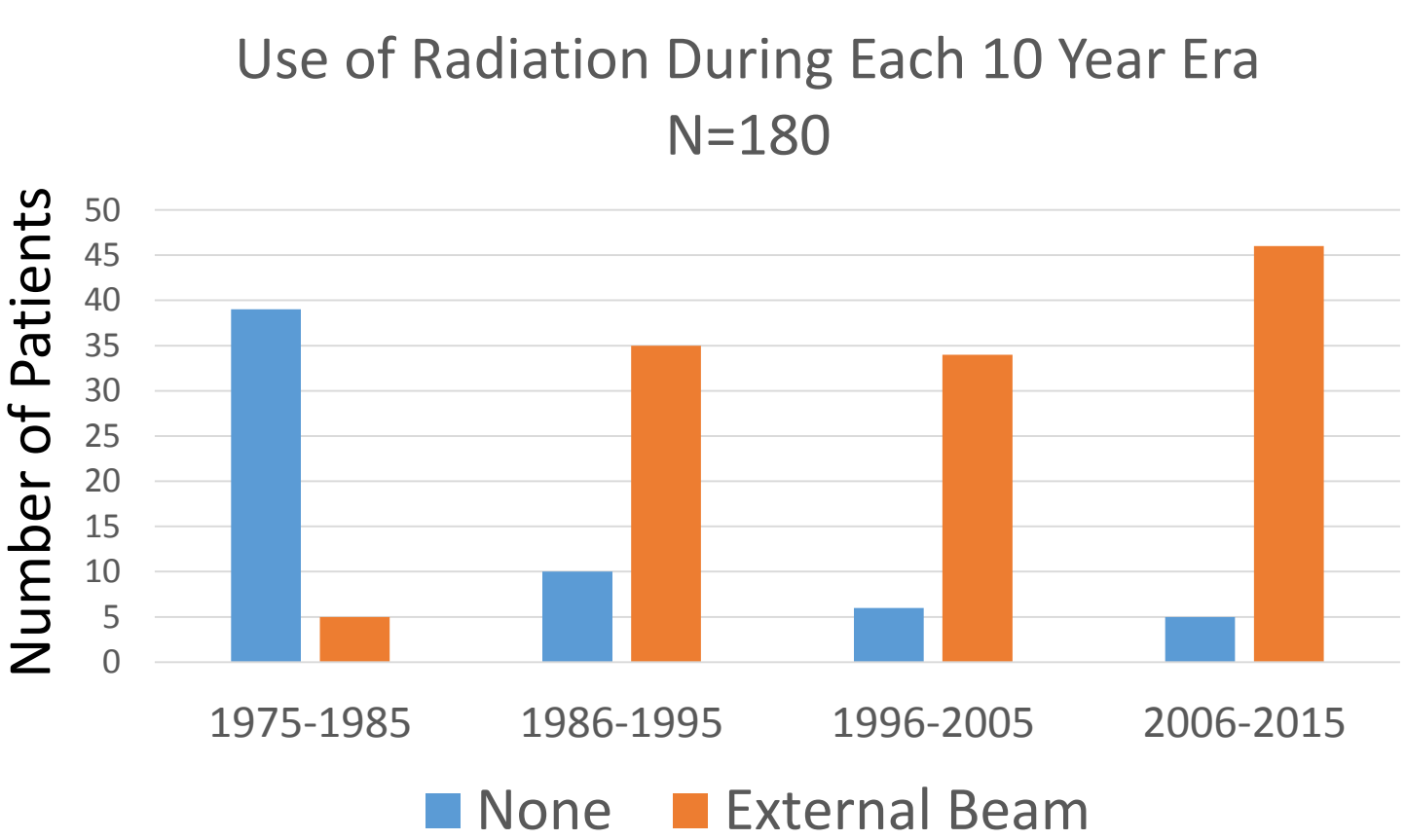
Olnes et al, ASCO 2018

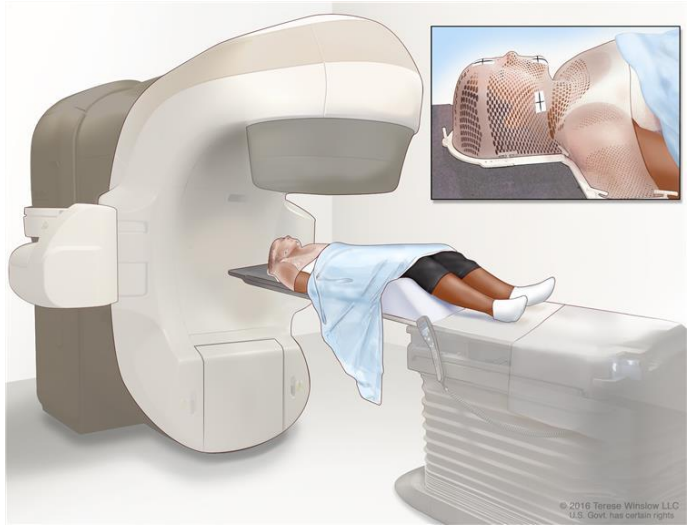
Chang ET, et al., Cancer Epidemiology, Biomarkers & Prevention. 2006, 15: 2356.

Chemotherapy for NPC in Alaska Native People



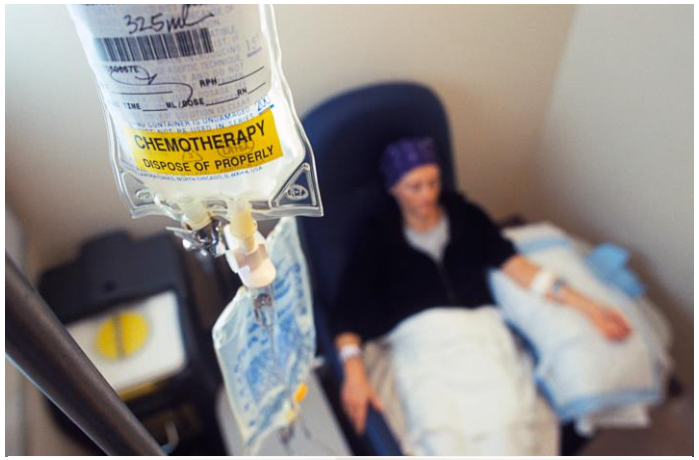
Radiation Therapy for NPC in Alaska Native People

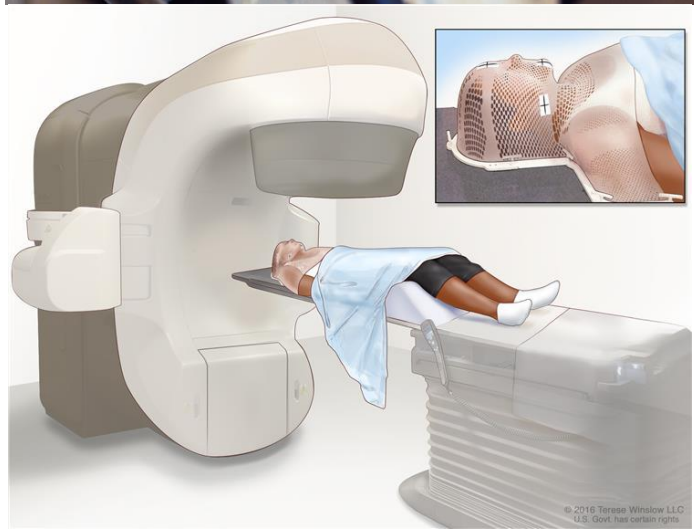




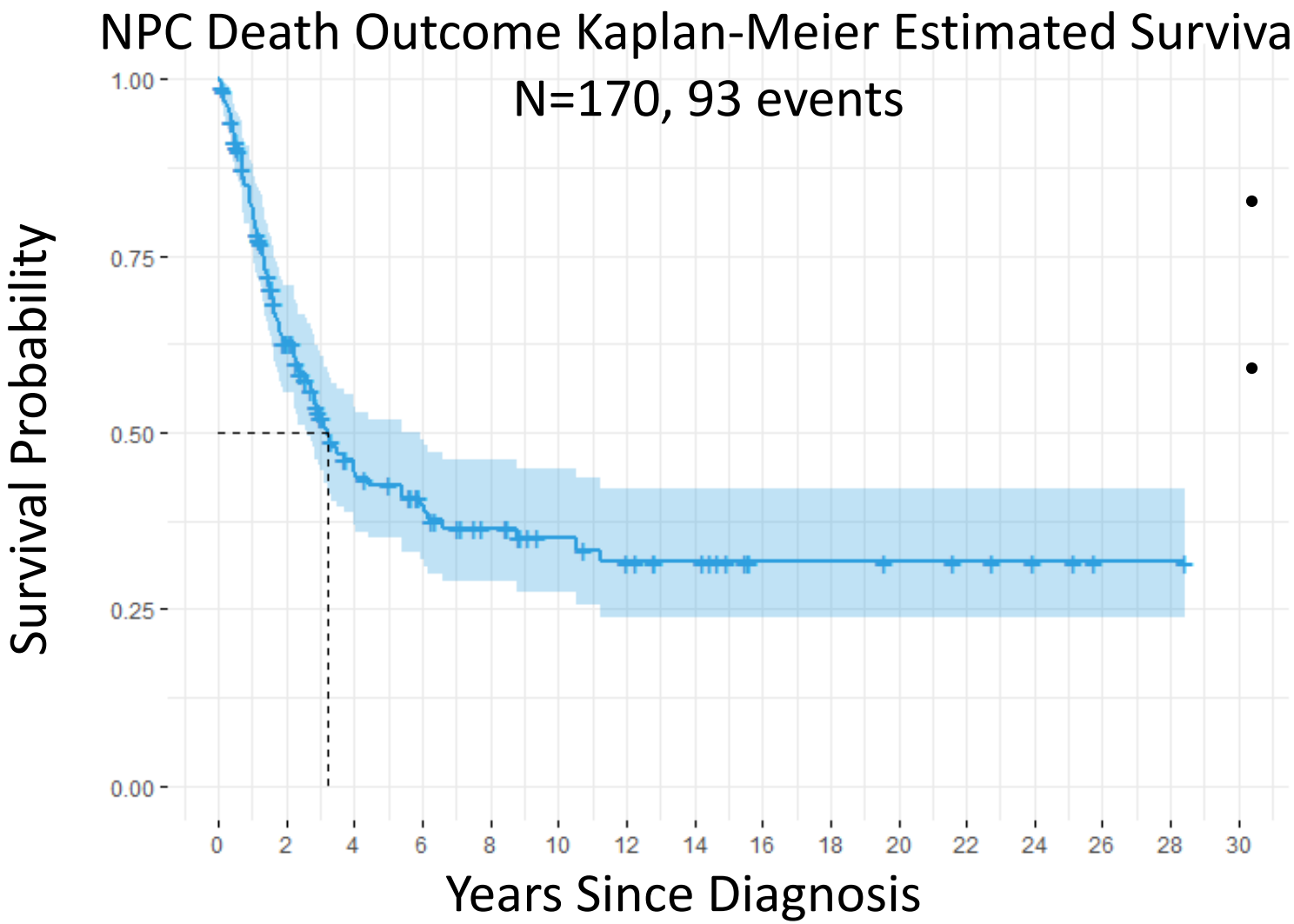
Initial Responses to Therapy

- Data available since 2006
  - 46 patients
  - 1 declined treatment
- Induction chemotherapy with platinum and taxane-> chemo-RT
- 32/45 (71%) complete remission
- Significant toxicity





NPC Specific Survival in Alaska Native Patients



- Median NPC survival 3.19 Years
  - 95% CI (2.6-5.94)
- 5 year NPC survival 41.7%
  - 95% CI 34.1%-50.9%

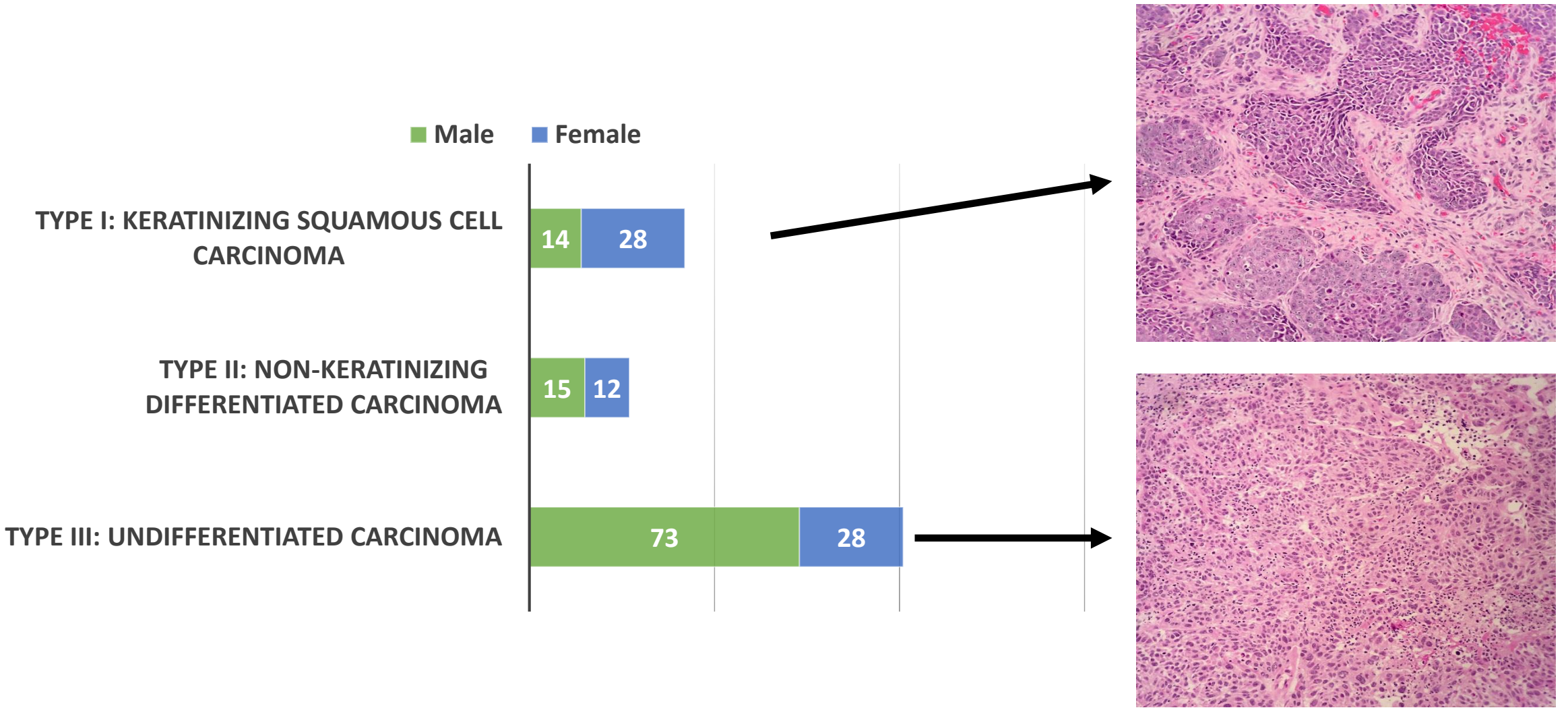
Olnes et al, ASCO 2018

Molecular Characterization of Nasopharyngeal Carcinoma

- **Hyothesis:** Molecular characterization of NPC tumors may identify genetic mutations that provide insights into the molecular pathogenesis of this cancer and suggest new options for treatment
- **Specific objectives:**
  - To characterize pathogenic EBV factors in NPC tumors
  - To characterize the frequency of biologically relevant mutations in NPC tumors to gain insights into the pathogenesis of this disease
  - To identify NPC molecular markers that carry prognostic significance
  - To identify potential new targets for directed therapies

Dr. Anne Lanier

Type III NPC most common among AN Patients



Ongoing Studies

- NPC tissue blocks from 75 patients stored at the at the Alaska Native Medical Center (ANMC) pathology laboratory archives utilized for this study
- Anonymized tissue blocks cut and placed onto glass slides for Next Generation Sequencing, IHC and *in situ* hybridization analysis
- Next generation DNA sequencing and/or Sanger sequencing performed at the MCCC to test for the presence of mutations in genes associated with NPC pathogenesis
- Immunohistochemistry (IHC) and *in situ* hybridization studies performed at the MCCC and University of Alaska Anchorage to evaluate gene and protein expression
- Bioinformatics analysis of the genetic mutations by MCCC bioinformatics core department staff members in collaboration with study investigators

NPC Conclusions

- NPC is the leading cancer health disparity among Alaska Native people
- Most patients are diagnosed at stage IV, most are WHO type III tumors
- Current standard of care treatment of NPC involves combinations of chemotherapy and radiation
- Approximately 70% patients respond initially to treatment
- Despite advanced chemotherapy and radiation techniques, 60% of patients with NPC die from their disease within 5 years
- Ongoing translational studies may yield insights into the biology of NPC and identify new prognostic markers and targets for more effective therapies

Collaborators

- Dr. Holly Martinson, UAA-WWAMI program
- Drs. Steve Alberts, Joaquin Garcia, Mayo Clinic
- Dr. Sarah Nash, ANTHC Epidemiology Center
- Erik Pihl, Mariah Minder, Julia Parrish, WWAMI Medical Students
- Dr. Peter Holck, UW
- Dr. Barb Stillwater, ANTHC Cancer program
- Linda O'Brien, ANTHC Tumor Registry
- Garrett Zimpelman, ANTHC Epidemiology Center

Research reported in this presentation was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number U54GM115371. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Thank You!

Contact Information:
mjolnes@anthc.org
Office Phone: (907) 729-1114