Head and Neck Cancers

What do you need to know?

- You need to know how pre-malignant mucosal lesions look:
  - Leukoplakia / Erythroplakia
- Correlate this with the macroscopic appearance of carcinomas
  - Ulcerative / Fungating – Exophytic / Infiltrative - Submucosal
- Examine your patients
  - Bi-manual oral and oropharynx examination / Neck
  - Remember that head and neck cancers have a loco-regional spread
- Help to expedite the process if you work in a setting where there is a time delay to refer the patients to a tertiary centre
  - Biopsy of primary / FNA node(s) / Bloods / TB / HIV
- Differentiate "hot" from "cold" neck masses
- Have a differential diagnosis of oral mucosal lesions

Historical context

History of Cancer

- First reported description of cancer
  - Edwin Smith Papyrus 3000 BC of breast cancer
  - Ebers Papyrus 1500 BC describes several types including skin, uterus, stomach, and rectum
  - Associated it with a curse of the gods
- Hippocrates (460-370BC)
  - First to use the word carcinoma
    - Crab and adheres to surroundings with claws
    - Excess of black bile - bloodletting
    - Galen (130-200) used the term oncos (swelling)
  - Wonderful era until ~ 300
    - Fall of Rome 476
    - Church banned autopsies in 1215
    - Nothing happened until the 16th century
- 18th century
  - 1775 Percival Pott noticed that chimney workers develop cancer of the scrotum
  - Ludwig Rehn observed the association between aniline dye and bladder cancer
  - Microscope
    - Virchow stated that cancer is a disease of cells
- 20th century
  - Proven association between chemicals and cancers
  - Expanded to include radiation and viruses (in chickens)
  - 1914 Theodore Boveri postulated chromosome and other genetic abnormalities

History of Cancer Surgery

- Egyptians
  - Various reports on cancer surgery, especially on the breast
- Important surgical dates
  - 1809, Ephraim McDowel removed the first ovarian tumour without anaesthesia!!
  - 1846 – anaesthesia (ether)
  - 1867 – antisepsis
  - 1873 – laryngectomy

        - Theodor Billroth
        - Considerable bleeding, coughing and arousal from anaesthetic
        - Patient lived for 7 months
        - He also performed the first esophagectomy (1871) & gastrectomy (1881)
        - 1880 – 50% peri-operative mortality
    - 1894, William Halsted introduced the radical mastectomy for breast cancer. He introduced the en bloc resection of all surrounding tissue – even humerus head. This became known as the "cancer operation"
    - It wasn't for 74 years before someone questioned this operation!
    - Fisher noted that a radical mastectomy was both too much for small tumours, and too little for large tumours
    - He also showed that less radical surgery with radiation accomplished the goal with much less morbidity

History of Radiation

- The era of radiation started in 1894
    - First documented success was in 1899, when Thon Stenbeck treated a 49 year old patient with a basal cell cancer of the nose. She was alive and well 30 years later on
- External beam radiation started in 1922
- In 1928 it was shown that head and neck cancers could be cured by fractionated radiation
- Radiation became very popular between 1920-1950
- By the 1950's it became apparent that no matter how complete the resection or how good the radiation, cure rates had flattened out
    - Only about a third of cancers could be cured

History of Chemotherapy

- The use of drugs to treat cancer began about 70 years ago (1950's). After World War II, Louis Goodman and Alfred Gilman and their colleagues at Yale University noted that people who had been exposed to mustard gas often had bone marrow suppression. They identified the active chemical in the gas, gave it to patients, and saw responses in patients with hematologic cancers. Thus, alkylating agents were developed and became key components of treatments for many forms of cancer.
- Not all useful drugs emerged as a product of accurate hypotheses. Sidney Farber mistakenly thought that leukemic cells looked megaloblastic, and so he gave folate to some children with acute leukemia. Their disease accelerated, and the children died. This led to the hypothesis that an antifolate agent might be effective, and aminopterin and amethopterin (methotrexate) were born

Treatment of HNC before 1990's

- Surgery first options and if feasible proceed to postoperative RT
- First available drug was methotrexate
- Cisplatinin was introduced in 1968 by Dr Rosenberg (it remains one of the mainstay chemotherapeutic agents till today)
- In 1984, Dr Muyi Al-Sarraf used the first combination chemotherapeutic agents neo-adjuvantly
    - Cisplatin and 5-FU
    - Clinically complete response rate in 40%
    - Led to the first trails to test "nonsurgical" treatment programs

- >50 years ago – radical surgery with minimal (no) regards to outcome

Current treatment

See below

Future Treatment Options

- Targets include
    - Modifying tumour suppressor genes

        - P53
        - CDKN2A
    - Oncogenes
        - RAS, RAF/MEK/ERK, PIK/AKT/MTOR, PTEN
    - EGFR, VEGF, PDGF, FGF, TGF-a, TGF-β, IL-8, PD-1, PD-L1
    - Gene silencing
    - Epigenetic targets
- Mechanisms of action
    - Anti-proliferative, pro-apoptotic, anti-angiogenic, CRT-sensitizing properties

Molecular changes

What changes are needed on a molecular level to develop a cancer?

- You need the following
    - Resistance to growth inhibition
    - Evasion of apoptosis
    - Angiogenesis
    - Evasion of the immune system
    - Ability to invade and metastasis
- Final common pathway is genetic alterations
    - Factors playing a role
        - Environmental
        - Tumour suppressors genes
        - Proto-oncogenes
        - Chromosomal abnormalities
        - Protein based alterations

For benign neoplasms you need

- Genetic mutations
- Evasion of apoptosis
- Uncontrolled replication
- Evasion of the immune system

And for malignant neoplasms you need

- All of the benign changes
- Angiogenesis
- Loss of inter-cellular adhesions
    - Metastases

A common feature of all malignant cancers includes genomic instability and a pro-inflammatory state.

Head and Neck Cancers in general

How does a cancer look?

Remember that cells can't "jump" from a normal cell to a malignant cell (the only exception might be oropharyngeal induced HPV cancers). There are steps in between and we refer to these as pre-malignant lesions. It is of vital importance that you need to know how they present, to refer these patients to your ENT specialist for further management. Pre-malignant lesions' macroscopical appearance are:

- Leukoplakia – white lesion that you can't wipe clean
- Erythroplakia – red lesion that you can't wipe clean
- Other
    - Submucosal fibrosis
    - Lichen planus (controversy if it is truly a pre-malignant lesion)

Microscopical they can report:

- Dysplasia (most important)
- Atypia
- Hyperplasia
- (Hyperkeratosis / Parakeratosis / Acanthosis)

Unfortunately, head and neck cancers does not have an orderly progression from dysplasia, to carcinoma in situ, to infiltrative carcinoma. If you compare it to cervical HPV induced cancer, which follow a "one-way" street (CIN I→CIN II→CIN III→CIS→CA), head and neck dysplastic can move in both directions. This makes managing patients with severe dysplasia challenging, especially the group with "field cancerisation" where large areas of the mucosa are affected.

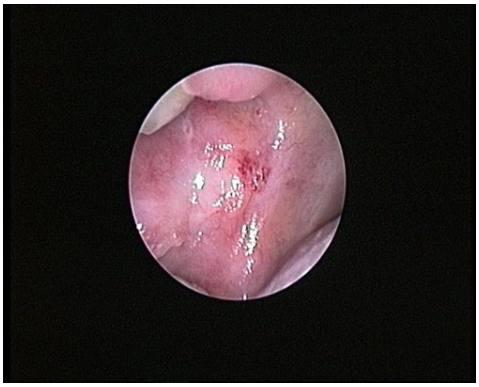
On the other hand, the macroscopical appearance of malignant tumours are

- Ulcerative
- Fungating - exophytic
- Infiltrative – submucosal

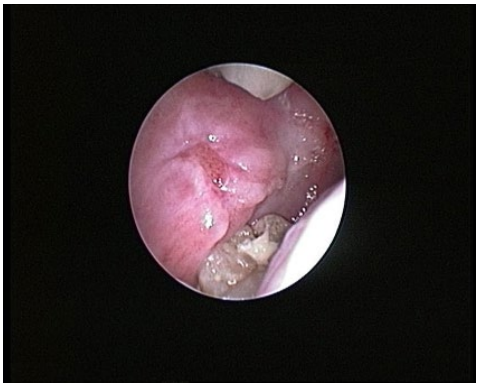
Microscopical they are classified according to their origin cell. Remember, that by far the majority of head and neck cancer you are going to see will be squamous cell carcinomas. The table below shows benign and malignant tumours in relation to their origin.

	Benign	**Malignant**
Epithelial	Papilloma	Sqaumous Ca
Salivary gland	Adenoma	Adenocarcinoma Mucoepidermoid Adenoidcystic
Bone	Osteoma	Osteosarcoma
Cartilages	Chondroma	Condrosarcoma
Vascular	Haemangioma Angioma	Angiosarcoma Kaposi
Muscle	Leiomioma Rhabdomioma	Leiomiosarcoma Rhabdomiosarcoma
Fibrous tissue	Fibroma	Fibrosarcoma
Fat	Lipoma	Liposarcoma
Haematopoietic	Paraganglioma	Lymphoma

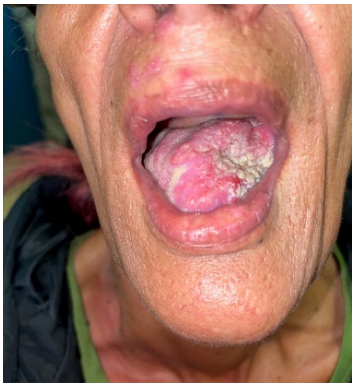
Clinical Pictures



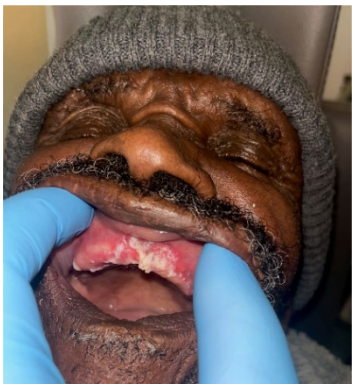
Area of erythroplakia in buccal mucosa.



Area of leukoplakia and erythroplakia in buccal mucosa.



Infiltrative (submucosal), ulcerative lesion in left anterior 2/3 of oral tongue.



Leukoplakia, erythroplakia, possibly ulcerative lesion of upper dento-alveolar ridge.

Cancer in South Africa

Cancer statistics are reported by Stats SA. According to them, South Africa had the following number of cancer cases as shown in the table below.

All cancer in South Africa

Number of cases	2008	2019
Females	28 748	43 811
Males	26 538	41 491
Total	55 286	85 302
Total deaths	33 720	43 613

Extracting Head and Neck cancer data from this report shows that it only accounted for 4.4% and 1.9% of all cancers for males and females respectively. In men, the most common Head and Neck cancer was the larynx (26%), followed by the mouth (21.6%), nasopharynx and oropharynx (21.4%), tongue (19.8%), salivary glands (7.4%), lips (2.3%), and lastly gums (1.5%). In females the mouth (27%) was the most common site, followed by the tongue (20%), nasopharynx and oropharynx (19.5%), and salivary glands (14.2%), larynx (12.8%), gums (4.2%), and lips (2.3%).

Head and Neck cancers – background

It is reported to be the fifth most common cancer in the world. A recent article reported 1.5 million new cases and 500 000 death per year (Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49.)

By far the majority is squamous cell carcinomas and the combined 5-year survival is unchanged at 50% over last 3 decades. Squamous cell carcinomas will be discussed in more detail. Remember that other benign and malignant tumours can occur in the head and neck such as:

- Salivary gland tumours (see separate chapter)
- Thyroid gland tumours
- Benign and malignant mesodermal tumours – all the sarcomas
- Haematological / Vascular tumours – Glomus, Lymphangioma, Haemangioma, Lymphomas
- Congenital tumours – Teratomas

Head and neck squamous cell carcinomas (HNSCC)

Epidemiology and Aetiology

- In 2020 more than 1.5 million people worldwide were diagnosed with HNSCC
    - With 500 000 deaths
- There are five major mucosal sites namely
    - Nasopharynx, Oropharynx, Hypopharynx, Oral cavity, Larynx
- Remember that skin cancers also spread to the lymphatics of the neck
    - In countries such as Australia, skin SCCs draining to the parotid lymph nodes are the most common reasons for parotid cancers (43% of all parotid tumours)
- The majority of HNSCC are related to tobacco and alcohol use
- However, in North America, Europe, and Australia, there is an epidemic of oropharyngeal SCC caused by infection with Human Papilloma Virus (HPV)
    - This has not been the case in South Africa, for reasons unknown to us currently (this might change)
    - HPV is discussed in more detail below
- Nasopharyngeal SCC is related to Epstein-Barr virus
- The incidence of most HNSCC has decrease globally, and this is strongly linked to the decrease in the rate of smoking
    - The rate of smoking has decreased from 43% in 1965 to 21% in 2004 in the USA
- Alcohol consumption is also decreasing. Adults, on average, consumed 5 litres of alcohol in 2013 compared to 3.9 litres in 2023
- However, the incidence for tongue, tonsils, salivary glands and thyroid cancers are on the increase
    - Only tonsils (oropharyngeal site) associated with HPV can be explained

Risk factors

- Smoking and alcohol are the most important risk factors
    - There is a synergistic interaction between alcohol and smoking, which is multiplicative for the oral cavity, additive for the larynx, and in between for the oesophagus
    - There is also a dose and time dependant relationship for alcohol and tobacco
        - This means the longer and more you smoke and / or drink, the higher your chance is
    - It has been calculated that the risk for smokers and drinkers, to ever develop a HNSCC, is 4-177 higher compared to non-smokers and non-drinkers
- Other risk factors implicated are
    - Previous head and neck cancer
    - Previous radiation
    - Genetic / Immunologic

        - Presents in younger patients and frequently in females
    - HPV
    - Other viruses
        - EBV
            - Nasopharyngeal cancers
            - EBV is classically associated with nasopharyngeal cancers, however more reports indicate that it might play a role in other head and neck cancers. The opposite is also true, in that HPV might play a role in nasopharyngeal cancers
        - HIV
            - Patients present with more advanced HNSCC
            - Associated with skin SCC
            - Kaposi sarcoma
            - Lymphoma
    - Pollutants / Occupational agents
        - Nickel / Mustard
        - Asbestos
        - Sulphuric and hydrochloric acid
        - Previous radiation
    - Betel nut
        - India / Asian countries
        - Many variations
        - Mainly chewed
    - Laryngopharyngeal reflux
    - Possible risk factors
        - Nutritional factors
            - High fruit and vegetables intake associated with a decreased risk
        - Poor oral hygiene
        - Marijuana
            - One study reported an overall increased risk of 2.6 compared to non-users, however in most studies the association is inconclusive

Smoking

- Types:
    - Smoking
    - Tobacco chewing
    - Reverse smoking – especially in India – even higher risk to develop HNSCC
    - Pipe / Cigar – increased risk to develop oral cavity SCC
    - Smokeless tobacco – increased risk to develop oral cavity SCC
    - Environmental / second hand / passive smoking also increases the risk to develop HNSCC
- Only became very popular after world war I & II.
- Single most preventable cause of death and cancer in the world.
- 7000 chemical compounds in a burning cigarette
    - More than 20 carcinogens
- Smoking and cancer
    - Causes mutations of P53 and P16 – loss of tumour suppressor genes
    - Chances of developing cancer is 23 times higher in males and 13 times higher in females who smoke
    - Chances of developing lung cancer before the age of 85 is 22% for males, and 12% for females (compared to 1%)
    - Smokers are three times more likely to die compared to non-smokers, and lose on average at least a decade of life
    - Each cigarette reduces your life by 11 minutes
    - At least half of smokers die as a direct result of smoking
    - In the USA alone, it accounts for roughly 500 000 premature death per year

    - Put into contexts this equates to 3 jumbo jet crashes every day without survivors
    - Economic impact is roughly $300 billion/year
    - For every death caused by smoking, 30 smokers will suffer from a chronic disease caused by smoking
- Incidence
    - 19.3% of adults in US smoke (2010)
    - Down from 20.9% (2005)
    - Down from 42% in the 1950's!
    - Smoking peaked in the 1960's in men and 1980's in women
    - Proportion of daily smokers who smoke one to nine per day increased from 16.4% to 21.8%,
    - Whereas the proportion who smoked more than thirty per day decreased from 12.7% to 8.3%
    - In South Africa
        - A study reporting on the age of onset of tobacco smoking in South Africa found that it peaks between the ages 15 to 22 years but varies by province, sex, location, race, and socio-economic status. It also reported that the lifetime prevalence of smoking was 20,5%. (Fagbamigbe AF, Desai R, Sewpaul R, Kandala NB, Sekgala D, Reddy P. Age at the onset of tobacco smoking in South Africa: a discrete-time survival analysis of the prognostic factors. Arch Public Health. 2020 Dec;78(1):128.)
        - A recent household survey of persons aged 15 years or older, the Global Adult Tobacco Survey (GATS) undertaken in 2021 by the South African Medical Research Council (SAMRC) under the auspices of the National Department of Health (NDoH), reported a higher tobacco use of 29,4%. Tobacco use among males was much higher than that reported among females, at 41,7% and 17,9% respectively. (03-08-002023.pdf [Internet]. [cited2023Dec10]. Available from:https://www.statssa.gov.za/publications/03-08-00/03-08-002023.pdf)
        - An MMED project at Tygerberg Hospital showed that 98% of of Head and Neck cancer ever smoked (www.scholar.sun.ac.za - 2024)
- Advertising (USA)
    - Cigarette companies are spending $1million / hour on advertising (2022)
    - Targeting the young
    - 3200 younger than 18 will start every day
- 70% of adults wants to quit
- Upon smoking cessation, the risk to develop a HNSCC is reduced by
    - 30% in the first 1-9 years
    - 50% in those who have stopped > 9 years

Alcohol

- The precise mechanism is unclear as alcohol itself is not a carcinogen
- It may act as a solvent increasing cellular permeability of tobacco carcinogens through the mucosa
- In terms of laryngeal SCC
    - Smokers develop more glottic SCC
    - Heavy drinkers develop more supra-glottis SCC
- It has a synergistic effect with smoking
- France
    - 34 higher chance of developing laryngeal cancer in patients who smoke and consume more than 1.5 L of wine per day
- Alcohol causes 79 000 deaths / year in USA (for any reasons)
- In South Africa
    - The South Africa Demographic and Health Survey of 2016 reported that 61% of men and 26% of women ever consumed alcohol, and 26% of men and 5% of women exhibited risky drinking patterns (SADHS 2016). (03-08-002023.pdf [Internet]. [cited 2023 Dec 10]. Available from: https://www.statssa.gov.za/publications/03-08-00/03-08-002023.pdf)
    - Naidoo K. (2019) reported that the incidence of smoking was 86.3% and of alcohol use was 74.25% in a cohort of 854 patients with Head and Neck cancers, at Tygerberg Hospital. (Naidoo

K. Descriptive epidemiological study in head and neck cancers at a single institution in Southern Africa [Internet]. Stellenbosch; Available from: http://www.sholar.sun.ac.za)

- It is thus clear from these data that our population has high exposure to the most significant risk factors causing Head and Neck cancers.

HPV

- Background
  - More than 200 subtypes
  - Most common STD in the USA
  - Two groups
    - Low risk (HPV 6 & 11)
      - Causes genital warts and respiratory papillomatosis
    - High risk (HPV 16 & 18)
    - Causes cancer of the cervix, penis, anus, and oropharynx
  - CDC
    - 90% will be infected with low-risk HPV subtypes, and 80% with high-risk HPV subtypes
    - Most high-risk HPV infections occur without symptoms, and will go away in 1-2 years
- Natural progression
  - HPV is transmitted mainly via sexual contact
  - The risk for oropharyngeal cancer increases with the number of oral sexual partners
  - It is estimated that at any given time, approximately 7% of the population has oral cavity / oropharyngeal HPV infection
  - The life-time oral exposure rate is unknown, but it is estimated that between 65-100% of sexually active adults have been exposed
  - The precise reason why some individuals develop oropharyngeal HNSCC is unclear, but a delayed clearance of the HPV by the immune system might be the reason
  - In 99% of individuals, the HPV is cleared by the immune system after 12-18 months, and they don't develop HNSCC
- HPV related head and neck cancers
  - Subset of tumours caused by HPV 16 and 18
  - At this stage only associated with oropharyngeal SCC – tonsils and base of tongue
    - It may be that other head and neck sites are also associated with HPV but currently there is no data to support this
    - Remember also cervix carcinoma
- Incidence
  - Massive increase oropharyngeal cancer in many countries since the turn of the century
    - From 1988 to 2004, there was a 225% population increase in HPV-positive oropharyngeal SCC in the USA, and a concomitant 50% decrease in HPV-negative oropharyngeal SCC
    - The overall HPV-positive oropharyngeal SCC increased from 16% to 70% over the same period (USA, UK, Australia, Scandinavia)
  - In South Africa
    - Importantly, studies have not been able to demonstrate the same rise in HPV related Head and Neck cancer in Sub-Saharan Africa as compared to the countries listed above.
    - A systematic review of 31 studies and 3,850 patients specific to Sub-Saharan Africa, the overall p16 positivity was 13.6% (41 of 1037 samples tested), with the highest proportion among oropharyngeal cancers (20.3%). The overall HPV polymerase chain reaction positivity was 15.3% (542 of 3,548 samples tested), with the highest proportion among nasopharyngeal cancers (16.5%). (Okerosi S, Mokoh LW, Rubagumya F, Niyibizi BA, Nkya A, Van Loon K, et al. Human Papillomavirus–Associated Head and Neck Malignancies in Sub-Saharan Africa: A Systematic Review. JCO Glob Oncol. 2023 Jan;(9):e2200259.)
      - P16 is a surrogate marker for HPV in the oropharynx
    - In a study from Tygerberg Hospital South Africa, testing P16 and HPV status, the incidence was only 5%. The exact reasons for this are unclear and warrant further investigation. (Dapaah G, Hille J, Faquin WC, Whittaker J, Dittrich CM, Ebrahim AK, et al. The Prevalence

of Human Papillomavirus–Positive Oropharyngeal Squamous Cell Carcinoma at One of the Largest Tertiary Care Centers in Sub-Saharan Africa. Arch Pathol Lab Med. 2022 Aug 1;146(8):1018–23.)
        - Furthermore, the burden of cancer is increasing in LMICs, and especially in Sub-Saharan Africa, where the incidence is approximately twice as high as compared to high income countries. (McGinnis GJ, Ning MS, Bvochora-Nsingo M, Chiyapo S, Balang D, Ralefala T, et al. Management of Head and Neck Cancers With or Without Comorbid HIV Infection in Botswana. The Laryngoscope [Internet]. 2021 May [cited 2023 Dec 10];131(5). Available from: https://onlinelibrary.wiley.com/doi/10.1002/lary.29206)
        - According to the World Health Organization, more than 70% of all cancer deaths occur in LMICs, where resources required for prevention, diagnosis, and treatment of cancer are limited or non-existent. (Cancer in developing countries: facing the challenge [Internet]. [cited2023Dec10]. Available from: https://www.who.int/director-general/speeches/detail/cancer-in-developing-countries-facing-the-challenge)
        - Sub-Saharan Africa has the greatest burden of HPV-driven malignancies, especially cervical cancer, and the highest global prevalence of HIV. This region is also home to two thirds of people living with HIV (PLWH) world-wide. (South Africa | UNAIDS [Internet]. [cited2023Dec10]. Available from: https://www.unaids.org/en/regionscountries/countries/southafrica)
        - Dhokotera T. et al. (2019) reported on the association between HIV and cancer in the South African public health sector, and about half of females with cancer, with a known status, were HIV-positive. (Dhokotera T, Bohlius J, Spoerri A, Egger M, Ncayiyana J, Olago V, et al. The burden of cancers associated with HIV in the South African public health sector, 2004–2014: a record linkage study. Infect Agent Cancer. 2019 Dec;14(1):12.)
        - HIV predisposes patients to increased rates of oral HPV infection and the risk of developing head and neck squamous cell carcinomas. (Okerosi S, Mokoh LW, Rubagumya F, Niyibizi BA, Nkya A, Van Loon K, et al. Human Papillomavirus–Associated Head and Neck Malignancies in Sub-Saharan Africa: A Systematic Review. JCO Glob Oncol. 2023 Jan;(9):e2200259.)
        - Oropharyngeal cancer incidence is 2-6 times higher in patients living with HIV. (Beachler DC, D'Souza G. Oral human papillomavirus infection and head and neck cancers in HIV-infected individuals. Curr Opin Oncol. 2013 Sep;25(5):503–10.)
        - Our local incidence remains below 15%
- Clinical presentation
    - Typically
        - Middle-aged white men from a higher socioeconomic status, with a history of multiple sexual partners (especially oral sex partners)
        - Presents with advance cystic metastatic lymphadenopathy with small primary tumours
    - However, newer report shows a more advanced age (60 years) and no sex predilections
    - Can also present like carcinomas with unknown primaries
    - Not related to smoking / alcohol but it can coincide
        - Remember that you might see a patient, where the HPV tests positive, but the cancer is due to smoking and alcohol (the HPV is an innocent bystander).
    - There are no pre-malignant lesions known at this stage
    - No screening method currently as opposed to PAP smears for cervical cancers
- Mechanism of inducing cancer
    - Produces E6 and E7
    - They bind the tumour suppressor genes *p53* and *pRB*
    - This leads to uncontrolled cell proliferation
- Treatment
    - They respond more favourably to chemo-radiation, and have a better prognosis than similar stage smoking / OH induced HNSCC
    - Vaccine
        - Definitely pre-exposure for girls and boys

- Efficacy post-exposure is unknown, however we do advise it

Approach to HNC

Managing your patients
By this stage, you should have a firm understanding of what is takes to make a cancer cell, know that cell first change to pre-malignant lesions and then into cancers cell, and cancer is classified according to its origin cell type. In the management of patients with head and neck cancers, you will always play an important role in firstly recognising cancers earlier (which translates to improved outcomes) but also in the follow up of patients. The more advanced cancers will always have post treatment sequelae, and they see their GPs for that.

The management follows the standard history, examination, special examinations process, but then and important step is to stage the patient. Families and patients are always focussed on 'what stage does a patient have'. From your perspective it is important to refer patients to units that have multi-disciplinary teams (MDT) caring for these patients. It takes a team effort and rigorous discussion before deciding on the final treatment. Unfortunately, some cases don't end up in MDTs and this negatively affects their outcomes. Only then is treatment offered and these patients are follow up for at least 5 years.

History
- Loco-regional
  - When did it start?
  - How did it start?
  - What initiated it?
  - Why did it start?
  - Progression?
  - Associated symptoms
- Risk factors
- Previous cancer of radiation
- HPV – sexual history
  - Be sensitive!
- Systemic
  - Pulmonary symptoms
  - Performance status
  - Loss of weight

Site specific history
- Lower airways
  - Voice
  - Feeding – LOW, odynophagia, dysphagia
  - Airway
    - Stridor / Stertor / Hot potato voice
- Lesion
  - Pain / bleeding / referred ear pain
- Trismus
- Nose, Oral cavity, Oropharynx, Nasopharynx, Hypopharynx, Larynx, Oesophagus

General examination
- JACCOLD
- Loss of weight / BMI
- General performance
  - WHO / ECOG
- Co-morbidity indexes
  - Charlson

ENT examination

- Ears
  - Ear pain
  - Blocked ears
- Nose
  - Blocked nose
  - Epistaxis
- Throat
  - Think
    - Voice
    - Aspiration
    - Swallowing
    - Airway compromise
  - Inspections
    - Oral cavity
      - Seven areas
      - Parotid duct opening (Stenson's duct)
      - Submandibular gland openings (Wharton's duct)
    - Oropharynx
      - Four areas
  - Palpation
    - Bimanual as well!
- Cranial nerves
- Neck (Think in terms of triangles or levels)
  - Inspections
  - Palpation
    - Midline (constant landmarks)
      - Supra-sternal notch, Trachea, Thyroid, Cricoid cartilage, Thyroid cartilage, Hyoid bone
    - Lateral
      - Sternocleidomastoid and trapezius muscles
    - Submandibular gland
    - Lymph nodes / Other masses
  - (Percussion)
  - Auscultation

Special investigations

- Bedside
  - (Flexible naso-pharyngo-laryngoscopy) – done by ENT
  - Functional evaluation of swallowing
  - Biopsies
  - FNAC / Core needle biopsy
  - Blood tests
- Radiology
  - Ultrasound
    - FNAC
  - CT
    - CT guided biopsy
    - Staging
  - MRI
  - PET-CT
  - Barium swallow

- Swallowing studies

Staging

All HNC patients are staged using the current 8th edition of the UJACC staging manual. It is based on a T-stage (primary), N-stage (neck nodes), and M-stage (metastases). The staging allows for clinical and radiological features to stage a cancer. Below is an example of the T-staging of glottic cancers.

	Supraglottis	Glottis	Subglottis
Tx	Tumour cannot be assessed		
T0	No tumour evident		
Tis	Carcinoma in situ		
T1	Limited to one subsite of supraglottis and mobile cords	T1a - One cord involved and/or anterior / posterior commissure involved, with mobile cords	Limited to subglottis
		T1b - Both cords involved and/or anterior / posterior commissure involved, with mobile cords	
T2	Invades more than one subsite of supraglottis. Invades one subsite of supraglottis and/or one or more subsite(s) of adjacent area such as glottis, BOT, vallecula, medial wall of pyriform fossa. Mobile cords	Involves adjacent subsite of either supra- or sub-glottis, or impaired cord mobility	Onto cords, ± impaired cord mobility
T3	Tumour limited to larynx with fixed cord, and/or invades paraglottic space, pre-epiglottic space, postcricoid area, inner cortex of thyroid cartilage (lateral pyriform fossa wall)	Limited to the larynx with cord fixed, and/or invasion of the paraglottic space, and/or invasion of inner cortex of thyroid cartilage	Limited to endolarynx with cord fixed
T4a	Moderately advanced local disease. Invasion of outer cortex of thyroid cartilage, extra-laryngeal spread such as oropharynx, trachea, cricoid, oesophagus, thyroid gland, neck soft tissue including strap muscles and extrinsic muscles of tongue		
T4b	Very advanced local disease. Invades prevertebral space, encases carotid artery, mediastinal structures		

Neck staging is shown below.

	N staging for cervical lymph node metastases and non-viral CUP	**Pathological N staging**	**N staging for HPV+ oropharyngeal CA**	**Pathological N staging for HPV+ / P16 + oropharyngeal Ca**	**N staging for EBV+ CUP**
N0	No regional lymph node metastases				
N1	Single ipsilateral lymph node ≤ 3 cm and ENE-		One of more ipsilateral lymph nodes ≤ 6 cm	1-4 lymph node(s)	Unilateral lymph node, and/or uni- or bilateral metastasis to retropharyngeal lymph nodes, and

					must be ≤ 6 cm and above caudal border of cricoid cartilage
N2a	Single ipsilateral lymph node 3-6 cm and ENE-	Same, AND Single ipsilateral lymph node ≤ 3 cm with pENE+	Contralateral or bilateral lymph nodes ≤ 6 cm	> 5 lymph nodes (N2)	Bilateral lymph nodes, and must be ≤ 6 cm and above caudal border of cricoid cartilage
N2b	Multiple ipsilateral lymph nodes ≤ 6 cm and ENE-			N/A	
N2c	Contralateral / Bilateral lymph node(s) ≤ 6 cm and ENE-			N/A	
N3a	Any lymph node(s) ≥ 6 cm and ENE-		Any lymph node(s) ≥ 6 cm	N/A	Any lymph node(s) > 6 cm, and/or extension below caudal border of cricoid cartilage
N3b	Any lymph node(s) with ENE+ (Clinical and Radiological)	A single lymph node > 3 cm with pENE+, or Any multiple, bilateral, contralateral lymph node(s) with pENE+		N/A	
	Can document ENE minor (<2 mm invasion beyond capsule), or ENE major (>2 mm invasion beyond capsule), for future changes. Tumour deposit within lymphatic drainage without identifiable lymph node would be recorded as pN+ and pENE+				

Thereafter, patients are staged. Patients and family members are always very keen to hear the "stage" of cancer. Be careful not to lose focus of the "patient" in front of you. Stages are more applicable for larger groups of patients with the same tumour. Nonetheless, below shows stages for non-HPV and non-EBV HNC.

Staging for Head and Neck Cancers				
	T1	**T2**	**T3**	**T4**
N0	I	II	III	IV
N1	III	III	III	IV
N2	IV	IV	IV	IV
N3	IV	IV	IV	IV
M1	**IV**	**IV**	**IV**	**IV**

Once patients have confirmatory histology and was staged, treatment is discussed at a multi-disciplinary meeting. At this meeting, we decide whether the goal / intent of treatment is curative, palliative, or end-of-life treatment (non-beneficial). Making these decisions takes years of knowledge and experience, but we take the following into account:

- Patient factors
    - Co-morbidities
    - Previous treatment
    - Wish
    - Follow up
- Tumour factors
    - Size, Extent, Position and other factors that might influence the choice of surgery versus radiation
- Doctor factors

    - Availability of surgical expertise
    - Availability of reconstructive options
    - Availability of radiation facilities
    - Availability of adjuvant therapies
    - Availability of other medical and support staff (anaesthiologist, ICU, speech therapy, dieticians, physiotherapy)

We measure these against the absolute ability to either improve quality of life, or significant increased survival, or both. If we cannot achieve either of these, one should seriously consider if curative treatment is indicated. Patients that either has an unacceptable high rate of morbidity or mortality with curative intent options, should receive palliative care.

Treatment of HNC
In general, the principles for treatment are:
Stage I & II:

- Single modality treatment
- Surgery or radiation

Stage III & IV

- Multi-modality treatment
- Classical options are
    - Surgery and post op radiation or chemo-radiation
    - Radiation
    - Chemo-radiation

Primary site surgery

- In general, surgery has become more functional, without compromising safe oncological principles
- Reconstruction also plays a major role
    - Local, distal and free flaps

Neck Surgery

- We went from doing a radical neck dissection regardless of nodal status, to a selective neck dissection even for N+ neck disease

Radiation

- Good data regarding dose
- Planning
- Intensity modulated radiotherapy
- Altered fractionation
    - Hyper-fractionated
    - Accelerated

Chemotherapy

- Adjuvant
    - After treatment
    - Eradicating residual micro-metastatic disease
    - Rarely used as single option after surgery
- Neo-adjuvant
    - Before treatment (*Induction)*
    - Response to induction chemotherapy correlated with a subsequent response to RT
- Concurrent
    - With treatment
- Organ preservation concept
    - Concept of offering chemo-radiation as first line options, keeping surgery for salvage

Targeted therapies / Immunotherapies

- Molecular targets are becoming more prominent in Head and Neck cancers
- Options are
    - Targeting growth factor independence
        - EGFR
        - Tyrosine kinase inhibitors
    - Targeted drugs that act as radiosensitizers
    - Antitumour immune response using monoclonal antibodies (also referred to as immune checkpoint inhibitors (ICI))
        - PD-1 / PD-L1
        - CTLA4
- While ICIs found initial success in trials for patients with recurrent / metastatic HNSCC, several subsequent phase 3 trials have yielded disappointing results of ICIs in the curative setting in combination with concurrent chemoradiotherapy.
- The negative survival signal seen in concomitant ICI therapy with chemoradiation has led to trials evaluating sequential administration of ICI either in the neoadjuvant or adjuvant phase of treatment.
- Based on promising response rates in early-phase trials, several phase 3 trials are currently underway to investigate whether ICI therapy with curative intent can improve survival in the difficult to treat locally advanced HNSCC population.

Cancer prevention

- Smoking
    - Causes 40% of all cancer related deaths
- Vaccines
    - HPV
        - Gardasil 9
    - Hep B
    - It is estimated that 20% of all cancers are caused in some way by viruses
- Chemicals
    - Anti-oestrogens – prevent ductal carcinoma
    - Finasteride – prevent prostate carcinoma
    - Aspirin – prevent colorectal carcinoma