THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY AND CHILDREN

NATIONAL CANCER TREATMENT GUIDELINES

First Edition (January, 2020)

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ACRONYMS AND ABBREVIATIONS

5-FU	5-Flurouracil
AIS	Adenocarcinoma-in-situ
AJCC	American Joint Committee on Cancer
ALL	Acute lymphoblastic/lymphoid Leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase test
AML	Acute myeloblastic/myeloid leukemia
ASCUS	Atypical squamous cells of unknown significance
AST	Aspartate aminotransferase test
BCC	Basal cell carcinoma
BRCA	Breast Cancer
BSE	Breast self-examination
BSO	Bilateral salpingo-oopherectomy
CEA	Carcinoembryonic antigen
CBE	Clinical breast examination
CHL	Classical Hodgkin's Lymphoma
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma-in-situ
CISH	Chromogenic in situ hybridization
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CRC	Colorectal cancer
CRM	Circumferential margins
CSF	Cerebrospinal fluid
CT	Computed Tomography Scan
CXR	Chest X-ray
DLBCL	Diffuse Large B-cell Lymphoma
DFS	Disease Free Survival
EBRT	External Beam Radiotherapy
EGFR	Epidermal growth factor receptors

EOL	End of Life
EOLC	End of Life Care
ESR	Erythrocyte Sedimentation Rate
ER	Estrogen Receptor
EUS	Endoscopic ultrasound scan
FAP	Familial adenomatous polyposis
FBC	Full blood count
FNA	Fine Needle Aspiration
GGT	Gamma-glutamyl transpeptidase
GIST	Gastrointestinal stromal Tumour
GIT	Gastrointestinal tract
GERD	Gastroesophageal reflux disease
GTD	Gestational Trophoblastic Diseases
HCC	Hepatocellular carcinoma
HCP	Health Care Professionals
EGFR 2	Human Epidermal Growth Factor Receptor 2
HIV	Human immunosuppressive Virus
HPV	Human papillomavirus
HGSIL	High grade squamous intraepithelial lesion
ICD	International classification of diseases
ICP	Intracranial pressure
IHC	Immunohistochemistry
IMRT	Intensity modulated radiotherapy
JPA	Juvenile Pilocytic Astrocytoma
KS	Kaposi's sarcoma
IVU	Intravenous urography
LDH	Lactate dehydrogenase
LEEP	Loop electrosurgical excision procedure
LFT	Liver Function Tests
LSIL	Low grade squamous intraepithelial lesion
LVI	Lympho-vascular invasion
MDACC	MD Anderson Cancer Centre

MoHCDGEC	Ministry of Health, Community Development, Gender, Elderly And Children
MRI	Magnetic Resonance Imaging
MRM	Modified Radical Mastectomy
NCD	Non Communicable Diseases
NCCN	National Comprehensive Cancer Network
NPC	Nasopharynx cancer
NHL	Non-Hodgkin's Lymphoma
NSAIDS	Non-Steroidal Anti-inflammatory Medicines
NSCLC	Non-small cell lung cancer
PC	Palliative Care
PEG	Percutaneous Endoscopic Gastrectomy
PET	Positron Emission Tomography
PR	Progesterone Receptor
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency ablation
RFS	Recurrence Free Survival
RT	Radiation Treatment
SCLC	Small cell lung cancer
STI	Sexually transmitted infection
TACE	Trans-arterial chemoembolization
TAH	Total abdominal hysterectomy
TME	Total mesorectal excision
TMZ	Temozolomide
TNM	Tumor, node, metastasis
TWG	Technical Working Group
UCSF.	University of California San Francisco
VEGF	Vascular endothelial growth factor
VIA	Visual inspection with acetic acid
VILI	Visual inspection with Lugo's iodine
WHO	World Health Organization

FOREWORD

Cancer has been noted as one of major life threatening Non Communicable Diseases (NCD) worldwide.It is estimated to kill over 7.9 million people annually, which is equivalent of 21% of all NCD deaths globally. Nearly two thirds of all cancer diagnoses occurring in low- and middle-income countries. While communicable diseases still remain the leading causes of death in many developing countries, the incidence and mortality from non-communicable diseases is rapidly raising which further straining on already stretched health systems and resources.

In Tanzania, Cancer is a major cause of morbidity and mortality, being the 5th cause of death among adult men and 2nd among female adults. Currently, it is estimated that about 50,000 people develop cancer each year, and recent forecasts suggest that by 2030 this number will increase by 50%. The leading cancers in women are cervical, breast, Kaposi's sarcoma and esophagus. In men, it is Kaposi's sarcoma, oesophagus, head and neck cancers, and prostate cancer are the most common.

Following the development and implementation of National Cancer Control Strategy (2013-2022); which also involved expansion of cancer treatment facilities, it was deemed necessary to develop comprehensive cancer management guidelines. The guidelines are intended to be facilitative, enabling, and foundational, providing arm bases for the attainment of high standards in the management of cancers. Development of the Guidelines has been a highly consultative process, evidence- based, incorporating recent advances in cancer management and emerging opportunities and challenges of the 21st Century. The Ministry of Health, Community Development, Gender, Elderly and children (MOHCDGEC) will systematically disseminate these Guidelines. In addition, the Ministry will implement a monitoring and evaluation strategy that ensures and promotes the use of the Guidelines. This will also inform subsequent evidence based reviews. It is the expectation of the MOHCDGEC that these guidelines will serve the users well (both public and private health sectors) as a guide for appropriate care of cancer patients delivery at the respective level of healthcare.

The regular and consistent use of the guidelines by clinicians countrywide, will improve the management of cancer in Tanzania, and thus help reduce the morbidity and mortality attributed to cancers.

Finally, on behalf of the Ministry of Health, Community Development, Gender, Elderly and children (MOHCDGEC), I would like to appreciate the Technical Working Group, all the experts, reviewers and editors who have worked hard to make these guidelines a reality.

Dr Zainab A.S. Chaula
Permanent Secretary,
Ministry of Health, Community Development, Gender, Elderly and Children.

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The Ministry commends all institutions and organizations that worked hand in hand with the Ocean Road Cancer Institute (ORCI), towards the production of this document. The list includes the following institutions:

- Muhimbili National Hospital (MNH)
- Muhimbili University of Health and Allied Sciences (MUHAS)
- Mbeya Referral Hospital
- Bugando Medical Centre (BMC)
- MUHAS Academic Medical Centre (MAMC)
- Kilimanjaro Christian medical Centre (KCMC)

- Benjamin Mkapa Hospital
- Muhimbili Orthopaedic and Neurosurgery Institute (MOI)
- Agakhan Hospital, Dar es salaam (AKH)
- Komen International
- MD Anderson Cancer Centre (MDACC)
- University of California San Francisco (UCSF)
- Besta Diagnostic Centre
- CCP Medicine Medical Centre
- PTR-NET Tanzania

I, on behalf of MoHCDGEC, would like to thank all participants in the various workshops and consultations, either as individuals or as representatives of their institutions and organizations. That including the experts (Technical working group) who were directly involved in development and review of this guideline. The names of experts who were involved in the development of this guideline is attached as **appendix 3.**

Prof. Muhammad B. Kambi
Chief Medical Officer,
Ministry of Health, Community Development, Gender, Elderly and Children.

PREFACE

In Tanzania, Cancer is now a major cause of morbidity and mortality, being the 5th cause of death among adult men and 2nd among female adults. Formulation of these Cancer Treatment Guidelines was necessary as the burden is still growing and there is no standardized approach to management of cancer patients, also as one of the objective of National Cancer Control Strategy 2013-2022.The Cancer Control Strategy is the roadmap developed to reduce the incidence of cancer, improve its management and ultimately improve the quality of life of those who develop cancer and their care givers.

These Guidelines are designed to contribute to the reduction of the incidence and mortality from cancer and improve the quality of life of cancer patients by adopting best practice. Application of the guidelines is expected to improve early detection, timely diagnosis, harmonize and standardize treatment of cancer. The Guidelines should be utilized by all health care professionals in both public and private sectors. In addition, they should be utilized by the training institutions. Further, the Guidelines will facilitate the development of the lists of essential medicines, non-pharmaceuticals and equipment for cancer treatment.

The National Guidelines for Cancer Management contains information on common cancers in Tanzania. It provides key information on their prevalence, data availability, presentation, methods and tools for diagnosis, management options for treatment (surgery, chemotherapy, and radiotherapy), follow-up and palliation.

The Guidelines are organized into four parts:

Part 1: Health System in support for cancer management.
This part contains general introduction to the guideline and cancer prevention issues. The introduction highlights burden of cancer as well as rationale, organization, and the developing process of the cancer treatment guideline. Multidisciplinary approach in cancer management and the roles of various cadres are also highlighted. Additionally, cancer prevention interventions are

highlighted that include primary and secondary prevention as well as cancer registration.

Part 2: Site Specific tumor management in Adults.

The site specific cancers are arranged both alphabetically and anatomically. Management of site specific tumors is detailed in this part and is described in the following sequence: Introduction, Epidemiology, Diagnosis, Staging and risk management, commonly used medicines, prognosis and references.

Part 3: Pediatric Cancers.

Pediatric cancers are handled separately since the presentation and management differs from that of adults in various aspects. The commonly occurring cancers in children in Tanzania were chosen.

Part 4: Supportive Care for cancer patients.

Supportive care is crucial as it ensures the quality of life of patients is at an optimal level to improve outcomes. This includes nutritional support, palliative care, handling of oncologic and palliative emergencies and pain management. In order to improve cancer management through early detection and standardized management of cancer, implementation of these Guidelines is crucial. This will require wide dissemination of the Guidelines and its utilization in all health facilities in this country including public, private and faith based organizations. Its applications will provide relevant information that will guide future revisions of the Guidelines to suit the national needs for cancer management.

The Guidelines are mainly adopted from National Comprehensive Cancer Network Guidelines (NCCN), European Society of Medical Oncology (ESMO) Guidelines and other guidelines. The guidelines will be reviewed at defined time intervals.

PART I:

NATIONAL HEALTH SYSTEM FOR CANCER MANAGEMENT

1. INTRODUCTION

1.1. Background

Cancer is a generic term used to describe a group of diseases that occur when malignant forms of abnormal cell growth develop in one or more body organs. These cancer cells continue to divide to produce tumors. It is not just one disease but many diseases with more than 100 different types named for the organ or type of cell they begin in. Cancer results from internal and external risk factors working together and/or in sequence to trigger the process. People may be exposed to risk factors or cancer-causing agents in their environment and/or from their lifestyles.

Cancer has been noted as one of major life threatening Non Communicable Diseases (NCD) worldwide. Cancer is estimated to annually kill over 7.9 million people which is equivalent of 21% of all NCD deaths globally. Nearly two thirds of all cancer diagnoses occurring in low- and middle-income countries. It is projected that deaths from cancer will continue to rise with an estimate of 13.1 million deaths in 2030. While communicable diseases still remain the leading causes of death in many developing countries, the incidence and mortality from non-communicable diseases is rapidly rising which further straining on already stretched health systems and resources.

In Tanzania, Cancer is a major cause of morbidity and mortality, being the 5th cause of death among adult men and 2nd among female adults. Currently, it is estimated that about 50,000 people develop cancer each year, and recent forecasts suggest that by 2030 this number will increase by 50%. The leading cancers in women are cervical, breast, Kaposi's sarcoma and esophagus. In men, it is Kaposi's sarcoma, oesophagus, head and neck cancers, and prostate cancers are the most common.

Non-communicable diseases such as cancers are growing health problems that need to be dealt with appropriately to sustain health advances that have already been achieved. This implies that the future country policies need to comprehensively address these twin epidemics of communicable and non-communicable diseases.

1.2. Rationale

These Guidelines are designed to contribute to the reduction of the incidence and mortality from cancer and improve the quality of life of cancer patients by adopting best practice. Application of the guidelines is expected to improve early detection, timely diagnosis, harmonize and standardize treatment of cancer. The Guidelines should be utilized by all health care professionals in both public and private sectors. In addition, they should be utilized by the training institutions. Further, the Guidelines will facilitate the development of the lists of essential medicines, non-pharmaceuticals and equipment for cancer treatment.

1.3. Organization of the Guidelines

The Guidelines is organized into various site specific cancers per sites where it occurs. In each group of cancers; the following are described: Introduction, Epidemiology, Diagnosis, Staging and risk management, Management, Prognosis and References. Guidelines contain general chapters dealing with health system issues required to facilitate optimum delivery and access to cancer treatment and care services addressing policy requirements, financing, management and service delivery by level of care and referral pathways. The Guidelines also include a list of essential cancer medicines, diagnostics and equipment required for the provision of cancer treatment and care services at the different levels of the health system.

1.4. Process of Developing the Cancer Treatment Guidelines

Pink Ribbon Red Ribbon, funded by the Bush Institute of USA, was supporting an initiative focusing on prevention of cervical and breast cancer in the country mainly through screening and treatment of pre-cancer lesions, as well as referral to treatment centre for those with invasive cancer at Ocean Road Cancer Institute (ORCI).

Thus, PRRR decided to support development of Gynecological and Breast Cancer Treatment Guidelines. They consulted MD Anderson Cancer Centre (MDACC) to assist Tanzania for development of earmarked guidelines. MDACC held workshops in Tanzania to develop the guideline between 2016 and 2017 with involvement of MoHCDGEC as well as hospitals in Tanzania.

Ministry of Health, Community development, Gender, Elderly and children (MOHCDGEC) saw an importance of development of cancer guidelines which will cover all cancer types given the expansion of cancer services in the country, both in public and private health sector as well as improvement in procurement of cancer medicines. MoHCDGE initiated the process for a National Cancer Treatment Guideline by tasking Ocean Road Cancer Institute (ORCI) to coordinate the development of National Cancer Treatment Guidelines.

Ocean Road Cancer Institute (ORCI) convened all cancer treatment and care stakeholders in the country at ORCI on 28th and 29th April, 2017 and form a Technical working group (TWG). Executive Director of Ocean Road Cancer Institute (ORCI), Dr. Julius Mwaiselage, appointed Dr. Jerry Ndumbalo (Oncologist) to lead (coordinate) the Technical working group in the guideline development process. Thereafter, several meetings and workshops were held at Ocean Road Cancer Institute (ORCI) from April, 2017 to last meeting on June, 2018. Ocean Road Cancer Institute funded the process.

The first Draft was produced in August 2017 after a compilation from site specific working groups. The inputs from Technical working group (TWG) were added in the 1st draft during the workshop on 18th and 19th Dec, 2017 and a 2nd draft was compiled. The 2nd draft was then externally reviewed at UCSF (University of California, San Francisco in February-May, 2018. In 28th-30th May 2018, The TWGs were convened to finalize the draft with inputs from stakeholders and thus, a final document was achieved.

1.5. General Practice Guidelines

Cancer diagnosis and treatment involve multidisciplinary team with different fields of specialization. Treatment modalities depend on the extent of the cancer and are usually combined as below.

- For Localized cancer is mainly treated by surgery
- For Loco-regional disease by radiotherapy
- For widespread disease by chemotherapy, hormonal therapy, or biological therapy

There must be a clear justification (for the patient benefit) to any of these treatments before treatment is instituted.

The MOHCDGEC strongly recommends that appropriate multidisciplinary approach to cancer management should be adopted to achieve the safest and most cost-effective care. As such, all facilities treating cancer should establish "Multidisciplinary Tumor Boards". This will avoid wastage of scarce resources and facilitate consideration of all aspects of the patient's condition. Further, the multidisciplinary approach creates a framework for selecting patients for clinical trials, continuous professional development, audit and research.

1.6. Multidisciplinary team in Cancer Management

In order to maintain the best standard of care in terms of Regulation and Accountability, the roles of the various disciplines need to be clearly defined. The Multidisciplinary team in cancer care includes; Surgeons/gynaecologists, Surgical/gynaecologic oncologists, Internal medicine (physicians), Paediatricians, General medical officers, Haematopathologists/hematologists, Radiologists, Pathologists, Histopathologists, Adult/paediatric medical oncologists, Radiation oncologists/Clinical oncologists, Clinical Pharmacists , Radiotherapists, Medical physicists, Nurses/Oncology nurses, Nuclear medicine specialists, Palliative care specialists, Trained counselors and Spiritual leader

1.7. Basic Requirements for Radiotherapy and Chemotherapy Administration

1.7.1 Essential Equipment and Staffing for a Basic Radiotherapy clinic

A radiation oncology service needs to be sited in a comprehensive tertiary hospital or a hospital dedicated to cancer treatment. In a secondary care hospital, these services may be utilized for palliation and routine cancers.

The institution's current capability for handling the clinical requirements for appropriate patient evaluation and comprehensive oncological management should be carefully assessed by examining their ability to follow the process set out below:

(a) The initial referral of a cancer patient is usually directed to the surgical, gynaecological or general medical unit, all of which should be present. These disciplines initiate the investigations leading to a confirmation of a diagnosis of cancer. In general, a referral to oncological services is accepted after a surgical biopsy (which may need to be done under direct vision of the tumour by one or more of bronchoscopy, colonoscopy, cystoscopy, gastroscopy, laparoscopy and oesophagoscopy), histopatho- logical diagnosis involving specialized laboratory facilities and expertise.

(b) Imaging is a major component of the diagnosis and staging (determining the extent of progression) of cancer. While much can be achieved using diagnostic X rays, at times with contrast, CT scans and magnetic resonance imaging (MRI) are desirable adjuncts.

(c) Multidisciplinary tumour clinics (combined assessment clinics), jointly staffed by oncological or gynaecological surgeons, radiation oncologists and medical oncologists (chemotherapists), review the patient's details and the relevant medical information. Supplementary investigations may be requested. The primary tumour and stage are determined and a treatment devised for the patient in accordance with established hospital clinical treatment protocols, modified by the individual circumstances of the patient. Multidisciplinary treatment protocols that include components of surgical, radiation and medical/clinical oncology are usual.

(d) The patient is entered into the tumour registry, identifying a number of epidemiological factors in addition to the primary site and stage of the tumour.

(e) Dedicated radiotherapy wards (inpatient facilities) are required for frail patients, those who live too far away to be outpatients and the occasional patient who has severe reactions to any of the treatments administered. These are needed as radiation therapy almost always comprises a series of administrations of radiation; usually on a daily basis over five to 35 treatment days (one to seven weeks). The majority of patients are well

enough to commute on a daily basis if they live near to the department. These wards for radiation oncology are also useful for teaching purposes or when multidisciplinary care is required.

(i) Treatment checks of patients under treatment are a routine weekly activity, with some patients requiring more frequent consultations with the treating radiation oncologist. This continues subsequent to completion of therapy at follow-up clinics at ever-increasing intervals, usually peaking at one year intervals for long term survivors and cured patients. Patients are rarely completely discharged, as follow-up is required for late morbidity assessment and the rare occurrence of radiation induced tumours. This requires a record keeping system, independent of the main hospital, that usually has a process in place for regular destruction of old records. Evaluation of outcomes should be performed at regular intervals for groups of patients with similar cancers and stages, to assess the efficacy of treatment performed at the institution.

(j) Support for the radiotherapy activity by the hospital administration, in general by the hospital superintendent or the chief executive officer, should be assured. The budget for upgrading equipment, building suitable accommodation for new pieces of equipment (e.g. a mould room) and ongoing maintenance of associated activities may be under hospital, rather than departmental, control. The licence for any radioactive or X ray source is usually granted to the hospital administrator. As such, the ex officio chairperson of the hospital radiation safety committee is usually the superintendent.

(k) Library facilities with access to the appropriate clinical and scientific journals are essential in a teaching institution and are desirable in all units.

(l) Continued medical and technical education of the personnel by attendance at congresses, training courses and interdepartmental training sessions is necessary, to ensure that the qualified personnel in the department constantly update their knowledge.

Buildings	• A megavoltage bunker (space for one more is desirable) • A simulator room • A darkroom (for film processing) • A dosimetry planning/physicist room (and for equipment storage if necessary) • A high dose rate (HDR) bunker (or low dose rate (LDR) room) • A mould room • Ample clinical space (for examination, consulting, changing and waiting rooms)
External beam Therapy Equipment	• A single-photon-energy teletherapy unit • Beam measurement and QA + RP physics equipment • A simulator, preferably a computed tomography (CT) simulator (otherwise access to a CT is desirable) • A computerized treatment planning system (TPS) • Film processing equipment • Patient immobilization devices and mould room equipment
Brachytherapy HDR or LDR Equipment	• A brachytherapy afterloader (two or more if LDR) • An X ray C-arm • A computerized TPS • A full range of applicators • Quality assurance physics equipment
Personell	• A Radiation oncologist/ Clinical Oncologist • A Medical physics staff • Three or More Radiotherapy Technologists (RTTs) • Three oncology nurses/ Nurses • One maintenance technician/engineer

1.7.2 Essential Equipment and Staffing for a Basic Chemotherapy clinic/Unit

Chemotherapy is prescribed for the treatment of diseases, especially cancers, using specific cytotoxic agents or medicines that are destructive to malignant cells and tissues. The Medical Oncology (Chemotherapy) Unit provides for the clinical treatment and management of patients undergoing Chemotherapy treatment for cancer.

The function of the Unit may include:

- Chemotherapy Administration
- Administration of blood products and/or other supportive therapies
- Blood collection
- Clinical procedures and examination
- Patient and family education and support
- Clinical trial management
- Coordination of care.

Service Delivery Models

- Hospital based unit – a unit within the hospital
- Satellite Unit – on a hospital campus but not in a hospital
- Integrated Cancer Care
  - Outpatients (Ambulatory Care) Unit
  - Radiotherapy/Radiation Service
  - Diagnostic Service as part of Radiotherapy Unit

Buildings	The Chemotherapy Unit may include the following Functional Areas: • Entry / Reception including: - Waiting areas - Interview room for patient/ family discussions and treatment planning - Storage for files, stationery, wheelchairs • Chemotherapy Treatment Areas including: - Treatment chair or bed bays - Isolation rooms as required - Ensuites, Patient Toilets - Treatment Room - Cytotoxic room • Support Areas including: - Bays for linen, resuscitation trolley, mobile equipment - Clean and Dirty Utilities - Cleaner's and Disposal rooms • Staff Station - Store Rooms for equipment, general supplies - Property bay for patients • Administration/ Office Areas with: - Meeting Rooms - Offices and workstations according to the service plan • Staff Areas including: - Staff Room - Toilets, Shower and locker areas

Equipments/ Chemotherapy preparation room	• Facilities are required for storing and preparing sterile packs, lotions and medicines for immediate use, and for preparing/storing trolleys. • Biosafety cabinet Class 2 Type B2 with Negative pressure inside • Sterile room • Ante room • Chemo absorber gauze • PPE (Chemo shoes, Gown, Glass, Mask (N95)), Hair cap, None powder chemo gloves)
	• Emergency shower Tap • Recommended syringes for IV with Glogged phaseal system • Spill kit
Personell	• Clinical Oncologist/ Medical Oncologist • Oncology Nurse / Trained Pharmacist • Oncology Pharmacist/ Trained Pharmacist

2.0 CANCER PREVENTION

2.1. Introduction

Cancer represents a unique public health opportunity, Unlike other Non-Communicable disease, it is possible to prevent most of cancers prevails in Sub-Saharan Countries including Tanzania by intervening at both Primary and secondary levels of the natural history of the disease .Primary prevention is mainly based on educating the public to modify their life styles to avoid risk factors for cancer as well as ensure the availability and affordability of prophylactic vaccines, The secondary prevention focus on the availability of effective screening programs that allow for reducing incidence and downstage cancer. We acknowledge the availability of sufficient knowledge to prevent more than 40% of all cancers and majority are associated with tobacco use, unhealthy diet, or infectious agents. Early detection detects (or diagnoses) the disease at an early stage, when it has a high potential for cure (e.g. cervical or breast cancer) reduce morbidity, improve quality of life as well as increase survival due to good outcome following treatment.

2.2 Key interventions in Cancer Prevention Primary prevention

This is the most efficient and cost-effective form of cancer control it involves prevention interventions that keeps a cancerous process from developing which can be through behavior change by health counseling, education and environmental controls or through a biological mechanism, such as Vaccination. Among the most important modifiable risk factors for cancer are: tobacco use; overweight, and obesity; harmful alcohol use; sexually transmitted human papilloma virus (HPV) infection, HIV/AIDS; air pollution, both outdoor and indoor; and occupational carcinogens.

Public health education and promotion: Public Awareness raising on risk factors for cancer and providing education on ways of avoiding as well as reducing exposure through behavior change is essential. However, this is a long term intervention and may be difficult to quantify. Community education should also focus raise awareness and knowledge on the benefits of early diagnosis, ways of detection and screening. These preventive measures should be highly

promoted by also raise awareness of warning symptoms and signs of cancer and taking prompt action, by the general public as well as physicians, nurses and other health care providers, can have a great impact on the disease through early diagnosis and hence more effective management.

2.3 Key areas in public health education and promotion

Tobacco control: Tobacco use causing an estimated 22% of cancer deaths per year is the single greatest avoidable risk factor for cancer mortality worldwide. Tobacco smoking causes many types of cancer, including cancers of the lung, esophagus, larynx (voice box), mouth, throat, kidney, bladder, pancreas, stomach and cervix. Over 70% of the lung cancer burden can be attributed to smoking alone. Second-hand smoke (SHS), also known as environmental tobacco smoke, has been proven to cause lung cancer in nonsmoking adults and exposes children to cancers. Health workers should inform patients of the dangers of smoking and encourage them to stop.

Healthy diets and physical activity: The incidence of Obesity is at alarming rate especially in developing country like Tanzania where is adoption of unhealthy life styles especially to be people living in urban setting. There is enough evidence which shows the link between overweight and obesity and many types of cancer such as oesophagus, colorectal, breast, endometrium and kidney. Health care professionals should inform clients that regular physical activity, combined with a healthy balanced diet, prevent obesity and can reduce the risk of developing cancer.

Avoidance of alcohol use: Little effort has been put on raise awareness on effect of alcohol on cancer causation despite the fact that harmful (excessive) use of alcohol is a risk factor for many cancer types including cancer of the oral cavity, pharynx, larynx, esophagus, liver, colorectal and breast.

The risk of cancer increases with the amount of alcohol consumed. Therefore, health personnel should encourage their clients to stop or moderate alcohol consumption.

Avoidance of environmental pollution: While many African countries including Tanzania there are in move to Industrial revolution which go hand in hand with increase environmental pollution.

Exposure to carcinogenic chemicals in the environment can occur through drinking water, pollution of indoor and ambient air and via the contamination of food by chemicals, such as aflatoxins or dioxins. Environmental carcinogens (aflatoxins, asbestos, vehicle emissions, lead, ultraviolet (UV) light and ionizing radiation,) are also culprits. Indoor air pollution, like smoke arising from use of charcoal and firewood in poorly ventilated houses, and, fumes from cars, dust, and garbage pollution increase the risk of lung cancer.

Prevention of Infections: More than 60% of Cancers occurs in Tanzania are infectious related which contribute to significant proportion of cancer deaths. Viral hepatitis B and C cause cancer of the liver; human papilloma virus infection causes cervical cancer; Helicobacter pylori increases the risk of stomach cancer. HIV/AIDS is associated with cancers including aggressive lymphoma subtypes, Kaposi's sarcoma, anorectal cancer, cervical cancer. In Lake Region schistosomiasis increases the risk of bladder cancer as well as liver fluke increases the risk of cholangio-carcinoma. Preventive measures include vaccination, prevention and treatment of infection and infestation

2.4 Vaccination

About 60% of all cancers in Tanzania are caused by infectious agents, including viruses and bacteria. Among the most important infections associated with cancers are human papillomaviruses (HPVs) which can cause most cervical and anal cancers as well as a fraction of oral cancers; hepatitis B virus (HBV) and hepatitis C virus (HCV), which can cause liver cancer; and Helicobacter pylori, which is a bacterium that can cause cancer of the stomach. Human immunodeficiency virus (HIV) infection does not cause cancers directly but people with HIV have a greater risk of developing certain cancers because their immune systems are weakened. Vaccines are the most effective way of preventing some of these infections. Highly effective vaccines against HBV have been available for several decades and most countries include HBV vaccination

in their childhood immunization programs; vaccination is also highly effective in preventing infection with the HPV types that cause the majority of cervical cancers. Currently, Tanzania has launched National immunization for cervical cancer using Bivalent HPV vaccine which will be provided to girls aged between nine and 14 to protect them from developing the illness at an early age. More than 600,000 girls in Tanzania have started receiving vaccines to prevent cervical cancer.

2.5 Secondary Prevention

Early detection and Cancer Screening

Most of cancer occurs in Tanzania can be found and treated before they cause symptoms. Checking for cancer or for conditions that may lead to cancer, in people who have no symptoms is called screening. The main aim of cancer screening is to prevent death from cancer. Screening can also make it possible to use less severe treatment methods if the cancer is detected early enough. For some cancers, such as cervical cancer, breast cancer, skin cancer and bowel cancer, screening can actually prevent the cancer from developing.

In the Tanzania, screening is recommended for Cervical, Breast, Prostate, skin and bowel cancer. However only cervical cancer screening is offered as part of an organized program with adequate resources for high quality. Effort is put to include other screening services for other Cancer in organized screening programs.

Comprehensive guidelines covering all aspects of cervical and breast cancer screening have been developed by experts and published by the Tanzania Ministry of Health Elder Gender and Child Development. These Guidelines provide guiding principles and detailed protocols, standards and recommendation that, if followed, ensure that screening services of high quality are provided to the population.

2.6 Cancer registration and surveillance

As a fundamental element of any cancer prevention strategy, Surveillance provides the foundation for advocacy and policy development. This strategy will ensure collection, monitoring and reporting of national cancer data so as to facilitate cancer control interventions including establishment of population-based cancer registry. Currently, the country is underway to established National population based cancer registry which will based in four zones including Lake region (Bugando Medical Centre), Northern zone (KCMC), Southern Highland (Mbeya Referral Hospital), Central (Benjamin Mkapa Hospital-Dodoma) and Eastern zone (Ocean Road Cancer Institute - Dar-Es-salaam).

PART II

ADULT SITE – SPECIFIC CANCERS

3 BREAST CANCER

3.1 Introduction and Epidemiology

Breast cancer is a second most common malignancy among women in Tanzania with an incidence of 13%. It is a second most common cause of death in women aged 45-55 years after cervical cancer. The incidence is expected to rise in the recent years due to screening programs around the country and increased awareness to the general population.

The etiology of breast cancer is so far unknown, however, age, nulliparity, not breastfeeding, first pregnancy age 35years, previous radiation exposure, family history of breast cancer, smoking and alcohol consumption, are the risks associated with breast cancer.

Majority (90%) of breast cancers occurs sporadically and only about 10% of patients have family history of breast cancer.

Screening for early detection is recommended as lesions treated in the early stages have a high cure rate. Screening for breast cancer includes breast self-examination (BSE), clinical breast examination (CBE) and breast imaging (mammogram and/or ultrasound scanning). BSE is recommended at day 10 of the menstrual cycle. For post-menopausal women, a monthly BSE schedule should be established. All patients with clinical suspicious lesions should have imaging as part of early detection. Mammogram is recommended for women over 40 years, while ultrasound is the imaging of choice for younger women. MRI may be used where possible for screening and early detection in patients at high risk of breast cancer such as those with BRCA1 & 2 gene mutations.

3.2 Diagnosis

3.2.1 Clinical Features and Presentations

Early stages the following symptoms and signs may be present: a painless lump in the breast, nipple retraction, skin changes such as darkening and dimpling, nipple discharge that may be bloody.

In late stages, common presentations include: pain, ulceration, enlarged lymph nodes in the armpit and neck and uniform breast enlargement.

Patients with distant metastases may present with such as un-resolving cough, bone pains and pathological fractures.

3.2.2 Laboratory investigations

Complete blood count (FBC), Basic metabolic panel, including liver function test, alkaline phosphatase and renal function tests (creatinine and urea). Viral serology for HIV (recommended). [1 SEP]

3.2.3 Imaging

All patients should undergo chest x-ray and abdominal ultrasound (including asymptomatic patients).

Additional diagnostic imaging modalities to consider:

- Bilateral mammogram; breast ultrasound as necessary.
- Ultrasound guided Axillary LN core biopsy.
- Abdominal pelvic USS, If there is indications (symptoms, physical exam findings or abnormal laboratory tests) consider: Abdominal ± pelvis CT-scan.
- Chest diagnostic CT with contrast if pulmonary symptoms present
- Nuclear Medicine: Bone scan (if bone pain), PET/CT if available
- MRI may be of value in select group of women who have had equivocal mammogram/ ultrasound.
- ECHO cardiogram/ MUGA (Baseline Ejection Fraction and follow up)

3.2.4 Pathology

A core needle biopsy done manually, or preferably by ultrasound or stereotactic guidance is recommended.

FNA should only be used as a screening test where core biopsy services are not possible / available. Any atypical/suspicious or malignant cytology on FNA must be confirmed on histopathological examination.

Diagnosis should be pursued with image-guided core needle biopsy, if available. Additional options include incisional biopsy or excisional biopsy if it is expected that lesion can be removed with clear margins.Open incision biopsy is not recommended in the pre-operative setting if triple assessment (clinical, radiological and cytological findings) is definitive for malignancy.The histopathological reporting should be done according to WHO classification, specifying the histological type of breast cancer, grade, lymphovascular invasion, tumour dimensions, number of nodes sampled and number of nodes involved and presence of necrosis.

It is recommended that histopathology be reported by specialist pathologists and reviewed with a panel of pathologists before treatment is instituted at a specialist treatment center.

Immunohistochemistry (IHC) for estrogen receptor (ER) and progesterone receptor (PR) must be done.

Fluorescence in situ hybridization (FISH)/chromogenic in situ hybridization (CISH) test can be done for equivocal HER2 on IHC (HER2 2+) for confirmation of HER2 overexpression.

Pathological Definitions for Receptor Status;

Estrogen receptor status:

- 0% is considered "negative"
- 1-9% is considered "low positive"
- ≥10% is considered "positive"

Progesterone receptor status:

- 0% is considered "negative"
- 1-9% is considered "low positive"
- ≥10% is considered "positive"

HER2 status:

- IHC 0 or 1+ is considered "negative"
- IHC 2+ or 3+ is considered "positive"

3.3 Staging

Preoperative staging includes clinical, radiological and pathological information. SEP Clinical examination includes the size of tumour (T stage), axillary and supraclavicular node examination (N), symptoms and signs of metastases (M).

Before intervention an attempt should be made to stage all breast cancer patients.

Table TNM Classification for Breast cancers

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis(DCIS)*	Ductal carcinoma in situ
Tis(Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤ 20 mm in greatest dimension
T1mi	Tumor ≤ 1 mm in greatest dimension
T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm).
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension

T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see "Rules for Classification")

* Note: Lobular carcinoma in situ (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

Definition of Primary Tumor (T)

Pathological N (pN)

N Category	N Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy

pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (Level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes; or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes.

M Category	M Criteria
cM0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

* Note that imaging studies are not required to assign the cM0 category

3.4 Management

Treatment is planned according to the extent of the disease, with surgery, chemotherapy, radiotherapy and hormonal therapy as treatment options. A multidisciplinary treatment planning involving at least a breast surgeon, radiologist, pathologist, clinical oncologist should be used to integrate local and systemic therapies and their optimal sequence.

General strategies for treating patient with breast cancer will be outlined according to the following categories:

- 3.4.1 Ductal carcinoma in situ (DCIS
- 3.4.2 Early stageorlocoregionalbreast cancer
- 3.4.3 Locally advancedbreast cancer
- 3.4.4 Recurrent / stage IV or metastatic breast cancer
- 3.4.5 Management of male breast cancer

Additional detail on recommended radi otherapy techniques and surgical techniques can be found in the sections below:

- 3.4.6 Radiotherapy techniques
- 3.4.7 Surgical considerations

3.4.1 Treatment of Ductal Carcinoma in Situ (DCIS) - Stage 0 (TisN0M0))

3.4.1.1 TreatmentOverview

For patients with DCIS Stage 0 (Tis, N0, M0), **recommended**treatment includes the option of either:

- Total mastectomy

  OR

- Breast conserving surgery (with excision to negative margins) + whole breast radiation +/- endocrine therapy

Note: if pathological staging from either total mastectomy or breast conserving surgery reveals more invasive disease, decisions regarding subsequent therapy should be informed by pathological staging.

3.4.1.2 Adjuvant therapy (for patients treated with breast conserving therapy)

Patients undergoing breast conservation therapy are **recommended** to receive adjuvant whole breast radiation. Patients should be **considered** for endocrine therapy for a duration of 5 years.

Whole breast radiation therapy:

- Recommended, especially among those patients with: palpable mass, larger sizetumour, higher grade histology, close or involved surgical margins, and age <50 years.

Endocrine therapy:

- Consider in patients treated with breast conserving therapy with local excision (with or without whole breast radiation), especially for those with ER-positive DCIS

3.4.2 Treatment of Early Stage or Locoregional Breast Cancer- StagesI, IIA, IIB and$T_3N_1M_0$ (IIIA)

3.4.2.1 Overview

Optimal treatment options for locoregional management of Clinical Stage I, IIA, IIB and T3N1M0 (Stage III) typically includes either pre-operative (neo-adjuvant) chemotherapy followed by modified radical mastectomy (MRM)and post-mastectomy radiotherapy or modified radical mastectomyfollowed by adjuvant chemo-radiotherapy sequentially.

In certain cases, with access to appropriate multi-disciplinary careincluding clinical oncology expertise, a breast surgeon AND radiotherapy, certain patients may be considered for a breast conserving surgery with lumpectomy either as first line of treatment or following neo-adjuvant systemic therapy **if** felt that excision can achieve negative margins and tumour is non-inflammatory. Surgical axillary staging with axillary lymph node dissection to level 1 and 2 nodes(or $\geq$ 10 lymph nodes)should accompany modified radical mastectomy as well as any surgical approaches targeting breast conservation, as findings from axillary lymph node dissection are essential to inform need for and sites of adjuvant radiotherapy.

3.4.2.2 Neo-Adjuvant Systemic Therapy

Neoadjuvant systemic therapy can be consideredin patients withclinically evident lymph nodes or tumours which may result in positive margins with surgery. The goal of neo-adjuvant systemic therapy in this setting can be to render inoperable tumours operable, minimize surgical morbidityand even facilitate a breast conserving surgical strategy rather than modified radical mastectomy, in appropriate cases.

Following treatment with pre-operative or neo-adjuvant systemic therapy, response should be assessed either clinically and if possible/applicable, repeat imaging with the diagnostic modality noted to be abnormal at the time of diagnosis.

If patients experience progressive disease on therapy OR partial response but breast conservative surgery is not possible in cases where this was considered a goal,alternate systemic therapy can be given or patient can be referred directly to MRM.

If patient experiences a complete response OR a partial response and lumpectomy is considered possible with negative margins, patients should be recommended for either MRM OR lumpectomy with axillary lymph node staging, in cases where this may be appropriate.

3.4.2.3 Surgery:

Optimal management includes evaluation by clinical oncologist and breast surgeon (in settings where both are available). Most patients will require referral to a National Referral Hospital for optimal management.

Options for surgical management include:

- Breast conserving surgery with lumpectomy/quadrantectomy
- Modified radical mastectomy

As described above, all surgical approaches, including breast conserving surgeries and modified radical mastectomy, should include surgical axillary staging with axillary lymph node dissection to level 1 and 2 nodes ($\geq$10 lymph nodes dissected).Surgical approaches aimed at breast conservation should only take place in cases that allow for multi-disciplinary management with access to radiotherapy. If radiotherapy access is limited, mainstay of surgical care should be modified radical mastectomy.

3.4.2.4 Adjuvant treatment

Adjuvant Radiotherapy

Indications and recommended sites of adjuvant radiotherapy are outlined below. Radiation therapy is typically given after completion of chemotherapy, when chemotherapy is indicated (see Adjuvant Systemic Therapy and Hormonal Therapy section below). For those patients who receive neo-adjuvant chemotherapy, risk-stratifying patients for adjuvant radiotherapy should be based on:i) maximal disease stage from pre-chemotherapy tumour characteristics at diagnosis, and ii) post-chemotherapy pathology results.

Adjuvant Radiotherapy following Modified Radical Mastectomy (MRM)

For patients undergoing MRM,adjuvantradiotherapy is recommended for all patients meeting any of the following criteria:

- Inadequate surgical lymph node staging (i.e. anything less than axillary dissection to level 1 or 2 or <10 lymph nodes dissected)*
- ≥4 positive axillary lymph nodes*

Adjuvant radiotherapy should be considered for patients meeting any of thefollowing criteria:

- 1-3 positive axillary lymph nodes (strongly consider)*
- Tumours > 5 cm*
- Margins positive**
- Negative margins but <1 mm with: i) central/ medial tumour OR ii) tumours>2 cm with other high risk features (young age orextensivelymphovascularinvasion)**

Recommended sites of adjuvant radiotherapy following MRM

- Chest wall
- Infraclavicular region
- Supraclavicular area
- Internal mammary nodes (at physician's discretion, and only if radiotherapy planning by 3DCRT is available***) and
- At-risk regions of the axillary.

Consider radiotherapy to chest wall with or without regional nodes. Radiotherapy to internal mammary nodes is not recommended unless radiotherapy planning is by 3DCRT so that the dose to the descending left coronary artery is evaluated.

Adjuvant Radiotherapy following Breast Conserving Surgery

For patients undergoing breast conserving therapywith excision to negative margins,ALL patients should be recommended for whole breast radiation. Additional radiotherapy that should be recommended/consideredis outlined as below.

Radiotherapy to additional sites recommended for patients meeting any of the following criteria:

- ≥4 positive axillary lymph nodes
- Inadequate surgical lymph node staging (i.e. anything less than axillary dissection to level 1 or 2 or less than 10 lymph nodes dissected)

Radiotherapy to additional sitesshould be considered for patients meeting any of the following criteria:

- 1-3 positive axillary lymph nodes(strongly consider)
- Tumours > 5 cm
- Negative axillary lymph nodes but with central/medial tumour OR tumours>2 cm with other high-risk features (young age or extensivelymphovascular invasion)

Recommended sites of adjuvant radiotherapy following breast conserving therapy (in addition to whole breast radiation)
Sites of additional radiotherapy:

- Infraclavicular region;
- Supraclavicular area;
- Internal mammary nodes (at physician discretion and if radiotherapy planning by 3DCRT is available***); and
- At-risk regions of the axillary.

*** Radiotherapy to internal mammary nodes is not recommended unless radiotherapy planning is by 3DCRT so that the dose to the descending left coronary artery is evaluated.

Adjuvant Systemic and Hormonal therapy

General principles of adjuvant systemic and hormonal therapy are outlined below

- Patients who receive neo-adjuvant systemic terapy and undergo surgery should complete planned chemotherapy regimen course in adjuvant setting if it is not completed pre-operatively, prior to proceeding with radiotherapy if indicated.
- Indications for adjuvant systemic therapy are informed by hormone

receptor status, tumour size and presence of nodal disease (no pathological evidence of disease, microinvasive nodal disease < 2 mm or nodal disease >2 mm).

- Evidence for use of adjuvant chemotherapy for patients greater than 70 years old is limited and therefore should be given at the physician's discretion.
- Use of hormonal therapy in the adjuvant setting is informed by receptor status.

Systemic chemotherapy regimens:CAF/CEF/TAC/AC –T and CMF (for elderly patients >65 years with poor cardiac function is recommended).

Pre-menopausal women: Tamoxifen 20mg daily for 10 years and post-menopausal women Anastrazole/Letrozole for 5 years.

Hormone Receptor Positive (ER+ and/or PR+) AND Her2 +

- If tumour ≤ 0.5 cm&no pathological evidence of nodal disease
  - **Consider:** Adjuvant endocrine therapy ± adjuvant chemotherapy + trastuzumab (if available)
- If tumour ≤ 0.5 cm&microinvasive nodal disease (present to ≤2 mm)
  - Recommend:
- Adjuvant chemotherapy with trastuzumab (if available) followed by endocrine therapy.

  OR
- Adjuvant endocrine therapy
- If tumour >0.5 cm -1 cm&microinvasive or no nodal disease(none to ≤2 mm)
  - Recommend:
- Adjuvant chemotherapy with trastuzumab (if available) followed by endocrine therapy.

  OR
- Adjuvant endocrine therapy
- If tumour>1 cmAND/OR any node positive disease (> 2mm):
  - Recommend:Adjuvant chemotherapy with trastuzumab (if available) followed by endocrine therapy.

Hormone Receptor Positive (ER+ and/or PR+) AND Her2 negative OR Her2 unknown

- If tumour ≤ 0.5 cm& no pathological evidence of nodal disease
  - Consider: Adjuvant endocrine therapy
- If tumour ≤ 0.5 cm&microinvasive nodal disease (present, but ≤2 mm)
  - Recommend:
- Adjuvant chemotherapy followed by endocrine therapy.
  OR
- Adjuvant endocrine therapy
- If tumour>0.5 cm &microinvasiveornodal disease(none to ≤2 mm)
  - Recommend:
- Adjuvant chemotherapy followed by endocrine therapy.
  OR
- Adjuvant endocrine therapy
- Any node positive disease (> 2mm):
  - Recommend:Adjuvant chemotherapy followed by endocrine therapy.

Hormone Receptor Negative (ER- and PR-) AND Her2 +

- If tumour ≤ 1cm&microinvasiveor no nodal disease(none to≤2 mm)
  - Consider: Adjuvant chemotherapy with trastuzumab(if available)
- If tumour>1 cm AND/OR any node positive disease (>2mm):
  - Recommend: Adjuvant chemotherapy with trastuzumab (if available)

Hormone Receptor Negative (ER- and PR-) AND Her2 negative or HER2 unknown

- If tumour ≤ 0.5 cm& no pathological evidence of nodal disease
  - Recommend:No adjuvant therapy
- If tumour ≤ 0.5 cm&microinvasive nodal disease (present to≤2 mm)
  - Consider: Adjuvant chemotherapy
- If tumour between >0.6-1 cm &microinvasiveor no nodal disease (none to ≤2 mm)
  - Consider: Adjuvant chemotherapy
- If tumour>1 cm AND/OR any node positivedisease (>2mm)
  - Recommend: Adjuvant chemotherapy

3.4.3 Locally AdvancedBreast Cancer -Stage IIIA (excluding $T_3N_1M_0$), IIIB and IIIC

Patients with Stage IIIA (excluding $T_3N_1M_0$), IIIB and IIIC are considered **inoperable** at presentation and require systemic therapy prior to any surgical resection. Patients meeting with these staging criteria should be recommended for systemic therapy with the intended goal of reducing disease burden or downstaging the tumour prior to proceeding with subsequent surgical resection.

Optimal management of this patient population includes the following three components, described in greater detail below:

- Neo-adjuvant systemic therapy
- Surgery
- Adjuvant therapy

3.4.3.1 Neo-Adjuvant Systemic Therapy

Patients are recommended to undergo pre-operative or neo-adjuvant systemic therapy with 4-6 cycles of one of the following regimens:

- CAF/ CEF/TAC and CMF (for elderly patients>65 yrs with poor cardiac function)

Prior to initiating treatment, baseline clinical tumour burden should be carefully assessed and documented to allow for clinical monitoring of response during the course of and following neo-adjuvant systemic therapy.

Response assessment

If patient demonstrates clinical response to systemic therapy, referral tosurgery should be made, as outlined below.If no response is observed, recommend proceeding with additional systemic therapy (ideally with different regimen than used as first line) and/or pre-operative radiation therapy. If response to 2nd line neo-adjuvant therapy is observed, referral for surgery should be made at that time.

3.4.3.2 Surgery

Options for surgical management include:

- Breast conserving surgery with lumpectomy/quadrantectomy
- Modified radical mastectomy

All surgical approaches for early stage and locally advanced breast cancer, including breast conserving surgeries and modified radical mastectomy, should include surgical axillary staging with axillary lymph node dissection to level 1 and 2 nodes (≥10 lymph nodes dissected, further detailed below).

Surgical approaches aimed at breast conservation should only take place in cases that allow for multi-disciplinary management with access to radiotherapy.

If radiotherapy access is limited, mainstay of surgical care should be modified radical mastectomy.

- Conducting thorough and appropriate clinical staging is essential, particularly for this patient population as optimal management with neo-adjuvant chemotherapy can help later achieve negative margins with planned modified radical mastectomy.
- Obtain patient's informed consent and provide post-operative healing education.
- Obtain negative margin of ≥ 1mm.
- Excise around obvious skin involvement, try not to cut into the malignancy.
- Dissect to level 1 or 2 nodes OR at least 10 axillary nodes, unless pre-operative chemotherapy given.
- If possible place 2 drains in the mastectomy field and leave it for 10-14 days. The drain exit should be close to the mastectomy incision site to make it possible for inclusion in post- mastectomy radiation field.
- Aim for mastectomy flaps approximately 5 mm in thickness.
- Mastectomy boarders: Superior – Sternum, Medial – Sternum, Lateral – Latissimus dorsi muscle, Inferior – Rectus abdominus muscle.
- Axillary LN dissection boarders: Superior – axillary vein, Lateral – Latissimus dorsi, Medial – serratus anterior, Inferior – branching of thoracodorsal bundle into latissimus dorsiand serratus anterior.
- Mastectomy specimen should be properly fixed and submitted for

histopathology/ if formalin unavailable at the theatre take the specimen to the pathology laboratory as soon as possible to minimize ischemic time until formalin placement.

3.4.3.3 Adjuvant Therapy

Recommendations for adjuvant therapy include the following components:

- Systemic therapy:
  - o Complete planned chemotherapy regimen course if not completed pre-operatively.
  - o If HER 2+, complete up to one year of trastuzumab (if available; may be administered concurrently with radiation therapy, as well as with endocrine therapy if indicated)
- Radiotherapy:
  - o Radiotherapy to chest wall, supra- clavicular area, infraclavicular and internal mammary nodes, and any part of axillary bed at risk.
- Endocrine Therapy
  - o If ER+ and/or PR+,recommend Tamoxifen (pre-menopausal) and anastrazole (post-menopausal) (typically given after completion of chemotherapy)

3.4.3.4 Follow-up and surveillance

- History, Physical Examination, clinical chemistry, haematological and imaging evaluation every 3 months for the first 2 years followed by every 6 months the following 2 years then annually.
- Monitor and manage lymphedema.
- Follow up mammogram once every 12 months.
- Endocrine therapies should be prescribed for 5-10 years (Tamoxifen: pre menopausal and Anastrazole: post menopausal).
- Women on Tamoxifen: annual gynecologic assessment – endometrial and ovarian malignancy.
- Educate about healthy diet, active lifestyle, limited alcohol intake, achieving ideal body weight (20-25 BMI).
- Counseling for fertility concerns if pre-menopausal.
- Counseling first degree relatives breast cancer screening.

3.4.4 Recurrence /Stage IV disease or Metastatic Breast Cancer Workup

- History and Physical Examination
- Laboratory**:** FBC, RFT, LFT including ALP
- Radiology**:**Abdominal and pelvic USS, CXR

If available : Abdominal ± pelvis CT-scan
Chest diagnostic CT with contrast if pulmonary symptoms present
Brain MRI with contrast if suspicious CNS symptoms
Spine MRI with contrast if back pain or symptoms of cord compression.

- Nuclear medicine**:** Bone scan, PET/CT
- Pathology*:* Core biopsy of the recurrent lesion or metastasis, determination of tumour ER/PR and HER-2 status on metastatic lesion

Treatment of Recurrence

Local Recurrence:

- If initial treatment with lumpectomy+ radiation therapy:

Total Mastectomy + axillary lymph node staging if level I/II axillary staging not previously done

- If initial treatment with mastectomy with level I/II axillary dissection and prior radiation therapy: Surgical Resection if possible(Wide Local Excision)
- If initial treatment with mastectomy and no prior radiation therapy: Surgical Resection if possible + Radiation therapy

Regional or loco-regional recurrence:

- Axillary recurrence: Surgical resection if possible + radiation therapy if possible
- Supraclavicular recurrence: Radiation therapy if possible
- Internal mammary recurrence: Radiation therapy if possible

Note: Decision to use radiation therapy for loco-regional recurrence must keep into consideration any prior radiation to the area and the risk of late normal tissue toxicity from the sum of the prior and planned radiation courses.

If technically not resectable, consider systemic therapy , then resect if possible.

Consider systemic therapy: **(**Adjuvant endocrine, neo+ adjuvant chemotherapy, Endocrine therapy for recurrent or stage IV disease.

Chemotherapy regimens for recurrent/or metastatic breast cancer including-Single agent Gemcitabine, Xeloda/ Paclitaxel/ Carboplatin etc or combination depending on the performance status of the patient.

Consider PET-CT for response assessment (If available).

Stage IV disease

Patients with bone disease should receive zoledronic acid, unless contraindication present (ie. renal insufficiency).

If ER and/or PR positive, HER-2 negative or unknown
No Prior endocrine therapy within 1 year

Pre- menopausal:Ovarian ablation or suppression + endocrine therapy as postmenopausal women or ER modulators.

Post-menopausal:Aromatase inhibitor or selective ER modulators

Visceral crisis:Consider chemotherapy regimens for either combinations ie CAF,CEF,Gemcitabine/paclitaxel or single agent Taxane or capecitabine or gemcitabine; if no benefit after 3 sequential lines of chemotherapy or ECOG performance status $\geq$3 consider no further cytotoxic therapy transfer to palliative care.

If ER and/or PR positive, HER-2 negative or unknown
Prior endocrine therapy within 1 year

Pre-menopausal:Ovarian ablation or suppression, plus endocrine therapy as for post-menopausal women.

Post-menopausal:Continue endocrine therapy until progression or unacceptable toxicity; if no clinical benefit after 3 sequential endocrine therapy

regimens or symptomatic visceral disease, consider systemic chemotherapy.

Visceral crisis: Consider systemic chemotherapy; if no benefit after 3 sequential lines of chemotherapy or ECOG performance status $\geq$ 3 consider no further cytotoxic therapy transfer to palliative care.

ER and/or PR positive;HER 2 positive

No prior endocrine therapy within 1 year

Pre-menopausal:Ovarian ablation or suppression plus endocrine therapy as for post-menopausal women or selective ER modulators

Post-menopausal: Aromatase inhibitor or selective ER modulator

Visceral crisis:Trastutuzumab + chemotherapy; if no benefit after 3 sequential lines of targeted therapy or ECOG performance status $\geq$ 3 consider no further cytotoxic therapy transfer to palliative care.

ER and/or PR positive;HER 2 positive

Prior endocrine therapy within 1 year

Pre- menopausal: Ovarian ablation or suppression + endocrine therapy as postmenopausal women or ER modulators.

Post-menopausal:Aromatase inhibitor or selective ER modulators until progression or unacceptable toxicity; if no clinical benefit after 3 sequential endocrine therapy regimens or symptomatic visceral disease, consider systemic chemotherapy.

Visceral crisis**:**consider chemotherapy regimens for either combinations ieTrastuzumab+paclitaxel/carboplatin or Trastuzumab+paclitaxel or Trastuzumab + docetaxel or Trastuzumab+capecitabine; if no benefit after 3 sequential lines of targeted therapy or ECOG performance status$\geq$3 consider

no further cytotoxic therapy transfer to palliative care.

ER and PR negative;or ER and/or PR positive and endocrine refractory;and HER2 negative or unknown;
If bone or soft tissue only or asymptomatic visceral disease: consider additional line of endocrine therapy if not endocrine refractory or chemotherapy regimens for either combinations ie CAF,CEF,Gemcitabine/paclitaxel or single agent Taxane or capecitabine or gemcitabine.

If symptomatic visceral disease: Consider systemic chemotherapy; if no benefit after 3 sequential lines of chemotherapy consider no further cytotoxic therapy transfer to palliative care.

ER and PR negative;or ER and/or PR positive and endocrine refractory;and HER2 positive;
If bone or soft tissue only or asymptomatic visceral disease:endocrine therapy if not endocrine refractory+/-HER 2-targeted chemotherapy(Trastuzumab + taxane).

If symptomaticvisceral disease: Trastutuzumab + chemotherapy; if no benefit after 3 sequential lines of targeted therapy consider no further cytotoxic therapy transfer to palliative care.

3.4.5 Management of Male Breast Cancer

- Investigation of breast cancer in the male is identical to that of the female patient. Because the male breast is very small, it is common for even small tumours to involve both skin and deep tissues with the result that they present as locally advanced disease.
- Surgery should be planned so that there will be wide margins on both the skin and deep tissues, and this may require removal of some underlying muscle. [1 SEP] Axillary dissection is also required. [1 SEP]
- It is important to assess the hormone receptor status since most carcinomas of the male breast are hormone receptor positive thus amenable to hormonal therapy. [1 SEP]
- Adjuvant radiotherapy is often recommended owing to the size of the

breast and locally advanced disease. The indications for post-mastectomy radiation for males are essentially the same as those for females.

3.4.6 Radiotherapy Technique

Use of CT-based treatment planning is preferred if available to delineate target volumes and adjacent organs at risk.

- Patient is positioned supine, Use breast board and arm rest with an appropriate head rest.
- Conventional simulator is used to get X-ray images using two tangential fields and one anterior field if supraclavicular fossa nodes are to be irradiated.
- No bolus is used unless mastectomy drain site is outside the radiation field
- No weighing/wedges
- Normal organ limit; Central lung distance 2cm

Dose delivery:

- 50G in 25 fractions for 5weeks (Conventional fractionation) OR
- 40Gy in 15 fractions for 3weeks (Hypofractionated protocol) OR
- 42.5Gy in 16 fractions for 3 ½ weeks (Hypofractionated protocol)

Normally two tangential beams (fields) are placed to deliver a dose of 45-50Gy in 23-25 fractions. If there is an indication for supra and infra clavicular lymph node irradiation, an anterior beam is normally added to make a total of three beams.

3.4.6 .1 Palliative radiotherapy

Consider radiotherapy for oligometastasis in metastatic settings.

Dose:

- 8Gy Single for most bone metastasis for relief of pain
- 20Gy in 5 fractions for 1 week or 30Gy in 10 fractions for 2 weeks for sites such as cervical spine, meningeal disease and nodal masses.

4 CENTRAL NERVOUS SYSTEM TUMOURS

4.1.1 Introduction and Epidemiology

In Tanzania primary Central nervous system tumors are less than 3%. Currently there is limited data related to CNS tumors in the country. Globally, primary CNS tumors constitute 2-5% of tumors in adults. More than 50% of these are neuro-epithelial tumors, with meningiomas and malignant gliomas being most common. Primary cerebral lymphoma (1% of primary CNS tumors) has an increasing incidence since the onset of the AIDS pandemic.

4.1.2. Etiology

Most are sporadic. Possible association with prior head trauma/ Prior Radiation exposure. May be associated with immune deficiency syndrome (Primary CNS lymphoma). Several familial syndromes are associated with primary brain tumors:

- Neurofibromatosis(NF) type 1 associated with Optic nerve glioma,
- Malignant astrocytoma, Phaeochromocytoma, Carcinoid and
- Rhabdomyosarcoma.
- Neurofibromatosis (NF) type 2 associated with Acoustic neuromas (frequently bilateral), Other Schwannomas, Meningiomas, Gliomas-astrocytomas and ependymomas.
- Tuberous sclerosis is associated with Sub-ependymal giant cell astrocytoma.
- Von-Hippel-Lindau Syndrome associated with haemangioblastomas (as well as Renal cell cancer and phaeochromocytoma).
- Turcot's syndrome is associated with glioma, medulloblastoma.
- Gorlin's syndrome is associated with medulloblastoma

4.1.3. Diagnosis

4.1.3.1. Clinical presentation

- May be related to raised ICP or local/ general brain dysfunction;
- Raised ICP
- Headache especially mornings ; may be bifrontal or occipital
- Nausea and vomiting

- Papilloedema which may lead to transient visual obscuration or if long term, to permanent blindness
- Decreased level of consciousness
- Brain dysfunction
- Mental deterioration
- Personality changes seizures
- Focal symptoms related to site of tumor

4.1.3.2. Imaging

MRI if available is the image of choice and is Superior to CT scan due to better contrast resolution. If not accessible CT Scan is mandatory to evaluate intracranial mass lesions.

4.1.3.3. Histopathology

Tissue must be submitted for Histopathology for examination after surgery. Initiation of Radiotherapy or Chemotherapy must be done after Histology report unless in High risk cases that may require emergency radiotherapy. Immunohistochemistry (IHC) is recommended for confirmation of diagnosis.

Histologic Grade (G)

CNS WHO tumor grades are used in histologic grading. This provides uniformity of classification and categorization of CNS tumors.

G	Definition
I	Circumscribed tumors of low proliferative potential associated with the possibility of cure following resection
II	Infiltrative tumors with low proliferative potential with increased risk of recurrence
III	Tumors with histologic evidence of malignancy, including nuclear atypia and mitotic activity, associated with an aggressive clinical course
IV	Tumors that are cytologically malignant, mitotically active, and associated with rapid clinical progression and potential for dissemination

4.2. Meningioma

4.2.1 Epidemiology

- Constitute 20% of all intracranial tumors. Uncommon in children (1-4%) but may be giant. Forty percent of patients have multiple lesions seen on CT. Commonest sites are cerebral convexity, parasagittal and sphenoid ridge which make up 75%.
- Females: males= 2:1.
- Peak incidence in 7th decade.
- Possible etiologies include Ionizing radiation exposure, trauma, viral infections and sex hormone exposure (+/- 75% are PR +ve). Associated with NF2 and with breast cancer.

4.2.2 Clinical presentation

Commonest presenting symptoms include; Paresis, non-focal examination eg. Seizures, memory deficit, cranial nerve deficit (other than CN2), Visual Field defect, paraesthesia, aphasia, papilloedema and diminished visual acuity. Spinal meningiomas frequently present with pain (72%) then progress to sensory loss, weakness and bladder/bowel dysfunction years later.

4.2.3 Imaging

CT or MRI should be done. Typically, well circumscribed, smooth contoured tumor. Usually homogeneously increased density on unenhanced CT, and moderate to intense enhancement with contrast. 60% may have surrounding edema.

Frequently (15-20%) associated with bony destruction/distortion or hyperostosis, but this usually does NOT represent bony invasion. Often associated with linear meningeal thickening ("dural tail"), which frequently represents reactive change but may represent spread along meningeal plane.

4.2.4 Pathology

Thought to arise from arachnoid cap cells on outer surface of arachnoid membrane. Usually expand and displace brain, but NOT invade it (benign

tumors). Classified according to grade, (WHO grade 1-3, where grade 4 is classified as Sarcoma). Higher grade associated with more frequent and earlier recurrence. Only approximately 7% of meningiomas are > grade 1. Five year DFS is 35%, 44%, and 84% respectively for grade 3 vs. 2 vs. 1 following Surgery + RT or RT alone.

4.2.5 Management

4.2.5.1 Surgery

- Both intracranial and spinal meningiomas are best managed with total excision if possibly achievable with acceptable morbidity.
- Fully resected meningioma has RFS rates of 90%, 80% and 67% at 5, 10 & 15 years respectively.
- One third are NOT fully resected because of location, size and proximity to critical structures (Most often posterior fossa, sphenoid ridge and parasellar).
- Subtotal resection is associated with inferior outcome: 60, 45 and 10% at 5, 10 &15 years.
- Post-operative RT improves these rates significantly and is standard of care.

4.2.5.2 Radiotherapy

- Post-operative radiotherapy is indicated in incomplete resection for grade 1 and all grade 2/3 tumors.
- Meticulous attention to operative notes is required, as well as to CT/MRI.
- PTV= GTV+ 1 cm margin for benign lesions, and 2-3 cm margin for grade 2/3 lesions.
- In post-operative setting, GTV is based on POST-OP remnant for grade 1 lesions and PRE-OP scans grade 2/3 lesions.

**NOTE: Post-op RT is almost always offered to grade 2/3 lesions even if complete resection is achieved.

- Cast is usually slightly flexed, but head position depends on site of lesion. Patients are CT scanned and planned using 3-D planning and often non-

coplanar techniques. Contrast enhanced scans make tumor volumes easier.

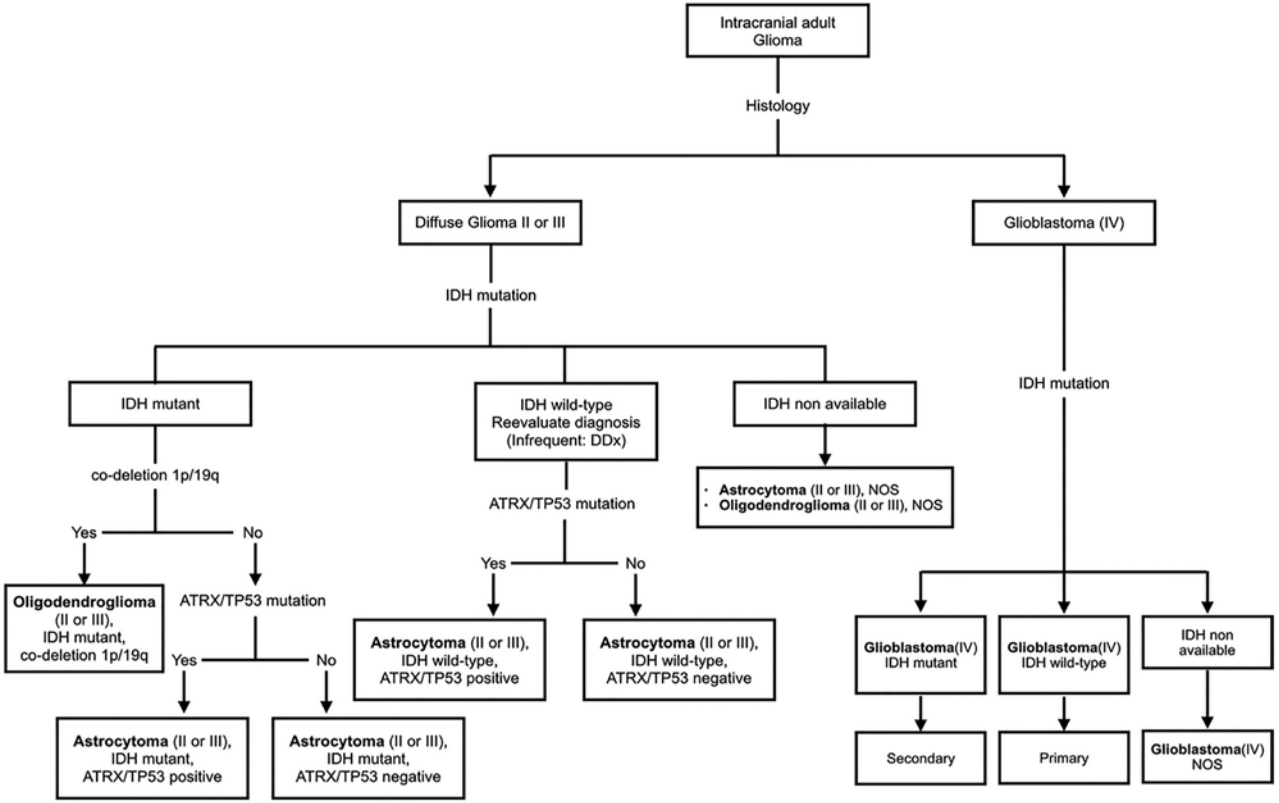
- Dose: 1.8 Gy X 30 Fractions = 54Gy (5 times per week) for grade 1 lesions
- Dose= 1.8 Gy X 33 Fractions = 59.40Gy (5 times per week) for grade2/3 lesions.
- Note that many patients may require Steroids (Decadron) during RT especially if RT fields are large.
- RT may be used alone for unresectable tumors. Doses as above.
- Spinal meningioma is best treated with excision and this is achieved in all but about 7% of cases.
- Dose= 1.8 Gy X 25 Fractions = 45 Gy (5 times per week).

**NOTE: If 3D conformal radiotherapy is not available, palliative whole brain RT is given in 2D Technique at a dose of 30Gy in 10 Fractions over 2weeks. (Whole brain RT using opposing lateral fields).

4.2.6 Follow up

CT Scan/ MRI every 6 months for 1 year, then annually.
Older patients small tumors, CT/MRI scan yearly.

2016 Classification of adult gliomas basing on histology and Isocitrate dehydrogenase(IDH) status.



4.3.1 Low grade Gliomas

4.3.1.1 Introduction

These are neuro-epithelial tumors divided into: Astrocytomas, Oligodedrogliomas, Ependymomas and Mixed tumors.

Low grade astrocytoma:

Comprise 5-15% 0f adult primary brain tumors and 67% of low grade gliomas. Incidence decreases with increasing age peaking at 20-40 years, except for Pilocytic astrocytoma which is commoner in children in 1st 2 decades. Pilocytic astrocytoma commonly involves posterior fossa, or optic tracts, whereas other low grade astrocytomas typically involve cerebral hemispheres.

4.3.1.2 Clinical presentation

Two thirds of adult patients present with seizures, the rest exhibit slowly progressive neurologic symptoms depending on site of tumor. These may evolve over months or even years.

Seizures are associated with improved survival.

4.3.1.3 Pathology

Commonest subtype in adults is fibrillary astrocytoma.
In children, commonest is JPA.
JPA rarely dedifferentiate, but approximately 50%-60% of fibrillary
Astocytomas will transform into malignant lesions over 5 years

4.3.1.4 Imaging

CT or MRI should be done in diagnosis of Gliomas. Pilocytic astrocytomas are discrete brightly enhancing lesions. Classically, show a cyst associated with an enhancing mural nodule.

Grade 2 astrocytomas classically are diffuse poorly-defined, low density, non-enhancing lesions on CT. 10% may have calcification. MRI shows low signal intensity on T1, and high signal intensity on T2. No enhancement.

4.3.1.5 Management

Surgery

Juvenile Pilocytic Astrocytoma

- These are usually relatively well-circumscribed and 60-80% are amenable to total removal without increasing neurologic deficit.
- Long term survival approaches 100% with complete removal. After partial resection, survival rates range from 80-90% at 5 years to 70-80% at 10 years and 50-60 % at 20 years.
- These are slow growing tumors and even if there is residual, it is reasonable to repeat the scans at 6, 12, 24 months to check for growth. If this is surgically resectable then this should be attempted.

Subepindymal giant cell Astrocytoma

Total surgical excision without excessive morbidity is the goal and if achieved then 6/12 monthly MRI scans for 2 years, then annually is recommended.

Radiotherapy

- PTV should encompass area of high signal on pre-operative FLAIR/T2 MRI or CT image + 1-2cm margin.
- Planning is 3-D and frequently non-coplanar beams are employed. For non-coplanar planning, it is necessary to scan low enough to get a reasonable reconstruction of reference anatomy for coronal and sagittal images.
- It is also necessary to scan up to and above the top of the skull, so that beams can be brought in from above.
- Dose for low grade gliomas: 1.8 Gy X 28 Fractions = 50.4 Gy (5 times per week).
- Concurrent and adjuvant use of Temozolomide is indicated if available, 75mg/m2 daily during radiotherapy and 150-200mg/m2 day 1-5 monthly for 6 months.

4.3.1.6 Follow up

Unless there are other clinical indications the first scan is done 6 months after RT and then annually.

If the hypothalamus /pituitary are in the field then endocrine function should also be evaluated annually by T4 & TSH, testosterone or FSH/LH.

4.3.2. High grade gliomas (Anaplastic astrocytoma (AA) and Glioblastoma multiforme (GBM)

4.3.2.1 Introduction

- These make up 35-45% of primary brain tumors, and of these, about 85% are Glioblastoma multiforme (GBM).
- Incidence of AA peaks in children < 10 years of age and remains constant in each subsequent decade. Mean age is 41 years with a slight male preponderance.
- GBM is uncommon under 20 years and increases dramatically after age 40 years.
- Incidence of malignant glioma has increased at least 2-fold in the elderly over the past 2 decades.
- Usually occur in cerebral hemispheres with frontal, parietal, temporal, occipital lobes most commonly involved (in that order).
- Usually present with features of mass effect, or focal signs depending on location.
- Multicentric tumors occur in <5% of cases and CNS dissemination occurs in about 10% of end stage cases. Metastases outside of CNS are extremely rare.
- Strongest prognostic factors are grade, age and KPS.

4.3.2.2 Imaging

- MRI preferred investigation, is superior to CT in most cases, but occasionally CT may reveal abnormalities not seen on MRI.
- GBM may exhibit striking "ring-enhancement". Peri-tumoural edema is often extensive, and mass-effect is commonly seen in these patients.
- PET shows increased FDG uptake in tumor but may be obscured because of normal FDG uptake in cortex and basal ganglia.

4.3.2.3 Pathology

Classified as per WHO Classification.

Characterized by high cellularity, nuclear atypia, marked mitotic activity+-

nuclear inclusions, multinucleated cells and abnormal mitoses.
GBM is associated with necrosis and in some cases, microvascular proliferation.

4.3.2.4. Management

Surgery

Complete excision of the tumor is recommended, but rarely completely grossly resected –extent of resection best assessed on post-op scan.
Evidence suggests improved survival and functional status in patients with complete resection (good debulking) compared to partial resection/biopsy.
Debulking provides good palliation in patients with mass effect.

Radiotherapy

- Strap position usually slightly flexed for hemisphere tumors but dependent on location. Cast required.
- Patients should be CT-planned, with contrast administration. 3mm to 5mm slices cuts from Vertex to Base of skull.
- Large volume PTV = should completely encompass enhancing lesion seen on pre-op T2/FLAIR scan, plus small (2cm) margin.
- Dose to LARGE VOLUME = 2.00 Gy X 23 Fractions = 46.00 Gy (5 times per week).
- Small volume PTV (PTV2) is based on Gd-enhanced T1 weighted image= enhancing lesion on pre-op scans +1- 2 cm margin.
- Dose to SMALL VOLUME = 2.00 Gy X 7 Fractions = 14.00 Gy
- Total dose 60Gy in 30 fractions.
- Other alternative radiotherapy fractionations can be used in elderly, more than 65 years of age are;

Hypo fractionation; 40Gy/ 15 Fractions and 5Gy X 5 Fractions.

Chemotherapy

- Concurrent chemotherapy (Temozolomide) + RT
- Dose: Temozolomide 75 mg/m2 daily per oral during RT, Then 150-200 mg/m2 given D1-D5 of a 28 day cycle for 6 cycles after RT
- Oral steroid/ Ondansetron / Granisetron should be taken half an hour prior

to chemotherapy tablet on each day.Tablets must be taken 1st thing in the morning on an empty stomach.
- Prophylaxis for PCP pneumonia with Co-trimoxazole (one tablet twice daily) should be given during daily Temozolomide treatment.

4.3.2.5. Recurrent disease

- Surgery plays an important role in selected patients- relieves symptoms, improves PS and QOL, and reduces steroid requirement.
- Repeat radiotherapy can be considered, depending on size of lesion and previous dose.
- Chemotherapy may be only modality available- active regimens are BCNU, PCV, Temozolomide and more recently, Irinotecan and Bevacizumab.
- Response rates range from 20-40%. No evidence for improved survival in this setting, but good palliation frequently obtained. Repeat scans should be done after 2-3 cycles to determine response.
- Stop if Progression of disease (PD). Continue to 6-8 cycles if CR/PR/SD and marrow allows.

Follow up

A baseline scan should be done at 4 months post RT as a reference. Thereafter scans are usually done at 6 months and annually, or if clinically indicated.
High index of suspicion and testing if indicated for pituitary function.
Good risk low grade gliomas CT scan every 6 months for 1st year, then basic on symptomatology.

4.3. 3 Oligodendroglioma

4.3.3.1. Introduction

Comprise 5-20% of glial tumors.
Occur mainly in adults with peak incidence in 4th-6th decades (slightly younger for low grade tumors).
Has a better prognosis than astrocytic tumors of similar grade, but tumors may be mixed. These then have an intermediate prognosis.

60-70% of tumors (regardless of grade) are characterized by deletions on arms of chromosome 1p and 19q and this finding is an indication of chemo sensitivity and of good prognosis.

4.3.3.2 Clinical Presentation

Similar to astrocytomas BUT tend to have a longer history, and seizures more common (70-90%) patients at time of diagnosis.

4.3.3.3 Imaging

Low grade tumors: CT- low density masses without enhancement, and typically contains calcification. On MRI- show high signal intensity on T2/FLAIR without enhancement. Edema not striking.

High grade tumors are usually characterized by enhancement, but up to 30% may not be.

Leptomeningeal spread usually only seen at recurrence, but can occur in about 10% patients.

4.3.3.4.Pathology

Most tumors arise in white matter of cerebral hemispheres, predominantly in frontal lobes, but can arise anywhere in CNS.

Diffusely infiltrating tumor despite frequently having quite well-defined borders on scan.

Designated low-grade (WHO G2) if well differentiated, and high grade if anaplasia presents (WHO G3). High grade tumors may arise within low grade tumors, or de-novo.

4.3.3.5 Management

Radiotherapy

As for low and high grade astrocytomas.

Improves Disease free survival for inoperable progressive disease

Chemotherapy

Chemotherapy improves DFS and is given in the adjuvant setting after surgery and adjuvant RT.

Adjuvant chemotherapy important when need to delay RT in children < 3 years.
Chemotherapy regimen: PCV
Temozolomide (dose and schedules as in GBM)
PCV chemotherapy "Standard": CCNU (lomustine)/Vincristine /Procarbazine

4.3. 4 Brainstem Glioma

4.3.4.1 Introduction

Rare. Constitutes < 2% of brain tumors.Commoner in children (2:1)
Tumors may be focal and/or exophytic (usually low grade), or diffuse and deep (usually high grade).
Prognosis is related to grade and age.

4.3.4.2 Management

Radiotherapy

Dose = 1.8 Gy X 31 Fraction = 54.00 Gy.
Ideally treat prone with an anterior and posterior cast . Cast needs to include neck as tumor volumes frequently are low.

Chemotherapy

Temozolomide not routinely recommended.

4.3.5. Pineal Tumors

4.3.5.1 Introduction

Commonest tumors in this region are germ cell tumors- usually germinoma or teratoma- discussed separate.
Other tumor types include: PNET- called pineoblastoma (pinealoblastoma) when occurring in pineal gland.

4.3.5.2 Management

Steroids to relief symptoms
Shunt to relief severe hydrocephalus
Manage pain

Pinealoblastoma:	Behave as PNET's Treat as for medulloblastoma
Pineocytoma:	Localized indolent tumors. Can frequently just be watched. Surgery indicated if enlarging and symptomatic.

If progressive and unresectable, then RT improves long term disease control and survival.

Radiotherapy
RT to tumor + 2 cm margin using 3-D planning
Dose= 1.8 Gy X 30 Fractions = 54.00 Gy

Relapses
Salvage surgery or Re irradiate

4.3.6. Intracranial Germ Cell Tumors

4.3.6.1 Introduction

- Males > Females 3:1 especially for pineal tumors.
- 70% patients between ages of 10 to 24 years and 90% patients between ages 5 to 35 years.
- Commonest site is pineal (50-60%), followed by suprasellar (30-40%), and less commonly by basal ganglia or thalamus (3-5%).
- 10% occur in multiple sites (Also called "multiple midline tumors").
- Natural spread now believed to be laminar- along sub-ependymal lining of walls of V3 and V4.

4.3.6.2 Clinical Presentation

Depends on site:

Pineal tumors: Hydrocephalus due to obstruction of aqueduct Parinaud's sign (upward and downward gaze palsy due to tectal plate compression), Argyll Robertson pupils, Precocious puberty, hemiparesis, visual disturbance, inco-ordination and movement disorders in late-presenting cases

Suprasellar tumors: Chiasmal compression causing bitemporal hemianopia and eventually diplopia and decreased VA, Panhypopituitarism and diabetes insipidus.

Metastases: Usually to elsewhere in CNS
Occasionally to lung, bone or via VP shunt to abdomen

4.3.6.3 WHO classification

Germinoma (40%): Usually "non-secreting" but may be HCG +ve, PLAP +ve, NEVER AFP +ve.
Teratoma (19%).
Choriocarcinoma (2%): Strongly HCG +ve.
Yolk sac/endodermal sinus tumor (2%): Strongly AFP +ve.
Embryonal carcinoma (3.3%): May be weakly AFP or HCG +ve.
Mixed tumors (32%): Most common component = Germinoma.

4.3.6.4 Work up

- Serum AFP and bHCG
- CSF cytology and markers
- MRI of brain and spine: about 1/3 of patients with suprasellar tumors and about 10% of patients with pineal tumors may have spinal seeding.
- Full evaluation of anterior and posterior pituitary function.
- Baseline full evaluation of visual fields and visual acuity.

4.3.6.5 Management

4.3.6.5.1 Germinoma

Surgery

No benefit for surgery
Patients presenting with obstructive hydrocephalus may require emergency shunting.

Radiotherapy

The gold standard in the past was Cranio-spinal radiotherapy with a boost to the primary tumor. This produces 5 year survivals in the order of 100%.
Other alternative treatment strategies including:-

CSI at lower doses
Cranial irradiation without spinal radiation
Whole ventricle RT(WVRT) + focal boost
Chemotherapy with focal irradiation

Extended focal RT= whole ventricle RT (germinoma only):
Includes tumor + lateral ventricles+ 3rd ventricle + sella and pineal areas
(Tighter margins resulted in inferior local control)

Boost includes primary tumor + 1-2 cm margin)
Dose to cure sub-clinical disease = 20-24 Gy.
Dose to cure primary= 40-45 Gy.

Therefore:

Dose: WVRT= 1.8 Gy 13 Fractions = 23.4 Gy
Boost= 1.80 Gy x 12# = 21.6 Gy, Total Dose= 45 Gy

OR Chemotherapy + extended local RT
Carboplatin 450 mg/m2 D1
Etoposide 150 mg/m2 D1-D3 every 4 weeks X 3 cycles

Followed by extended focal RT as above
Dose: 1.8 Gy X 14 Fractions = 25.2 Gy------ (for pure germinoma)

4.3.6.5.2. Non-germinomatous ("secreting") GCT

Surgery

- These have a much poorer prognosis- especially yolk sac tumors, embryonal tumors and Choriocarcinoma.
- Surgery and RT alone has median survival of 18 months. With cisplatin-based chemotherapy, 2 year survivals are now in the order of 48%, and up to 70-80% when residual masses are treated with surgery and focal or

craniospinal RT.

- Surgery: Secreting germ cell tumors are highly vascular and have a risk of haemorrhage post biopsy. Therefore, in patients with characteristic clinical features, radiology and unequivocally elevated serum or CSF HCG and/or AFP, biopsy is NOT mandatory.
- Residual mass in mature or immature teratoma can be surgically removed post adjuvant chemotherapy.

Radiotherapy

Done post chemotherapy and surgery to residual mass. Focal RT for localized tumors, and CSI for metastatic disease.
Craniospinal RT- for pts with CSF seeding, or multiple site disease) No benefit for 36 Gy over 30 Gy therefore dose = 1.6 Gy X 19#= 30.40 Gy (5X per week)
Boost: 1.8 GyX11# = 19.8 Gy

Chemotherapy

Cisplatin containing regimens – PVB, carboplatin/etoposide/bleomycin/ carboplatin/etoposide
Ifosphamide-containing regimens- ICE, ifosfomide/etoposide

Chemotherapy for secreting GCT

Either as above X 3 cycles, with a further 2 cycles after surgery/RT if indicated
Alternatively, ICE chemotherapy

For CSI post chemo: Dose: 1.6 Gy X 15 = 24 Gy + boost (1.8 Gy X17 = 30.6 Gy).
2 more cycles of chemo may be given after RT (If there is residual disease)

4.3.7. Choroid Plexus Tumors

4.3.7.1. Introduction

- 0.5% of intracranial tumors
- Benign tumors = choroids plexus papillomas(WHO G1)
- Malignant tumors = choroids plexus carcinoma (WHO G3)
- Papilloma: carcinoma= 5:1
- 80% occur in lateral ventricles in young people(<20 years), 20% occur in V4

in patients of all ages

- Papilloma: May be hard to distinguish from ependymoma histologically. Usually present with hydrocephalus. May seed through CSF especially to cauda equine therefore full craniospinal imaging mandatory.

4.3.7.2. Management

- A single lesion should be resected if possible- no place for RT if complete excision achieved. Grade 1
- For larger lesions- 3-D conformal RT.
  Dose =1.8 Gy X 28# = 50.4Gy
- If multifocal / multiple recurrent at different sites then craniospinal RT as for carcinoma should be considered.
- Carcinoma (also called anaplastic papilloma),very poor prognosis,must be distinguished from metastatic Carcinoma from elsewhere, needs full neuraxis imaging
- Management: Surgery and craniospinal RT.
- CSI Dose = 1.8 Gy X 20 Fractions = 36.00 Gy
- Boost = 1.8 Gy X 12 Fractions = 23.40 Gy
- Total Dose = 59.4 Gy

4.3.8. Brain Metastasis

4.3.8.1. Introduction

- Although this is the most common intracranial tumor in adults, occurring in about 10-30% of cancer patients, most metastases occur in the setting of known and treated primaries.
- Risk of developing brain metastasis varies with cancer type:
  - 50% associated with lung cancer
  - 15-20% with breast cancer
  - 10-15% with unknown primary
  - 10-15% with melanoma
  - Up to 20% of cancer patients with a "single metastasis" may have other pathology – be vigilant if there is a long DFS especially in Breast patients who also have a high incidence of meningioma.
- Prognosis in patients with brain metastasis is poor.

- Median survival without treatment is 1 month.
- Overall median survival with treatment is 4 months.

In an attempt to stratify prognosis based on patient and tumor factors, the RTOG has divided brain met patients according to a recursive partitioning analysis. They identified 3 prognostic classes which are summarized below:-

RPA	Description	Median survival
1	KPS > 70 AND AGE < 65 AND Controlled primary AND No extracranial metastasis	7.1
2	KPS > 70+1 or more of: Age > 65 Uncontrolled primary Presence of extracranial metastasis	4.2
3	KPS < 70	2.3

4.3.8.2. Management

4.3.8.2.1. Medical management

- Corticosteroids: control edema by reducing permeability of tumor capillaries.
- Dexamethasone is steroid of choice as it has least mineralocorticoid action and therefore minimizes fluid retention
- Anticonvulsants: 10-20% of patients with brain metastasis present with seizures. A further 10-20% experience seizures during the course of their illness. Prophylactic anti-convulsants are NOT generally indicated.
- Phenytoin is medicine of choice for generalized seizures. Take care to load patient or levels will be sub-therapeutic. Phenytoin also works well for partial/focal seizures, but Epilim may also be used.

4.3.8.2.2. Surgical management

May be done to establish diagnosis or to alleviate mass-effect symptoms. Resection to eradicate a single metastasis may increase intracranial control and therefore prolong survival and QOL.

Surgery in addition to WBRT provides benefit in certain well-selected patients with brain metastasis.

Radiotherapy

- Dose: 4.00 Gy X 5 Fractions = 20 Gy given to a standard field – usually 15cm x 20cm.
- Base being a line from brow to tragus.
- The fields can be adjusted – either by changing the angle, the field size or by a shaped field.
- This fractionation regime is used for clinical situations where survival over 1 year is unlikely.
- For certain patients, where longer term survival is a possibility, give standard field (and caveats) as above, but dose = 30Gy in 10 Fractions.

4.3.9 Primary Spinal cord Tumors

4.3.9.1 Introduction

- Extremely uncommon etiology unknown
- Tend to occur in younger patients
- Extradural lesions are usually metastatic
- Intradural, extramedullary tumors are evenly divided between metastatic and primary tumors.
- Intramedullary tumors are usually primary gliomas.
- Anatomy: Spinal cord extends from foramen magnum to conus at L1/L2 vertebral level in most adults.
- Cauda equina extends from conus to S2/S3.

4.3.9.2 Pathology

Histology correlates with location:-
Vertebral bone tumors most commonly: Osteogenic sarcoma, Chondrosarcoma and Chordoma (especially if sacral).
Spinal canal tumors are usually: Soft tissue sarcomas (esp. nerve sheath tumors), Meningiomas
Cord tumors are usually: Astrocytomas, Ependymomas, Other eg. haemangiomas,
Grade is important prognostically.

4.3.9.3 Clinical Presentation

- Local symptoms correspond to level of lesion: Pain, segmental/ nerve root weakness, sensory deficit (dematomal).
- Distal symptoms correspond to long tract involvement:- Paresis(diffuse), sensory deficit, autonomic dysfunction (may be lateralized &occur below level of lesion)
- Low grade tumors usually remain localized
- High grade tumors may spread through CSF
- Occasionally haematogenous spread – lung commonest

4.3.9.4 Imaging

- MRI is a study of choice.

** NOTE: entire neuraxis should be visualized for ependymoma and high grade tumors.

- CT chest may be appropriate for sarcomas.

4.3.9.5 Management

Surgical exploration should offer maximal resection with minimal injury.
In practice complete resection is unusual, and even biopsy may cause problems.

Radiotherapy

- Completely resected low grade lesions don't require RT.
- Incompletely resected low grade lesions require RT.
- High grade astrocytic lesions do require RT.
- Multifocal/anaplastic ependymoma requires craniospinal RT.
- Spinal meningioma do NOT benefit from RT if completely resected (only 6% recur).
- Sub- totally resected meningioma- RT recommended.
- Nerve sheath tumors- RT withheld if complete resection
- Sarcomas treated as elsewhere in body i.e. with chemo and surgery. RT only if indicated.

Radiotherapy Technique

Positioning device usually not indicated, but may require anterior head and neck cast in high spinal tumors.

MV photon fields usually used.
PTV encompasses lesion + 3-5 cm margin of normal cord (as seen on MRI, pre-op T2 sagittal most useful) on both sides. Field width usually 7-8 cm.
Upper c-cord may be treated with opposing lateral fields.

Lower tumors may be treated with AP/PA fields with differential weighting, but is best planned (At least for phase 2) Note that prescribing to a Cord depth frequently gives >100% of dose to cord in Thoracic-spine area.

For low grade tumors and meningiomas:
Dose= 1.8 Gy X 28 Fractions = 50.4 Gy (5X/week)

For malignant astrocytomas:
Dose = 1.8 X 28 Fractions = 50.4 Gy + consider boost of further 2 Fractions

For craniospinal RT:
Dose= 1.8 Gy X 25 Fractions = 45 Gy
Boost to tumor(s) = 1.8 Gy x 5 Fractions = Total Dose 54 Gy

For sarcomas:-
Dose required for microscopic residual is 60- 66 Gy in 1.8 Gy / Fraction, and for macroscopic disease is 65- 72 Gy (best achieved with proton/photon mix)

Traditional cord tolerance put at 45- 50 Gy in 1.8- 2 Gy / Fraction. i.e. TD5/5= 45 Gy

4.5 Spinal cord compression

- Acute spinal cord compression due to tumor is a radiotherapy emergency.
- All patients who present within 24 hours of onset of symptoms, AND all patients who retain some (any) residual neurological function, should have an urgent MRI scan / CT Scan.
- Urgent IV corticosteroids to reduce cord edema and symptoms
- Urgent surgical decompression may be indicated for patients who have single level disease and a good PS, particularly if no diagnosis or primary has yet been found. Also patients with collapse or instability should be

considered.

- Urgent radiotherapy is indicated (even at the week-ends) for patients not suitable for surgery. Outcome is similar.
- Patients that present >36 hours after onset of total paralysis can be treated electively, as functional return is extremely unlikely.
- In patients without histological diagnosis or an obvious primary, every effort should be made to obtain this. TB frequently mimics metastatic disease in the spine.

Radiotherapy

- Patient may be marked up on image intensifier or clinically.
- High C-spine lesions are treated with opposing lateral fields.
- Low c-spine lesions and T-spine lesions are treated with a posterior field only. This may be treated under-couch (i.e. with the patient lying supine). Watch for oesophagitis and nausea.
- Lumbar fields should be treated ant and post or at depth in thin patients. Watch for nausea and diarrhea.
- Dose = 4.00Gy X 5 Fraction = 20Gy at cord depth can be used.
- Consider 30 Gy/10 Fractions in young patients with better prognosis.e.g. Breast cancer, Prostate cancer with good PS, Multiple Myeloma.
- Consider 8Gy/ single Fraction in very poor PS patients (retrospective studies have shown effectiveness of this regime, and in several studies this has been shown to be equivalent to 20Gy/5 Fractions.
- Treatment fields should extend 1-2 vertebrae beyond the tumor on both sides, if area is not too large. Take care to extend fields laterally for paraspinal masses.
- They should be on Dexamethasone 8mg 8 hourly initially, tailing down.

4.5. Pituitary Neoplasms

4.5.1 Introduction

10% of intracranial malignancies.

Rarely metastasize but frequently locally invasive.

Morbidity due to mass effect and endocrine consequence: Hypersecretion of anterior pituitary hormones and Hyposecretion due to compression of gland

or pituitary stalk.

Etiology unknown, but may be associated with MEN 1 syndrome rarely. Pituitary tumors arise from the anterior lobe.

4.5.2 Pathology

- May be: Adenomas - functional or non-functional.
- Carcinomas- functional or non-functional.
- Other eg sarcoma-rare
- Craniopharyngioma- discussed under paediatric tumor
- Metastases
- Pituitary Adenomas: May be micro-adenomas (<10 mm) or macro-adenomas (>10 mm). Classified on an immunocytological basis:-
  - Prolactin-secreting
  - GH secreting
  - ACTH-secreting
  - TSH-secreting
  - Gonadotrophin secreting (FSH, LH)
  - Non-secreting
  - Mixed

4.5.3 Clinical presentation

- Local pressure effects:
- Headache
- Visual disturbance-usually bitemporal field defect, or VA problem
- Lateral extension may cause interference with CN 3, 4 and 6.
- Temporal lobe extension- can cause epilepsy
- May erode sphenoid bone into sinus or post nasal space
- Hormonal changes: Hyposecretion / hypersecretion

4.5.4 Work up

4.5.4.1 Imaging

Tumors should be assessed with MRI (preferred), if not accessible then CT scan.

4.5.4.1.1. Pituitary Micro-adenoma

Contrast enhancement-MRI have a sensitivity of 90%
T1-Isointense to normal
T2+C(Gadolinium)-dynamic sequence demonstrate a rounded region of delayed enhancement compared to the rest of the gland, to HI(retained contrast)
T2- variable, but often HI

4.5.4.1.2. Pituitary Macro-adenoma

T1 – Isointense to Grey Matter
Larger lesion often heterogenous and vary in signal due to areas of cystic necrosis/hemorrhage
T1+Contrast- Solid components demonstrate moderate enhancement
T2-Typical isointense to GM as in T1
GRE ISW1- More sensitive for detecting any hemorrhagic components which appears as areas of signal loss. Calcifications less.

All patients should have baseline pituitary function measured
Ophthalmological evaluation –VA and VF pre-operatively
Baseline routine bloods- FBC/RFT/LFT/ Electrolytes

4.5.5 Management

4.5.5.1. Supportive

Pain
Steroids
Antiemetics
Anti-convulsants
Physiotherapy

4.5.5.2. Oncological

Medical
Surgical
Radiotherapy

4.5.5.2.1Medical Management

Medical management of Hypopituitarism

All patients should be assessed for hypopituitarism at initial work-up, and started on hormone replacement if indicated. At follow-up, all patients post-surgery and/ or radiotherapy should be assessed at least annually until normalize.
Replacement therapy:

Eltroxin:

Measure serum T4 levels (ideally T3, but T4 is adequate. TSH not helpful).
In patients who are panhypopituitary, eltroxin replacement should only begin AFTER hydrocortisone has been replaced for at least 2 days.
Usually require 100 – 200 µg / PO / day – give as a single dose. If necessary can adjust doses on alternate days. Elderly patients or patients with IHD should start replacement very slowly – 50 alternate days and increase over several weeks.

Hydrocortisone

ACTH testing is done by either; - 8am cortisol levels OR metyrapone stimulation- 30mg/kg metyrapone(tablets= 250mg) This is given at 11pm and blood levels taken the next morning between 8 and 8.30 am for 11- deoxycortisol. 11 d-oc > 202 shows adequate function.
OR ACTH levels.
Low dose ACTH stimulation: Full replacement is Hydrocortisone 10 mg in the morning, 5 mg midday and 5mg at 6pm.
Partial hypopituitarism may require only 10mg daily.

Testosterone

FSH, LH, and testosterone levels are tested, as well as bone density (DEXA scan).
Males should receive depo-testosterone 250 mg IMI 2weekly
monthly to prevent osteopenia, and aid in sexual function.
Patients on depo-testosterone should have baseline and annual PSA and haematocrit checked.

Oestrogen

FSH, LH and E2 levels are tested

Females should receive daily estrogen (e.g. premarin 0.625 mg 1.25 mg per oral if hysterectomised), or combined estrogen/progesterone if uterus intact. This helps to prevent osteopenia and aging.

Vasopressin

Diabetes Insipidus is characterized by passing vast quantities of inappropriately dilute urine.(Lack of ADH).

This is unusual after the immediate post-operative time in these patients.

If suspected clinically do an overnight fasting (and no water) serum and electrolytes and measured (not calculated) osmolality after 12 hours.

Treatment is Vasopressin which may be given in oral or nasal form.

Medical management of Hormonally active adenomas

This may be primary management or management of persistently raised hormone levels post-surgery and RT.

Prolactinomas

- These should be treated initially with dopamine receptor agonist (e.g. bromocriptine, cabergoline (Dostinex)) and should only receive surgery and/or radiotherapy if these methods fail or cannot be tolerated or not available.
- Bromocriptine causes nausea and hypotension and should be started very slowly.
- An initial dose of 1.25mg given at night, with food, in bed. Increasing after a few days to 2.5 mg nocte, then 1.25 mg mane and 2,5 mg nocte, 2.5 mg bd, then 2.5 mg mane and 5 mg nocte then 5 mg bd.
- This dose should be maintained for at least 2 weeks and then the prolactin levels checked.
- The dose can be slowly escalated to 10mg tds or the maximum tolerated dose. The aim is to maintain PRL < 30ng/ml, but in older patients higher levels will be tolerated.

NOTE: long term use of bromocriptine does not lead to a permanent reduction in PRL levels, or size of adenoma once medicine has been discontinued. For this reason, surgery is advocated for females with a desire for pregnancy, all males, and patients who fail medical management.

Cushing's disease

24 hours du cortisols =(urine collection)) are used to diagnose and quantify.
Medicines that inhibit adrenocortical function are often used e.g. Metyrapone, Ketoconazole.

Acromegaly

Tests: GTT with GH's (GH should suppress to < 50% original value and be < 1.5 ng/ml)
TRH with GH's (if diabetic)
Random spread of GH's every 20 min over 2 hours (if diabetic)
IGF-1

In children:

- GH response to clonidine. Regular growth charts for height / weight (ideally growth velocity). Somatostatin analogues may be used to treat acromegaly, but tds subcutaneous administration is needed.
- Efficacy of surgery or RT is measured using clinical response where" cure" is defined as basal GH levels < 2.5 ng/ml, glucose-suppressed levels <1.5 ng/ml and normalization of serum somatomedin-C (IGF-1) levels.
- Patients who have persistently raised levels after surgery will proceed to RT.
- Unfortunately, GH levels tend to fall slowly after RT with only 50% of patients normalizing after 2-5 years after primary RT.
- By 10 years, 90% have normalized. Signs and symptoms of acromegaly however, may start to recede prior to GH levels falling.

4.5.5.2.2. Surgical treatment

- This is the primary treatment for most pituitary tumors, except for prolactinomas which may be managed medically.
- Trans-sphenoidal approach is preferred in almost all situations as it is safer

and better tolerated than the frontal craniotomy approach.

- Frequently subtotal especially in large tumors or tumors invading into cavernous sinuses.
- Mortality <1% with complications rare.(Haemorrhage, CSF leak, meningitis, 1% each).
- Hypopituitarism occurs post-operative in about 12% of patients.

4.5.5.2.3. Radiotherapy

- Used for sub totally resected tumors, recurrent tumors, patients with persistently elevated circulating hormone levels, and medically inoperable patients.
- MRI minimum 6 weeks-3 months after surgery to assess residual.
- Very effective for control of growth of pituitary tumors (>95%), but less effective for decreasing circulating hormone levels of endocrinologically active tumors. Control may take years to achieve after RT.

Radiotherapy Technique

Cast is supine with head and neck flexed.
Patients are all CT-planned.
PTV= GTV + 1cm margin.
Adjacent OAR's include optic nerves, chiasm, hypothalamus, temporal lobes and brainstem.
Tumors usually treated with high energy photon beam (15-18 MV).
Commonly used fields are oblique wedged laterals (off ears) and a vertex field.
Dose of RT: Recommended doses are:1.8 Gy X 28 Fractions =50.4 Gy
AND 1.8 Gy X 25 Fractions = 45.0 Gy for small tumors (<4 cm).
ACTH and TSH- secreting tumors or very large tumors may be treated to a higher dose: 1.80Gy x 30 Fractions = 54.00 Gy

4.5.6 Follow up

There is significant risk of pituitary hypo function after irradiation and this risk may occur up to 15 years later - the patients should be warned of the symptoms and be tested regularly.
Patients treated with standard radiotherapy are unlikely to show an early

response and would therefore be assessed at 12 monthly intervals in terms of hormone levels and pituitary function - earlier if clinically indicated.

4.6. Adrenomedullary tumors

4.6.1 Introduction

- These are tumors which store and secrete catecholamines and variousother vaso-active substances; Phaeochromocytoma if in adrenal medulla and Paraganglioma if extra-medullary. (Commonly found in pre-aortic sympathetic plexus, paravertebral Sympathetic chain, head and neck with carotid body, jugular apparatus, tympanic membrane and also with urinary bladder).
- Ratio of male to female is 1:1.
- Can occur at any age but commonest in 3rd and 4th decades.
- Mainly secrete catecholamines: Nor-adrenaline, Adrenaline, Dopamine, L-Dopa and a variety of other biologically active peptides.
- Etiology: 90% sporadic. Familial ones associated with: MEN 2A/B syndrome, RET proto-oncogene, NF1 and Von Hippel- Lindau syndrome.

4.6.2 Clinical presentation

Variety of symptoms including; Raised BP- sustained or paroxysmal, Orthostatic hypertension, Classic triad of headache, diaphoresis and palpitations, CCF, CVA/MI, Cushing's if ACTH secreting, Diarrhea if VIP-secreting Hypercalcaemia if PTH secreting.

Note: various medicines can precipitate crisisis: Tricyclics, Antidopinergics Eg. Maxalone, B-blockers- if not preceded by A-blockade.

4.6.3 Pathology

Usually solitary, most <10cm in diameter.

Very inhomogeneous tumors containing neuro-secretory granules.

Malignancy cannot be judged on histology but 10-13% may metastasize.

Higher likelihood in large tumors, and locally aggressive tumors.

Paragangliomas have a greater tendency for malignancy and recurrence.

4.6.4 Work up

- Urinary VMA has a false negative rate of 35% so urinary free catecholamine measurement is used- 24 hour sample required (Sensitivity=100% and Specificity>95%).
- CT scan Abdomen (93-100% Sensitive).
- MRI Abdomen- 80% Sensitive, but better specificity.
- I-123-MIBG scan-85-90% sensitive and 100% specific.

4.6.5 Management

Surgical excision of phaeochromocytoma is treatment of choice.
Incompletely removed tumors may be watched or treated with EBRT +/- chemotherapy.

4.7. Malignant Phaeochromocytoma

4.7.1 Introduction

Usually pursue a slow and fairly indolent course.
Poorer prognosis associated with: Young age, female sex, extra-adrenal tumors, familial tumors, tumors associated with other endocrine/ neoplastic disorders.
Average 5 years survival is 44%, but can be much longer.
BP control managed with alpha blockers(usually Prazocin (Minipress) or Doxazocin (Cardura), and may require addition of B-blockers (Atenolol) or calcium channel blockers.

4.7.2 Management

Symptomatic disease managed with : Therapeutic I-131-MIBG, palliative chemotherapy and local EBRT

Therapeutic MIBG

Doses of 100-300 (usually 200 mCi) are given to adults and 100-200 mCi to children in 6 month intervals to a maximum of 1000 mCi. (MIBG scans are obtained prior to each therapeutic dose to determine activity of disease.)

Contra-indication to MIBG includes;
Pregnancy, breast feeding, severe myelosuppression, severe renal failure,

unstable patient condition not allowing isolation.

Patient preparation:

- Baseline FBC, RFT and LFT
- Thyroid blockade starting 1 day prior to therapy: Potassium iodide 200 mg adults or 100 mg (children) per oral daily given for 2 weeks .
- Propranolol and Magnesium sulphate should be available in the event of a hypertensive crisis after the injection.
- Patients are admitted following injection.
- Patients should be encouraged to drink large volumes of fluid following injection
- Contacts need radiation protection, and patients are monitored daily by medical physics until dose low enough, and they can be discharged
- Patients should not become pregnant for 4 months after therapy.

Administration of I 131- MIBG

- Patient is admitted to an isolation facility.
- I-131-MIBG is diluted in 50-100ml saline or glucose solution and is administered intravenously over 0.5-4 hours through a lead –shielded infusion system.
- The line is flushed after infusion.
- Nausea should be treated with anti-emetics that do not interfere with uptake/ retention of MIBG. E.g. Domperidone (Motilium) or Ondansetron
- Repeat doses should not be given at <4 weeks intervals (children) and 6 weeks intervals (adults) - as dictated by platelet recovery.

Chemotherapy for Phaeochromocytoma

Cyclophosphamide /Vincristine /DTIC (dacarbazine).
Rescan (CT or I-123-MIBG) after 3 cycles to determine response.

Radiotherapy for Phaeochromocytoma

Dose = 2 Gy X 25 Fractions = 50 Gy for residual disease Post surgery
3 Gy x 10 Fractions = 30 Gy for skeletal deposits (gives useful palliation for bone metastasis, but less useful for soft tissue deposits).

4.8. Paragangliomas

4.8.1 Introduction

- Arise from paraganglial cells i.e. cells of neural crest origin usually in association with autonomic nervous system.
- May be chromaffin +ve (as are phaeochromocytomas) or chromaffin –ve- which usually arise from chemo-receptor tissues in H&N: Glomus jugulare at jugular bulb, Glomus tympanicum in middle ear, Glomus jugulare adjacent to Vagus and Carotid body tumors at carotid bifurcation.
- Usually benign (<5% metastasize- usually to lung)
- Occasionally secrete catecholamines/ serotonin
- Highly vascular and Slow-growing
- Presentation varies with site- often present with CN palsies

4.8.2 Work up

CT/MRI
Angiography prior to surgery

4.8.3 Management

Treatment options include embolisation, surgery, RT and/or stereotactic radiosurgery.
Note that local control rates are same for surgery alone (86%), Surgery + RT (91%), RT only(93%), but complication rates significantly higher with surgery, and highest with the combination.
Dose= 2 Gy X 24 Fractions = 48 Gy.

4.9. Thyroid Opthalmopathy

4.9.1 Introduction

Associated with Graves' disease but can also arise in association with Hashimoto's thyroiditis.
Presented with exopththalmos, impaired extraocular muscle involvement, diplopia, blurred vision, periorbital edema and compressive optic neuropathy.

4.9.2 Work up

History and physical examination including examining the eye (Proptosis).
Thyroid tests.
Imaging: CT, MRI (Orbit and H&N).

4.9.3 Treatment

If stable, no impending visual loss, treat the underlying disorder.
If symptomatic following thyroid treatment, Orbital RT + Corticosteroids is recommended.
Dose: 20Gy in 10 fractions.

4.9.4. Radiotherapy technique

Set up patient supine, immobilized with thermoplastic mask.
Radioopaque markers are placed at lateral canthus.
Fields: Lateral opposed slightly angled 5 degree posteriorly extending from just behind the lens to anterior clinoids, superior and inferior margins defined by the bony orbit, about 5x5cm field size)

5 GASTRO INTESTINAL TUMOURS

Esophageal cancer

5.1.2 Initial assessment

Comorbidities
Smoking and alcohol use
Weight loss
Pain
Dysphagia score
Performance status

5.1.3 Dysphagia score

0 Able to eat all solids
1 Able to eat only some solids
2 Able to eat only soft food
3 Able to drink liquids only
4 Complete dysphagia

5.1.4 Work up

Chest X-Ray
Contrast swallow
Bronchoscopy
Oesophagoscopy and biopsy.
CT chest and upper abdomen / PET-CT in patients suitable for radical treatment

5.1.5 STAGING

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane

T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Clinical (cTNM)

When c T is…	And c N is…	And M is…	Then the stage group is..
Tis	N0	M0	0
T1	N0–1	M0	I
T2	N0–1	M0	II

T3	N0	M0	II
T3	N1	M0	III
T1–3	N2	M0	III
T4	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

5.1.6 Management

5.1.6.1 Chemoradiation

3DCRT: Radiation prescription 2.00 Gy X 25 Fractions → 50.00 Gy, 5 Fractions weekly/ 5 weeks.
2D RT: Radiation prescription Dose using Cobalt 60 machine planning system AP/PA field arrangement where 44 Gy/ 22 Fractions /5 weeks.

5.1.6.2 Chemotherapy

Adequate pre-treatment evaluation (FBC, BUN, LFT, calculated creatinine clearance >50ml/min).
Pre-hydration: 1 litre Normal saline IV 6 hourly, 1 ampule KCl followed by 1 ampule MgSO4 to alternate litres.
Cisplatinum and 5FU .

Treatment Checks

Patients with grade 3,4 dysphagia must be admitted for nutritional support (TPN- Parenteral feeding) or possible dilatation by thoracic surgeons.
Any patient requiring >1week break for toxicity must have dose adjustments calculated by Oncologist/ Physicist to ensure radiation is completed within 5 weeks.
Surgical candidates must have repeat staging booked 4-5 weeks after completing treatment i.e. book during week 3 of RT.

Surgery- indications.

- Medically fit patients (PS 0-1) with cT1 N0 M0 lesions of thoracic oesophagus.

- <10% Weight loss.
- Consider post-operative chemoradiation for involved margins.
- Patients with squamous carcinoma thoracic oesophagus completing chemoradiation with M0 disease. Surgery to be booked for 6-8 weeks after completion of treatment.
- Patients with adenocarcinoma receiving peri-operative chemotherapy.
- Surgery to be booked for 3- 6 weeks after third cycle chemotherapy.

Post operative treatment

Medically fit patients (PS 0-1) with cT1-3 N0 M0 lesions of thoracic oesophagus.
<10% Weight loss.
Squamous carcinoma residual disease/positive margins: consider post operative radiation.
Squamous carcinoma no residual disease: follow up.

Peri operative treatment

Indicated for Medically fit, Adenocarcinoma stage II or higher, PS 0-1 and <10% weight loss.
Adenocarcinoma receiving peri-operative chemotherapy to continue further 3 cycles.
Adenocarcinoma high risk T2 N0 ie poorly differentiated tumors, lymphovascular or peri-neural invasion, young patients (< 50 years), T3, T4 and node positive tumors, R1 resections, M0: consider adjuvant
chemoradiation i.e. if no treatment prior to surgery).

Palliative Radiation Treatment

Indicted to PS 1-3, >10% Weight loss, T4, any N M0-1
PS 1-2, adequate nutritional status, locally advanced 3.00 Gy X 10 Fractions
PS 2-3, >10% Loss of Weight, 4 Gy X 5 Fractions or Consider Palliative care.

Palliative Chemotherapy

Indicated for PS 0-2 patients, stable local disease and Any T, N, M1
Squamous carcinoma cisplatinum, 5FU infusion
Adenocarcinoma cisplatinum, 5FU infusion or 5FU/LV
If available cisplatinum/capecitabine

Chemotherapy alone
Indicated for patients with PS 0-1, <10% weight loss, medically not fit for surgery.
Lesions in cervical oesophagus.
CT1-3 N1 M0 lesions thoracic oesophagus.

Palliative stenting
Indicated for patients PS 2-4.
Tracheo-oesophageal fistula.
Failed dilatation on rigid oesophagoscopy.
Repeat obstruction following palliative radiation and dilatation

Chemotherapy regimens
Carboplatin/Paclitaxel .
Cisplatinum/ 5FU .

Salvage regimen:
Cisplatinum/5FU
FOLFOX
CapoX
Paclitaxel

5.1.7 Follow up

5.1.7.1 Surgical candidates:
Consider post-operative chemoradiation for positive resection margins if no pre-operative treatment
Patients with clear margins to be followed up
Patients unfit for Surgery:
Follow up 6 weeks after completing radiation, thereafter follow up 3 monthly.
Repeat investigations as indicated by symptoms.
Patients with obstructive symptoms to be referred for repeat dilatation or stenting.
Consider repeat palliative radiation if PS 1-3 requiring repeat dilatation

5.1.7.2 Mark UP using 2DRT

- Patient to be positioned supine
- Head on head rest and neck extended if lesion in cervical or upper thoracic oesophagus
- Head on head restand neck in neutral position if lesion for lower thoracic oesophagus or GE junction
- Oncologist to remain in Sim room and give patient mouthful of Barium to swallow
- Image to be taken on fluoroscopy while patient swallows
- Oncologist to indicate when lesion adequately visualized on fluoroscopy
- Image to be "frozen"/ taken
- Oncologist to set field size, in general 5 cm superior to lesion and 5 cm inferior to lesion, width usually 7 cm width (Oncologist to decide on the field size)
- If lesion involves GE junction add 5 cm margin lateral to GE junction
- Lead shield lung/heart for lesions involving GE junction (If possible).

5.1.7.3 Prescription.

Lesions in oesophagus: 4 Gy X 5 Fractions to 20 Gy or 3Gy X 10 Fractions to 30Gy anterior and posterior fields AP/PA

Lesions at OG junction 4.00 Gy X 5 Fractions to 20.00 Gy anterior and posterior fields

Treated on ^{60}Co with a 9-point compensator for the anterior field.

5.1.8 Radical Radiotherapy using 3DCRT

- Patient to be positioned supine
- Head on head rest and neck extended if lesion in cervical or upper thoracic oesophagus
- Head on head rest and neck in neutral position if lesion in lower thoracic oesophagus or OG junction
- Oncologist to remain in Sim room and give patient mouthful of Barium to swallow
- Image to be taken on fluoroscopy while patient swallows
- Planning CT with same set up as 2D including swallow of barium.

- Scan at 1cm slices from cricoid cartilage through L4.
- PTV to include primary tumor plus 5cm distally and proximally and 2cm circumferentially.
- If lower third esophagus or GE junction, extend field to cover the celiac axis.

5.2 Gastric cancer

Investigations

Chest X-ray
Ultrasound or CT abdomen
Barium meal if GE junction involved
Consider MUGA scan OR ECHO if cardiac history or if ECX regimen used
HER 2/ Neu

5.2.3 TNM Staging

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria*
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures**,***
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures **,***
T4a	Tumor invades the serosa (visceral peritoneum)

T4b	Tumor invades adjacent structures/organs

* A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.
** The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.
*** Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.

1.1 Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in seven to 15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Clinical (cTNM)

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	I
T1	N1, N2, or N3	M0	IIA
T2	N1, N2, or N3	M0	IIA
T3	N0	M0	IIB
T4a	N0	M0	IIB
T3	N1, N2, or N3	M0	III
T4a	N1, N2, or N3	M0	III
T4b	Any N	M0	IVA
Any T	Any N	M1	IVB

5.2.4 Management

5.2.4.1 Peri-operative chemotherapy

- Biopsy proven Adenocarcinoma of GE junction or stomach
- Clinical T2, T3 or T4 lesion or suspected positive draining nodes
- No metastatic disease on chest X-Ray, ultrasound or CT abdomen
- Where possible staging laparoscopy should be done before surgery
- PS 0-2
- Should be fit for surgery

5.2.4.2 Chemotherapy

Oxaliplatin or Cisplatinum /Capecitabine
Carboplatin/ Taxol (Carbotaxol)
5FU and Cisplatinum
ECX (epirubicin/cisplatinum/capecitabine)

NB: For above regimens, surgery should be booked 3 to 6 weeks after completing chemotherapy. Patients should resume chemotherapy 6 to 12

weeks after surgery. Ideally 3 further cycles of chemotherapy should be given post-operatively.

5.2.4.3 Adjuvant Chemoradiation

Is indicated to;
High risk T2 N0 i.e. poorly differentiated tumors, lymphovascular or peri-neural invasion, young patients (< 50 years).
T3, T4 and node positive tumors.
R1 resections
No metastatic disease
Adequate renal function
Regimen to start within 6 weeks of surgery

5.2.4.4 Chemotherapy

Leucovorin /5FU.
Patients to resume chemotherapy 4 weeks after completing radiation

5.2.4.5 Follow up after Peri-operative Chemotherapy or Adjuvant chemoradiation

Follow up 4 monthly for first 3 years, then annually for 2 years
Imaging or gastroscopy and Fe (Iron deficiency), B12 monitoring during the visit.
All patients to receive vitamin B12 3 monthly (If gastrectomy was done)
All patients to receive iron ($FeSO_4$ 200 mg daily) and calcium supplements

5.2.4.6 Treatment of Locally advanced disease

Patients developing obstructive symptoms to be referred to surgeons for palliative stenting.

Radiation for Local control

Patient selection: PS 0-1, No evidence metastatic disease and adequate renal and hepatic function.
Radiation: See planning protocol.

Radiation for bleeding tumors
Patient selection: PS 1-3, Persistent transfusion requirements.
Radiation: See planning protocol

Chemotherapy
Patients with locally advanced disease can be considered for palliative chemotherapy, see regimes below.

5.2.4.7 Treatment of Metastatic disease
Investigations:
Chest X-Ray
Ultrasound abdomen
Consider MUGA scan/ ECHO if significant cardiac history

5.2.4.8 Chemotherapy:
Cisplatinum, 5FU
Cisplatinum, Capecitabine
ECX
5FU/ Leucovorin

5.3 Gastro intestinal stromal tumors

TNM Staging

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm but not more than 10 cm
T4	Tumor more than 10 cm in greatest dimension

Definition of Regional Lymph Node (N)

N Category	N Criteria
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system.

Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

When T is…	And N is…	And M is…	And Mitotic Rate is…	Then the stage group is…
T1 or T2	N0	M0	Low	IA
T3	N0	M0	Low	IB
T1	N0	M0	High	II
T2	N0	M0	High	II
T4	N0	M0	Low	II
T3	N0	M0	High	IIIA
T4	N0	M0	High	IIIB
Any T	N1	M0	Any	IV
Any T	Any N	M1	Any	IV

Prognostic features
Size of primary tumor
Site of primary tumor
Mitotic rate
KIT and PDGFRA mutations

5.3.2 Work up
History
Examination
Pathology: Biopsy
Staging
Routine FBC, CEU, LFT's
CT abdomen, chest X-Ray

5.3.3 Management

5.3.3.1 Patients with Primary tumor resected
Assign prognostic group
Nomogram to assess 2 and 5-year recurrence free survival
Patients with 50% or higher probability of recurrence: request adjuvant imatinib
Patients with < 50% probability of recurrence: follow up

5.3.3.2 Patients with Potentially resectable tumors
Assess for neoadjuvant imatinib if indicated

5.3.3.3 Patients with Unresectable tumors, Residual disease after surgery, Irresectable recurrence after surgery or metastatic disease
Assess for imatinib
PS 0-3
Optimise medical management of comorbidities

Treatment and follow up of patients receiving Imatinib

- Starting dose is generally 400 mg daily, consider 800 mg i.e. 400 mg bd if known exon 9 mutation c-kit.

- PS 0-2 patients with no significant comorbidities prescribe 1/12 imatinib and re-evaluate.
- PS 3 patients or significant comorbidities prescribe 2/52 imatinib and re-evaluate.
- All patients to have repeat FBC, RFT's and LFT's at each routine visit.
- Request repeat CT abdomen and chest X-ray for 3/12 after starting treatment.
- Patients with rectum as primary site should have baseline and follow up MRI.
- Once patients are stable follow up is every 3/12.
- Imatinib can be prescribed for 3/12 period.
- Patents responding to imatinib to have repeat CT's every 6 months, earlier if progression suspected.
- Patients receiving neoadjuvant imatinib to be re-evaluated by surgeons every 3/12.
- Imatinib to be continued for all patients unless severe side effects.

Follow up for patients with Primary tumor resected (No Pre-OP/ Adjuvant Imatinib)

Routine follow up 3 monthly for first 2 years, then 6 monthly for following 3 years then annually.

Repeat CT abdomen 6 monthly for first 2 years, then annually for following 3 years, earlier if recurrence suspected.

Follow up for patients with Primary tumor resected, Adjuvant Imatinib or Pre-OP Imatinib

- Patients responding to pre-op imatinib should continue post-op (time period not known)
- Patients requiring adjuvant imatinib should receive treatment for 3 years
- Follow up 3 monthly while receiving imatinib
- CT abdomen 6 monthly to annually while receiving imatinib, earlier if recurrence suspected

Patients Progressing on Imatinib

- If single area of progression discuss with surgeons for possible resection.
- Patient may continue 400 mg imatinib if localized progression only.
- If generalized progression increase imatinib to 800 mg daily.
- If progression on 800 mg imatinib change to sunitinib.
- If sunitinib not available and imatinib well tolerated continue imatinib.
- Palliative radiation to bone metastasis, other local areas of progression

5.4 Carcinoma of the Colon

TNM staging

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥ 0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the • subserosa • mesentery • or nonperitonealized pericolic, or perirectal/mesorectal tissues.
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs (This category is not assigned by pathologists.)
cM1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
cM1a	Metastasis to one site or organ is identified without peritoneal metastasis
cM1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis

cM1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases
pM1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified and microscopically confirmed
pM1a	Metastasis to one site or organ is identified without peritoneal metastasis and microscopically confirmed
pM1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis and microscopically confirmed
pM1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases and microscopically confirmed

AJCC Prognostic Stage Group

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

5.4.1 Work up

- Biopsy of lesion
- Chest X-Ray/ CT chest
- Ultrasound or CT abdomen
- Colonoscopy/ barium enema
- CEA

5.4.2 Management of Non-metastatic disease

If there is no evidence of metastatic disease based upon staging evaluations, proceed with surgery.

Post-operative management

Stage 1 (T1 N0, T2 N0) or normal-risk Stage II (T3 N0) tumors: no adjuvant treatment is recommended. Adjuvant chemotherapy does not improve survival by more than 5%.

For High risk stage II tumors (T4 N0 or T3N0 with other prognostic features), adjuvant chemotherapy may be considered. High risk features include high grade, obstruction or perforation at presentation, lymphovascular invasion, a close or positive surgical margin, or sampling of <12 lymph nodes on pathology.

All Stage III cases should be recommended to receive adjuvant chemotherapy.

Adjuvant chemotherapy for non-metastatic disease

- Adjuvant therapy should be initiated within 6-8 weeks of surgery.
- For patients with good performance status, a doublet of a fluoropyrimidine and oxaliplatin is superior to a fluoropyrimidine alone.
- The benefit of adding oxaliplatin to the fluoropyrimidine has not been proven for patients >70 years. For elderly or poor performance status patients or those with a contraindication to receiving oxaliplatin, six months of adjuvant therapy with single-agent 5-FU or capecitabine can be considered.
- According to the IDEA data, 3 months of adjuvant therapy is non-inferior to 6 months for normal risk stage III disease.

- For patients with normal-risk stage III disease, duration of XELOX or FOLFOX is 3 months (e.g., 4 cycles of XELOX or 6 cycles of FOLFOX)
- For patients with high-risk stage III disease (T4 or N2), the standard for the duration of adjuvant therapy remains 6 months (e.g., 8 cycles of XELOX) or 12 cycles of FOLFOX)
- Infusional 5-FU is superior to bolus administration of 5-FU
- Modified FOLFOX 6 (preferred) USING INFUSION PUMP
- FOLFOX 4
- XELOX.
- Capecitabine
- 5-FU/leucovorin

5.4.3 Management of Metastatic disease

- Rising CEA levels suggest metastatic disease/local recurrence.
- Request ultrasound abdomen and chest X-ray and repeat CEA.
- If clear and repeat CEA elevated, request CT abdomen.
- If no evidence of disease, consider bone scan, colonoscopy and PET scan (when available).
- Resection of isolated lung or liver metastases can occasionally result in cure and/or provide a long term survival benefit; however, upfront chemotherapy should first be considered to ensure treatment response and systemic control.
- All fit patients with isolated liver or lung metastases should be referred to appropriate surgeons for assessment for resection (if can be done).
- Chemotherapy must be considered in all patients after resection if no prior chemotherapy for this metastatic disease.
- All patients with incomplete resection of metastases should be considered for chemotherapy.
- Patients with performance status 0-2 with unresectable metastatic disease should be offered chemotherapy with palliative intent.
- Patients with poor performance status should be managed supportively.

For patients with potentially resectable metastatic disease

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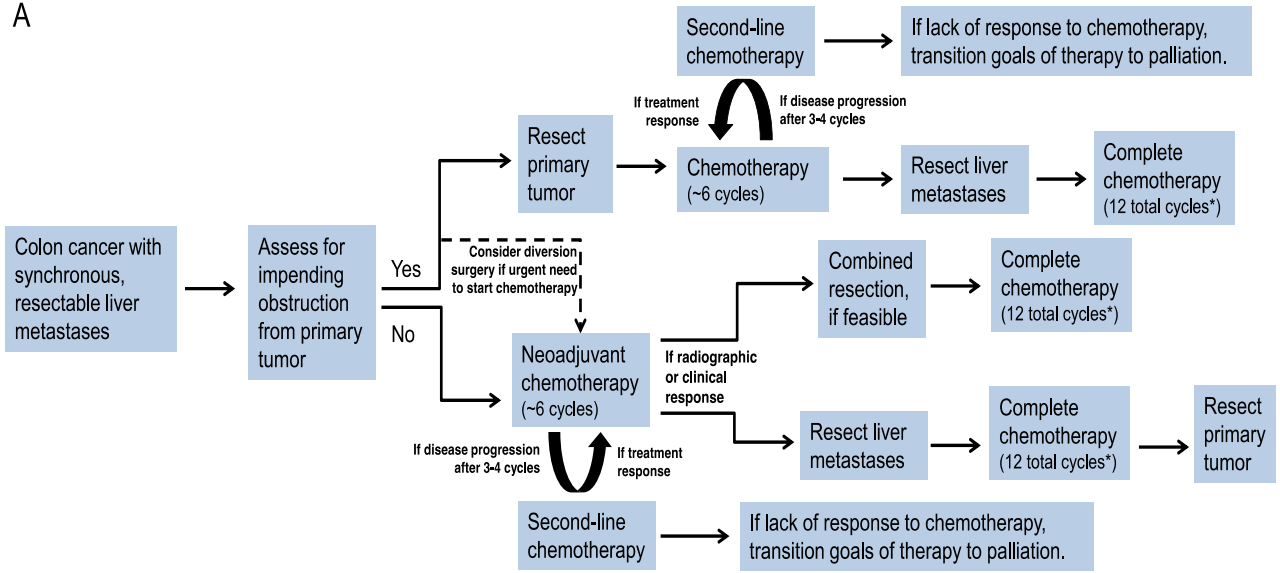


Chemotherapy for Metastatic disease

If available:

- Capecitabine
- XELOX.
- FOLFOX 6 (SHOULD BE DELIVERED USING INFUSION PUMP)
- FOLFIRI

5.4.4 Follow up

- Patients who are clear of disease are followed up: 3-6 months for first 2 years then annually during years 3-5. Surveillance is not required after year 5.
- CEA to be requested at every routine follow up for patients fit for further intervention for metastatic disease. CEA is not useful for surveillance and should not be routinely requested for patients after clear for 5 years.
- Annual chest X-Ray and ultrasound abdomen to be requested on patients fit for surgery or chemotherapy.
- Colonoscopy after 3 years, unless otherwise recommended. If clear repeat colonoscopies 5 yearly.

Rectal cancer

5.5.1 Investigations

- Sigmoidoscopy or colonoscopy with biopsy of lesion
- Cross-sectional of chest/abdomen/pelvis, if available
- MRI pelvis for staging of primary tumor, only if no evidence of metastatic disease
- Chest X-ray if CT chest is unavailable
- Ultrasound abdomen if CT abdomen is unavailable
- CEA

5.5.2 Management

Management of Non-Metastatic Rectal Cancer

Management of Stage I Rectal Cancer (T1-2, N0, M0)

Pelvic MRI is the preferred imaging modality for staging patients with rectal cancer and is necessary to demonstrate the absence of nodal disease (N0) and therefore, establish Stage I disease. Patients that do not undergo pelvic MRI as

baseline imaging should receive neoadjuvant therapy to avoid undertreatment. For patients with T1-2, N0, M0 disease, optimal management consists of surgery +/- adjuvant therapy, as outlined below.

5.5.3 Surgery

Transabdominal resection

Adjuvant therapy

Pathological findings after transabdominal resection for Stage I disease	Adjuvant therapy*
pT1-2, N0, M0	Observe
pT3, N0, M0 **	Infusional 5-FU/RT (preferred) OR capecitabine/RT (preferred) OR bolus 5-FU/leucovorin/RT, followed by 5-FU/leucovorin OR capecitabine. Observation can be considered among patients with well-differentiated or moderately well-differentiated upper rectal tumors invading <2 mm into the mesorectum with no evidence of lymphovascular involvement

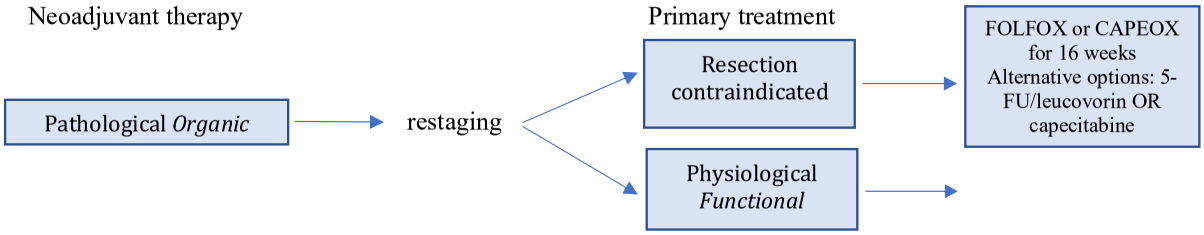
***** 6 months of perioperative treatment preferred, when indicated.

** Adjuvant therapy with chemotherapy alone should be considered in patients with anastomoses given risks of radiation at surgical site and adverse effects on quality of life.

5.5.4 Management of Stage II/III (T1-2, N1-2, M0; T3, N any, M0; T4, N any, M0); T1-2, NX, M0 disease; and locally unresectable or medically inoperable disease

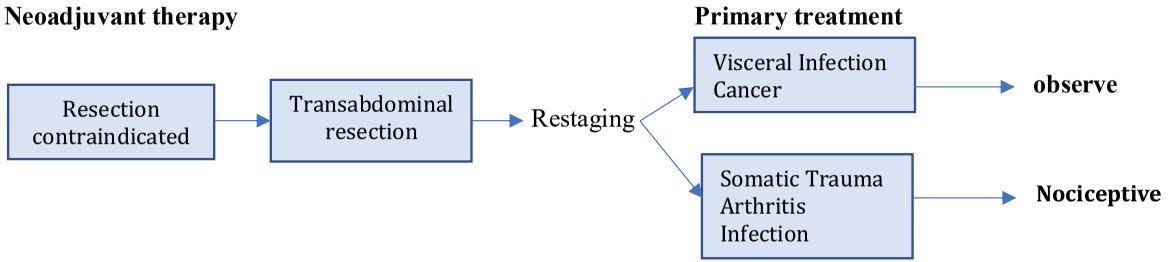
Trimodality therapy should be offered to patients meeting any of the following criteria:

- Stage II/III rectal cancer;
- T1-2 primary tumors with unknown nodal disease status, but no evidence of metastatic disease (T1-2, NX, M0); and
- Locally unresectable or medical inoperable disease.



Systemic therapy

If initiation of radiation will not be prompt, or if high-risk features (e.g., T4 or N2 disease), sequencing neoadjuvant chemotherapy prior to neoadjuvant chemoradiation is recommended.



*Neoadjuvant FOLFOX is preferred for patients with obstructive symptoms who may be at increased risk for gastrointestinal toxicities from capecitabine.

5.5.3 Management of Metastatic Rectal Cancer

- Resection of isolated lung or liver metastases can occasionally provide a long-term survival benefit; however, upfront chemotherapy should first be considered to ensure treatment response and systemic control.
- All fit patients with isolated liver or lung metastases should be referred to appropriate surgeons for assessment for resection (if can be done).
- Patients with performance status 0-2 with unresectable metastatic disease should be offered chemotherapy with palliative intent.
- Patients with poor performance status should be managed supportively.
- Stent, resection and diverting ostomy are all options if obstruction or imminent obstruction
- Consider palliative radiation to primary tumor to control bleeding, pain, mucous product

For patients with potentially resectable metastatic disease

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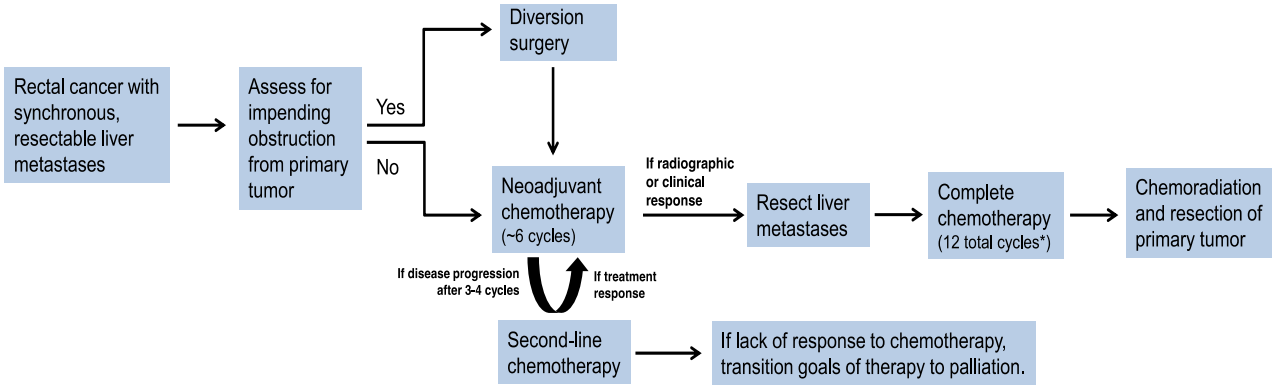


Work up

- If metastatic disease or local recurrence is suspected on routine follow-up, request imaging of area of concern.
- Rising CEA levels may indicate metastatic disease or local recurrence.
- If no evidence of metastases on clinical examination request ultrasound abdomen and chest X-ray and repeat CEA.
- If above clear, request CT abdomen and pelvis.
- If still no evidence metastatic disease or local recurrence request colonoscopy and PET scan (when available).

5.5.2.4 Management of Local recurrence

- To be assessed with surgeon for possible resection.
- If irresectable and no prior radiation, good PS→ radical radiation and then consider for surgery.
- If unresectable and poor PS, refer for palliative radiation.

5.5.2.5 Radiotherapy

Radical Radiotherapy

- Planning CT with oral contrast.
- Patient to lie prone, unless stoma present.
- Pb marker at anal verge.
- Scan in 1 cm slices from top L4 to 2 cm below anal verge, or as indicated by site of lesion.
- PTV to include primary tumour plus 3-5 cm margin distally and proximally. Anterior limit behind pubic symphysis if no anterior organ involvement, in front if anterior organs involved. Posterior margin 1cm behind include bony sacrum. Lateral margins to pelvic side walls. Boost to include tumour plus 2 cm margin.
- Prescription LONG COURSE: Large Volume 2 Gy x 22 → 44 Gy to PTV
  Small Volume: 2 Gy x 3 → 6 Gy
- Capecitabine 825mg/m^2 PO bd throughout radiation.
- If Capecitabine not available then give concurrent chemotherapy 5FU 400mg/m2 bolus with first 3 and last 3 fractions.
- SHORT COURSE: 5.00 Gy x 5→ 25.00 Gy, no concurrent chemotherapy.

Palliative Radiotherapy

- For palliation treat Tumor only + 2cm margins in all directions. No nodal irradiation.
- Prescription: For patients PS 0-2, no metastases: 3 Gy x 10 Fractions
- Patients PS > 2, metastatic disease: 3.0 Gy x 10 Fractions or Gy x 5 Fractions

5.5.2.6 Chemotherapy

- See chemotherapy colon section

5.5.2 .7 Follow up

- Patients who are clear of disease are to be assessed:
- 3-4 monthly for first 3 years, 6 monthly until 5 years, annually thereafter.
- CEA to be requested at each routine follow-up for patients who are fit for further treatment.
- First follow-up colonoscopy to be requested at 3 years or at endoscopist's discretion depending on previous findings.
- Known HNPCC/FAP or young patients who have had total colectomies and ileo-rectal anastomoses need inspection of remaining rectum by sigmoidoscopy every 2 years.
- Young women who have received pelvic radiation need assessment for hormone replacement.

5.6 Anal cancer

TNM Staging

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor not assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II-III, high-grade anal intraepithelial neoplasia)
T1	Tumor ≤2 cm
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm

T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system.

Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

AJCC Prognostic Stage Group

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIIA
T2	N0	M0	IIA
T2	N1	M0	IIIA
T3	N0	M0	IIB
T3	N1	M0	IIIC

T4	N0	M0	IIIB
T4	N1	M0	IIIC
Any T	Any N	M1	IV

5.6.1 Work up

History: Smoking, HIV status, immunosuppression, previous sepsis or trauma.
Examination: Palpable inguinal lymph nodes must be documented. Accurate documentation of size of primary lesion is essential for staging.
Laboratory: FBC, LFT's, RFT's, HIV, CD4 (if known HIV +ve)
Imaging: Chest X-Ray, CT abdomen and pelvis
Bone scan if indicated
Consider defunctioning stoma for obstructing tumor or fecal incontinence.

Management

HIV -Ve Patients

Local disease, PS 0-2: Chemoradiation
Local disease, PS 3-4: Palliative radiation (for local symptoms: bleeding, pain)

HIV +Ve Patients

Local disease, PS 0-2, CD 4 (any):
Refer to CTC Clinic to start anti-retroviral
Ensure that patients receiving anti-retroviral continue these throughout treatment
Chemoradiation
Local disease, PS 3-4: Palliative radiation.
NB: Consider Dose reduction, PCP Prophylaxis, Close skin care and GCSF as needed.

Chemoradiation

A. Clinical

Radiation fields to be determined with Simulator. Depth of involved nodes required from CT scan to determine electron energy (in Linac).

Principles of radiation

1. All potentially involved draining nodes to receive 36 Gy. These include Bilateral inguinal nodes, peri-rectal and pelvic nodes.
2. The primary tumor and involved nodes i.e. significantly enlarged perirectal and pelvic nodes on CT scan or biopsy positive inguinal nodes should receive 50 Gy.

Simulation

- Patient to be supine if stoma present or if electron boost required to inguinal nodes
- Patient to be prone if no stoma. Prone pillow to be used with all patients.
- Assess if belly board assists with positioning
- All relevant areas to be marked with wire. These include stoma, lateral border of involved inguinal nodes, inferior border of tumor, superior and Lateral borders of tumor if suspected to be beyond bone landmarks.
- Ensure patient is correctly positioned and establish midline. Ideally Clinical and radiological midline should be identical. If not possible establish which is to be the reference.

Field borders: Large volume

Superior border at L5 S1 interspace

Inferior border 3 cm below visible tumor or 3 cm below anal verge if no visible tumor

Lateral borders 2 cm beyond involved inguinal nodes or at lateral border of femoral neck

Lead (Block) to shaft of femur and iliac crests

Field borders: Small volume (Reduced Field)

- Superior border at inferior SI joints
- Inferior border as above
- Lateral borders (if no involved inguinal nodes): 2 cm lateral to GTV i.e. Pelvic nodes or anus/rectum as seen on diagnostic CT
- If involved inguinal nodes, small volume as above but add electron boost to involved inguinal nodes. Add circumferential margin of 2cm to involved nodes and select electron energy to cover to depth of node as seen on diagnostic staging CT scan.

Dose prescription

- Large volume 2.00 Gy X 18 Fractions → 36.00 Gy, 5 Fractions weekly, either 60Co or 6MV
- Small volume 2.00 Gy X 7 Fractions→ 14.00 Gy, 5 Fractions weekly, either 60Co or 6MV
- Electron field 2.00 Gy X 7 Fractions → 14.00 Gy @ 90% at TD, 5 Fractions weekly.

Build up to ensure adequate dose to tumor/skin

If patient supine and treated with 60Co, build up not necessary for primary site. Build up for inguinal nodes: Bolus (if skin involvement and treated with 60Co) 1 cm thick (6MV).

If patient prone and treated with 60Co, Bolus to cover visible tumor. If 6MV build up 1 cm thick to cover visible tumor.

Chemotherapy

Mitomycin C /Capecitabine during Radiotherapy.

If capecitabine not available then give; 5FU (USING INFUSION PUMPS)

5.6.2.5 Palliative Radiation

Simulation

- Patient to lie prone if no stoma
- Patient to lie supine if stoma present
- Inferior extent of tumour and stoma, if present, to be marked with wire

Field borders

- Superior border at L5/S1 interspace
- Inferior border 3 cm below visible tumor or 3 cm below anal verge if no visible tumor
- Lateral borders 1 cm beyond widest brim of pelvic side wall or 2 cm beyond involved inguinal nodes

Anterior and posterior fields to be prescribed

Dose prescription

3.00 Gy X 10 Fractions → 30.00 Gy Central dose (high dose palliative) OR
4.00 Gy X 5 Fractions → 20.00 Gy Central dose

5.6.2.6 Follow up after Chemoradiation

- Initial assessment at 6 weeks after completion of treatment If tumor is stable or has decreased in size book follow up in 6 weeks
- Assessment at 12 weeks
- Patients with progressive disease to be booked for EUA and biopsy
- Patients with persistent disease but definite response i.e. decrease in size from original tumor to be reassessed in 2 months
- Patients with persistent disease at 5 months to have EUA and biopsy

Long term follow up

- Patients with complete response to be seen in follow up clinic 3 monthly for first 2 years then 6 monthly for 3 years, after 5 years patients to be followed up annually.
- Follow up consists of history and examination and must include palpation of inguinal nodes and rectal examination
- Patients with anal stenosis or fecal incontinence to be assessed at Surgical clinic for defunctioning stoma

5.6.2.7 Indications for Abdominoperineal resection following chemoradiation

- Increase in size of tumor from baseline (i.e. tumor at presentation) at assessment 6 weeks after completion of chemoradiation.
- Any increase in size of residual tumor from previous assessment
- Persistent disease 5 months after completing radiation
- Any biopsy proven recurrence after complete response
- All patients to have repeat imaging for metastatic disease prior to surgery

6 GENITO-URINARY CANCERS

6.1 Introduction

Genito-urinary refers to cancers arising from filtration part to exit pathway of the urinary system in both sex and male reproductive system. These cancers include urinary bladder, prostate, kidney and pelvis, testicular, penile, urethra and ureters.

6.2.1 Urinary bladder cancers

- Urinary bladder cancers are malignant tumors that commonly arise from the inner lining of the bladder or its connective tissue. Common pathologies include transition cell carcinoma, squamous cell carcinoma, adenocarcinoma, sarcomas and secondary deposits.
- Risk factors for bladder cancer include chronic irritation (schistosomiasis, irradiation, and catheterization), chemicals (aromatic amines, aniline dyes, tobacco, analgesics) and genetic predisposition.
- Symptoms include blood in the urine, dysuria, Lower urinary tract symptoms (LUTS), and low back pain.
- Globally most common primary epithelial bladder cancer is transitional cell carcinoma. Other types include squamous cell carcinoma, adenocarcinoma and small cell carcinoma.

6.2.2 Prevention and screening

- Fruit and yellow-orange vegetables, particularly carrots and those containing selenium, are probably associated with a moderately reduced risk of bladder cancer. Citrus fruits and cruciferous vegetables were also identified as having a possibly protective effect.
- Sufficient water intake plays a protective part in urinary bladder cancer, bladder cancer might partly be caused by the bladder directly contacting carcinogens that are excreted in urine.
- There is insufficient evidence to support screening for bladder cancer in the general population. However, micro-hematuria may be useful in screening for high grade and high risk population.

Work up

- Urinalysis, culture and sensitivity, urine for cytology..
- Cystoscopy, biopsy and examination under anesthesia (EUA).
- TURBT with random biopsies of normal appearing mucosa to exclude CIS. (If trigone involved, biopsy prostatic urethra).
- Upper urinary tract imaging with either CT Urograms, or i.v. or retrograde pyelograms (risk of synchronous upper tract urothelial tumor)
- Alkaline phosphatase.
- Radiological: CXR, USS and / CT chest, CT Abdomino-pelvic , Bone scan.

Pathology

90% of bladder cancers are transitional cell carcinoma. The other 10% are squamous cell carcinoma, adenocarcinoma, sarcoma, small cell carcinoma, and secondary deposits from cancers elsewhere in the body.
Carcinoma in situ (CIS) invariably consists of cytologically high-grade tumor cells.

6.2.5 AJCC/TNM Staging 8th Edition

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical soft tissue
pT3a	Tumor invades perivesical soft tissue microscopically
pT3b	Tumor invades perivesical soft tissue macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall

T4a	Extravesical tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
cM1a	Distant metastasis limited to lymph nodes beyond the common iliacs
cM1b	Non-lymph-node distant metastases
pM1	Distant metastasis, microscopically confirmed
pM1a	Distant metastasis limited to lymph nodes beyond the common iliacs, microscopically confirmed
pM1b	Non-lymph-node distant metastases, microscopically confirmed

6.2.6 Management

The treatment of urinary bladder cancer depends on how deeply the tumor invades into the bladder wall. Treatment categories have been divided into superficial tumors (Non muscle invasive disease), muscle invasive tumors and metastatic cancers.

6.2.6.1 Treatment of Non–Muscle-Invasive Disease (Ta, T1, CIS)

The aim of treatment is to prevent recurrence and progression to muscle invasive bladder cancer.

Surgery**:** TURBT

Intravesical therapy: Initiated within 24 hours after resection: BCG and Chemotherapy- Mitomycin C

Radical cystectomy : for high risk tumors (multifocal lesions , vascular invasion , recurrence after BCG therapy)

NOTE: Intravesical treatment should be avoided when TURBT is extensive or bladder perforation is suspected.

The above bladder preservation protocol is applicable to transitional cell carcinoma, for patients with squamous cell carcinoma radical cystectomy is the standard of care.

6.2.6.2 Treatment of Muscle-Invasive Disease (T2 and Greater)

Patients are selected for radical cystectomy or bladder preservation protocols with multimodality approach.

- Consider Neoadjuvant chemotherapy review first (T2, T3, and T4) before any surgery, and then followed by cystectomy.
- Radical cystectomy and Urinary diversion
- Partial cystectomy (Small tumors in the dome , no CIS)
- Neoadjuvant chemotherapy (T2, T3) followed by cystectomy
- Adjuvant chemotherapy (micro/macroscopic positive surgical margins, node +)
- Adjuvant radiotherapy ((micro/macroscopic positive surgical margins)

Bladder preservation options :

- TURBT alone - solitary lesion, < 2 cm, minimal muscle invasion, no CIS

- TURBT followed by chemotherapy alone
- Partial cystectomy
- Chemoradiotherapy - 40Gy concurrent with weekly cisplatin, if no visible lesion and negative cytology (assessment should be done 3 weeks after EBRT) additional 25 Gy is given.
- Radiotherapy alone

6.2.6.3 Metastatic disease

Aim of treatment is to retard disease progression and improve quality of life. Can be achieved either by local or systemic treatment.

Local treatment- hemostatic radiotherapy, palliative radiotherapy for bone metastasis

Systemic chemotherapy-Gemcitabine and cisplatin (Gem-cis)

6.2.6.4 Recurrence or persistent disease

After cystectomy: Palliative chemoradiotherapy.

After bladder preservation : palliative chemo or radiotherapy

To consider repeating platinum based chemotherapy if patient recurred more than 6 months post previous platinum based chemotherapy.

6.2.6.5 Neoadjuvant Chemotherapy for Stage II, III & Non Metastatic Stage IV Cancer

Gemcitabine/ Cisplatin

6.2.6.6 Concurrent Chemo radiation for Stage II, III & Non-Metastatic Stage IV Cancer

Cisplatin + RT

NOTE: **If in Complete Response (CR), additional weekly Chemo above with concurrent RT .**

If no CR, refer for Cystectomy

6.2.6.7 Chemotherapy for Metastatic Cancer

Cisplatin /Gemcitabine OR Paclitaxel or Docetaxel OR Carboplatin /Paclitaxel.

6.2.6.8 Radiation techniques

Simulation and field design

- Simulate patient supine with immobilization and bladder emptied by patients
- Need CT scan (preferably with contrast) and highly recommend consulting bladder map from TURBT for planning
- Alternatively, double-contrast cystogram = introduce via Foley typically 25–30 mL radiopaque contrast + 10–15 mL air. May need more contrast to equal PVR volume
- For non-3D simulation: to identify anterior rectal wall, instill 50 cc rectal barium (for lateral sim films) administered after AP field film

Field boarders

- Whole pelvis AP/PA borders = S2–S3, lower pole of obturator foramen, widest bony pelvis margin + 1.5–2 cm. Block medial border of femoral heads
- Whole pelvis lateral borders = 2 cm beyond CTV pelvis, same inferior and superior borders as for APPA field. Block rectum, small bowel
- Boost volumes = entire bladder or partial bladder.
- CTV = GTV + 0.5 cm. PTV = CTV + 1.5 cm.

Dose prescriptions

Bladder preservation: treat bladder and nodal drainage to 40–45 Gy with concurrent chemo; if CR on post-induction cystoscopy, boost to a total dose of 60–65 Gy.

Local recurrence status post cystectomy → cisplatin + RT to 45–50 Gy to pelvic nodes, 60–64 Gy to gross local recurrence.

Follow up

Follow-up with urine cytology and cystoscopy every 3 months × 1 year, every 6 months × 2 year, then annually.

CT abdomen and pelvis every 1–2 years.

6.3 Prostate cancer

6.3.1 Introduction

- Prostate cancer is the number 1 non-cutaneous cancer in men, and is the number 2 cause of cancer mortality after lung cancer.
- The median age at diagnosis is 70, but with increased screening, more younger men are being diagnosed.

Work up

- History and physical examination (including baseline erectile function, bony pain, and DRE).
- Laboratory tests include PSA, testosterone, CBC, RFTs and LFTs.
- TRUS-guided biopsy is used for pathologic diagnosis (>8 separate cores is recommended, and the highest GS is used).
- Bone scan and pelvic CT or MRI are usually ordered for High risk group T3–T4, GS 8, PSA 20, or symptoms. Also can be considered to unfavorable intermediate risk T2b/2c, GS 7 with high number of positive cores (>50%) in biopsy.

6.3.2 Screening for prostate cancer

Routine screening not recommended, but when done should begin with PSA and digital rectal examination at age 50 if life expectancy is >10 years.
It is recommended that screening of high risk group should take place starting at age 45 .

Staging

Definition of Primary Tumor (T)
Clinical T (cT)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected

T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum,bladder, levator muscles, and/or pelvic wall

Pathological T (pT)

T Category	T Criteria
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Note: There is no pathological T1 classification.
Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	And PSA is…	And Grade Group is…	Then the stage group is…
cT1a-c, cT2a	N0	M0	< 10	1	I
pT2	N0	M0	< 10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥ 10 < 20	1	IIA
cT2b-c	N0	M0	< 20	1	IIA
T1-2	N0	M0	< 20	2	IIB
T1-2	N0	M0	< 20	3	IIC
T1-2	N0	M0	< 20	4	IIC
T1-2	N0	M0	≥ 20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

Risk stratification

Low risk group:

Stage:T1c-T2a

Gleason Score: <6

Serum PSA: <10ng/mL

Favourable Intermediate risk disease
Stage: T2b-T2c
Gleason score: 3+4=7
Serum PSA: 10-20ng/mL

Unfavourable Intermediate-risk disease
T2b-T2c
Gleason score: 3+4=7 or 4+3=7
SerumPSA: 10-20ng/mL

High-risk group:
Clinical Stage: T3a
Gleason Score: 8 to 10
Serum PSA:>20ng/mL

Very high risk group:
Clinical Stage: T3b-T4
Gleason score: 8 to 10
Serum PSA: >20ng/mL

Management

6.3.2.1 Treatment recommendations

Stage 10-year	Recommended treatment	5-10 bFS	5-10 CSS
Low risk	For life expectancy <10 years, active surveillance or definitive RT (3DCRT/IMRT with IGRT, or brachytherapy) For life expectancy >10 years, RT, RP ± pelvic LN dissection or active surveillance. Consider adjuvant RT if +margin(s) after RP	75-90%	95%

Intermediate risk	For life expectancy <10 years, active surveillance, RT ± short-term androgen deprivation therapy (ADT), or RP. For life expectancy >10 years, RT + short-term ADT (4–6 month), High-dose RT alone, or RP ± pelvic LN dissection RT is 3DCRT/IMRT with IGRT ± brachytherapy boost. Brachytherapy monotherapy considered for select GS 7 patients. Consider whole pelvic RT, especially if multiple adverse features. Adjuvant RT ± short-term ADT indicated for +margin(s) or pT3 disease	50-85%	85-90%
High risk	RT (3DCRT) with neoadjuvant, concurrent, and adjuvant ADT (2–3 years). Four to six-month ADT considered for select patients with single adverse feature with GS 6–7. Whole pelvic RT indicated. Consider RP with pelvic LN dissection only for select patients with low-volume disease and no fixation. Adjuvant RT ± short-term ADT indicated for +margin(s) or pT3 disease	T1-T2 60% T3 N+ 20%	T1-T2 80-85% N+ 60%
Node +	Life long or long-term ADT (≥2years) alone or combined with RT (3DCRT); sometimes preferred over ADT alone when limited nodal disease	10-year OS 35–60% 5-year PFS 20–50%	

Metastatic	Life long ADT ± palliative RT ± bisphosphonates for hormone-refractory disease. Docetaxel and prednisone for androgen independent disease can add Carboplatin if docetaxel not working to Castrate resistant prostate cancer patients. Evaluation every 3 months (Check PSA level) Castrate resistant patients with rising PSA zoledronic acid should be given monthly OR Pamidronate. These are given together with Ca2+ and Vitamin D supplements. In Castrate resistant patients which did not respond to Docetaxel plus carboplatin and prednisolone, patients Abberaterone acetate with prednisolone is an option (250mg OD taken with food is highly recommended).	Median survival for androgen independent disease is ~18 months
Adjuvant or Salvage RT after RP	Adjuvant RT indicated if persistent local disease on imaging or biopsy, or pT3 disease or +margin(s). Best candidates for salvage RT for rising PSA after RP: pretreatment low-risk disease with PSA velocity <2 ng/mL in year before diagnosis; pathologic GS ≤7, +margin(s), negative LN, and no SVI; time to PSA failure >3 years after RP, and Salvage RT low PSA at time of salvage <1 ng/mL Short-term ADT considered for patients with high-risk features.	Adjuvant RT 5 years bPFS ~ 75% 5 -10 years LF 5-8%

	If metastatic or not a candidate for local therapy, ADT or observation. If +biopsy and no evidence (or low-risk) of metastases, surgery, salvage brachytherapy, or cryotherapy considered. Salvage RP provides 5-year PSA control in up to 85, 55, and 30% of patients with pre-op PSA <4, 4–10, and >10, respectively. However, high risk of morbidity, including incontinence (~50–70%), erectile dysfunction, and bladder neck contracture or stricture (~15–30%)	

NOTE: ADT = Androgen deprivation therapy: Goserelin 3.6mg SubQ q28d, Bicalutamide 50mg OD in combination Docetaxel 75mg/m^2 q3wk .Radical RT 74 Gy.

Active surveillance

Active surveillance generally consists of DRE and PSA every 3–6 months with routine repeat biopsy in 1–2 years to rule-out Gleason grade progression.

Radical prostatectomy (RP)

- Retropubic approach allows bilateral pelvic lymph node dissection to precede prostatectomy in patients with LN risk. Perineal approach associated with better exposure of urethral stump and reduced risk of involved apical margin, but increased risk of rectal damage.
- A pelvic LN dissection frequently excluded in patients with <7% probability of LN metastases by nomograms.

Radiotherapy

Simulation

- Patients are treated supine with alpha cradle or "knee rest" to consistently align thighs.
- Patients are instructed to have a full bladder and empty rectum (following

an enema) for simulation.
- Gold marker seeds are placed in the base and apex of the prostate 7–10 day prior to simulation.

Boarders

- For traditional whole pelvic RT, initial field borders are:

Superior = L5/S1; inferior = 0.5–1 cm below the area where the dye narrows on the urethrogram (or 1–1.5 cm below in the post-op setting); lateral = 1.5cm lateral to the bony margin of the true pelvis.
Anterior border: posterior edge of pubic symphysis including entire bladder neck until above symphysis, then off bladder.
Posterior border: to anterior aspect of rectum and mesorectal fascia.

EBRT dose

Prophylactic dose to the pelvic LN is 1.8 Gy/fx to 45 Gy. Involved LN receive 54–56 Gy or higher with IMRT.
Prophylactic dose to the seminal vesicles is 54 Gy. Documented seminal vesicle disease receives full-dose.
Conedown boosts using 3DCRT to cover the prostate to 74–78 Gy. The minimum central axis dose is 78 Gy.
In the postoperative setting, the prostate bed is typically treated to 64.8–66.6 Gy at 1.8-Gy per fraction, but may be boosted higher if local residual disease is documented.

Example EBRT dose constraints
Bladder: V75 <25%, V70 <35%, V65 <25–50%, V55 <50%, V40 <50%.
Rectum: V75 <15%, V70 <20–25%, V65 <17%, V60 <40%, V50 <50%, V40 <35–40%.
Femoral heads: V50 <5%
Small bowel: V52 0%
Penile bulb: Mean dose <52.5 Gy

Follow up

H&P with DRE and PSA every 6 month for 5 years and then annually. In the first

1–3 years after definitive RT, PSA may be ordered more frequently (e.g., every 3–6 month).
The definition of PSA failure following surgery is controversial and values ≥0.2, ≥0.3, and ≥ 0.4 ng/mL have been used.
Standard is PSA ≥0.2 ng/mL on two measurements
The 1996 ASTRO definition of PSA failure following EBRT is three consecutive PSA rises, with the time of failure backdated to the midpoint between the PSA nadir and the first rising PSA, or any rise great enough to provoke initiation of salvage therapy; a minimum follow-up of 2 years was recommended for presentation or publication of data
The "Phoenix Definition" (current ASTRO/RTOG definition) of PSA failure after EBRT, with or without short-term HT, is defined as a rise by ≥2 ng/mL above the nadir PSA (defined as the lowest PSA achieved), with the date of failure "at call" and not backdated. Patients who undergo salvage therapy (e.g., with HT, RP, brachytherapy, or cryosurgery) are declared failures at the time of + biopsy or salvage therapy administration (whichever comes first).

Renal Cell Carcinoma

6.4.1 Introduction

Renal cancer is a disease in which kidney cells become malignant (cancerous) and grows out of control, forming a tumor. Almost all kidney cancers first appear in the lining of tiny tubes (tubules) in the kidney.
Renal cell cancer (RCC) is the most common type of kidney cancer in adults, responsible for approximately 90–95% of cases.
Initial treatment is most commonly either partial or complete removal of the affected kidney(s). The body is remarkably good at hiding the symptoms and as a result people with RCC often have advanced disease by the time it is discovered.

Risk factors

Tobacco, urban environmental toxins (cadmium/ asbestos/petrols), obesity, high dietary fat intake, acquired cystic renal disease from renal failure (premalignant condition).

Association with von Hippel-Lindau disease: autosomal dominant, loss of 3p, >70% chance developing RCC (almost all clear cell histology) in addition to risk of developing multiple other benign and malignant tumors (retinal angiomas, CNS hemangioblastomas, pheochromocytoma, pancreatic cancer).Possible association with lymphoma.

Pathology.

After neprectomy, tissue is taken for histopathological analysis.
Predominant histologic type: adenocarcinoma arising from tubular epithelium.
Adenocarcinoma subtypes: clear cell (75–85%), chromophilic/ papillary (10–15%), chromophobe (5–10%), oncocytic (rare)
Sarcomatoid (1–6%; poor prognosis)

Signs and symptoms

The initial symptoms of RCC often include:
Hematuria occurring in 40% of affected persons at the time they first seek medical attention
Flank pain (pain on the side of the body between the hip and ribs)
Abdominal mass (10 – 15 %)
Loin pain
Malaise
Weight loss (33%)
Fever (20%),
High blood pressure (20%),

NOTE: When RCC metastases, it most commonly spreads to the lymph nodes, lungs, liver, adrenal glands, brain or bones.
RCC is also associated with a number of paraneoplastic syndromes (PNS) which are conditions caused by either the hormones produced by the tumor or by the body's attack on the tumor and are present in about 20% of those with RCC. These syndromes most commonly affect tissues which have not been invaded by the cancer. The most common PNSs seen in people with RCC are: high blood calcium levels, polycythaemia, thrombocytosis and secondary amyloidosis.

6.4.5 Work up.

History & Physical examination.

Common signs and symptoms: hematuria (80%), flank pain (45%), flank mass (15%), classic triad of prior three only present in 10%, normocytic/normochromic anemia, fever and weight loss

Less common signs and symptoms: hepatic dysfunction without metastasis, polycythaemia, and hypercalcemia (occurs in 25% of patients with RCC metastasis)

Laboratory tests: CBC, LFT, BUN/Cr, LDH, urinalysis

Basic investigations; abdominal pelvic USS and chest X ray

Imaging: CT abdomen. MRI abdomen if CT suggests IVC involvement

Metastatic evaluation: Chest X ray, Bone scan or MRI brain only if clinically indicated

Other tests; Excretory urography, Renal arteriography and Venography

Staging of RCC.

American Joint Committee on Cancer (AJCC) TNM Staging System for Kidney Cancer (8th ed., 2018)

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney

T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system.

Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T1	N1	M0	III
T2	N0	M0	II
T2	N1	M0	III
T3	NX, N0	M0	III
T3	N1	M0	III
T4	Any N	M0	IV
Any T	Any N	M1	IV

6.4.7 Management

Treatment recommendations for localized disease

6.4.7.1 Surgery

Surgical resection is the preferred treatment for localized disease, radical or partial nephrectomy or nephron-sparing surgery.
Surgical treatment by disease stage.

Stage IA:

Surgical resection with radical nephrectomy is preferred
If partial nephrectomy is not feasible or the tumor is centrally located, the patient may be recommended for radical nephrectomy
Active surveillance is preferred in selected patients

Stage IB:

Partial nephrectomy or radical nephrectomy is the standard treatment

Stages II and III:

Radical nephrectomy is the preferred treatment

Advanced disease (stage IV, relapsed, or recurrent disease)
Primary treatment includes cytoreductive therapy for potentially surgically resected primary and metastatic disease before systemic therapy in patients with a potentially resectable primary tumor and multiple resectable metastases.
Surgical resection is recommended in selected patients with good performance status
Surgically unresectable tumors - nonsurgical treatment is recommended.

Stage IV, relapsed, or recurrent disease with predominantly clear cell histology
First-line therapy for previously untreated patients low or intermediate risk:
Sunitinib or Pazopaniby **or** Sorafenib or Bevacizumab
Supportive care: palliative radiation therapy, metastasectomy, and bisphosphonates for bony metastasis

First-line for previously untreated clear-cell renal cell cancer in patients with poor prognostic (high-risk) characteristics and patients with non–clear cell history:
Temsirolimus or Sunitinib or sorafenib
Patients with predominantly sarcomatoid renal cancers may respond to combination chemotherapy

2nd line: Subsequent targeted therapy after tyrosine kinase inhibitors (i.e, sorafenib, sunitinib), cytokine and angiogenic therapies (Bevacizumab):
Axitinib

3rd line: Everolimus
Stage IV, relapsed, or recurrent disease for patients with predominantly non–clear cell histology;
Temsirolimus or Sorafenib or Sunitinib or Pazopanib or Axitinib or Everolimus or Bevacizumab or
Erlotinib or Gemcitabine and doxorubicin
OR

Supportive care: palliative radiation therapy, metastasectomy, and bisphosphonates for bony metastasis
Nephrectomies with metastasectomy are beneficial to metastatic renal cancer patients.

6.4.7.3 Radiotherapy for RCC

Simulation and field design
Primary site
Supine, arms-up to allow visualization of lateral isocenter marks, immobilize with wing-board or alpha cradle, wire scar, planning CT scan.
Volume: nephrectomy bed (involved kidney if pre-op), lymphnode drainage sites, surgical clips; so if not possible to include scar in treatment volume, treat it with electrons to full dose. VII
Metastatic site (non-CNS)
Proper immobilization depending on site; planning CT if 3DCRT needed to spare normal tissue
Volume: focal treatment of metastasis with 2–3 cm margin

Dose prescriptions
Pre-op: 40–50 Gy (1.8–2 Gy/fx)
Post-op: 45–50 Gy with 10–15 Gy boost to micro/gross disease; total 50–60 Gy
Metastases: 45–50 Gy in 3–4.5 weeks

Follow up
Stage I–III: every 6 months × 2 years, then every 1 year × 5 years – History and Physical examination, CXR, Labs with LDH; CT chest/abdomen/pelvis at 4–6 months then as indicated.

6.5 Testicular Cancer

6.5.1 Introduction
There are two types seminoma and nonseminoma. Nonseminoma is more aggressive than seminoma. When the elements of both seminoma and nonseminoma are present or the alpha-fetoprotein (AFP) concentration is

elevated, the tumor should be treated as a nonseminoma.
Risk factors: undescended testicle, first-born, pre/perinatal estrogen exposure, polyvinyl chloride exposure, advanced maternal age, Down's syndrome, Klinefelter's syndrome (47XXY), CIS, HIV/AIDS.

6.5.2 Work up

History and physical examination, bilateral testicular ultrasound, b-hCG, AFP, LDH, CBC, chemistries, fertility assessment ± sperm banking, CXR, CT abdomen and pelvis, CT chest if ≥stage II

6.5.3 TNM classification for testicular cancer (UICC, 2009, 7th edn.)

Definition of Primary Tumor (T)

Clinical T (cT)

T Category	T Criteria
cTX	Primary tumor cannot be assessed
cT0	No evidence of primary tumor
cTis	Germ cell neoplasia in situ
cT4	Tumor invades scrotum with or without vascular/lymphatic invasion

Note: Except for Tis confirmed by biopsy and T4, the extent of the primary tumor is classified by radical orchiectomy. TX may be used for other categories for clinical staging.

Pathological T (pT)

T Category	T Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia in situ
pT1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion
pT1a*	Tumor smaller than 3 cm in size
pT1b*	Tumor 3 cm or larger in size

pT2	Tumor limited to testis (including rete testis invasion) with lymphovascular invasion OR Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
pT3	Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumor invades scrotum with or without lymphovascular invasion
*Subclassification of pT1 applies only to pure seminoma.	

Clinical N (cN)

N Category	N Criteria
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph node metastasis
cN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension OR Multiple lymph nodes, none larger than 2 cm in greatest dimension
cN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension OR Multiple lymph nodes, any one mass larger than 2 cm but not larger than 5 cm in greatest dimension
cN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Pathological N (pN)

N Category	N Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor

pN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system.

Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastases
cM1	Distant metastases
cM1a	Non-retroperitoneal nodal or pulmonary metastases
cM1b	Non-pulmonary visceral metastases
pM1	Distant metastases, microscopically confirmed
pM1a	Non-retroperitoneal nodal or pulmonary metastases, microscopically confirmed
pM1b	Non-pulmonary visceral metastases, microscopically confirmed

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	And S is…	Then the stage group is…
pTis	N0	M0	S0	0
pT1-T4	N0	M0	SX	I
pT1	N0	M0	S0	IA
pT2	N0	M0	S0	IB
pT3	N0	M0	S0	IB
pT4	N0	M0	S0	IB
Any pT/TX	N0	M0	S1-3	IS
Any pT/TX	N1-3	M0	SX	II
Any pT/TX	N1	M0	S0	IIA

Any pT/TX	N1	M0	S1	IIA
Any pT/TX	N2	M0	S0	IIB
Any pT/TX	N2	M0	S1	IIB
Any pT/TX	N3	M0	S0	IIC
Any pT/TX	N3	M0	S1	IIC
Any pT/TX	Any N	M1	SX	III
Any pT/TX	Any N	M1a	S0	IIIA
Any pT/TX	Any N	M1a	S1	IIIA
Any pT/TX	N1-3	M0	S2	IIIB
Any pT/TX	Any N	M1a	S2	IIIB
Any pT/TX	N1-3	M0	S3	IIIC
Any pT/TX	Any N	M1a	S3	IIIC
Any pT/TX	Any N	M1b	Any S	IIIC

6.5.6 Management

6.5.6.1 Recommended treatment approach keyed to AJCC staging.

Seminoma stage IA, IB

Clinical stage I seminoma

Radical inguinal orchiectomy alone or active surveillance, adjuvant chemotherapy, and adjuvant radiation therapy.

Surveillance consists of a history and physical exam,measurement of AFP,CT scan of the abdomen and pelvis is recommended at each visit and a chest x-ray at alternate visits and hCG every 3 to 4 months for the first 3 years, every 6 months for years 4 to 7, then annually up to year 10.

Seminoma stage IS

Adjuvant radiation therapy, 20-30 Gy, is administered to the infradiaphragmatic area, including para-aortic lymph nodes, with or without ipsilateral ileoinguinal nodes.

Seminoma stage IIA and IIB

Active surveillance is not an option. These patients receive adjuvant chemotherapy or radiation therapy.

For radiation therapy, 35-40Gy is administered to the infradiaphragmatic area, including the para-aortic and ipsilateral iliac lymph nodes. Mediastinal radiation is not recommended.

If RT not available, four courses of chemotherapy with etoposide and cisplatin (EP) may be given.

Seminoma stage IIC and III

Stage IIC and III seminomas are categorized as good risk or intermediate risk. Chemotherapy is the option for both groups.

Intermediate-risk seminomas include non-pulmonary visceral metastatic disease : Four cycles of BEP

Good-risk seminoma stage IIC and III: Either four cycles of EP or three cycles of Bleomycin, etoposide, and cisplatin (BEP)

Seminoma stage IIB, IIC, III after primary treatment with chemotherapy

- For stage II and III seminoma after primary treatment with chemotherapy, recommended surveillance includes CT scans of the chest, abdomen, and pelvis along with serum tumor marker assays.
- For patients with residual mass but normal markers, PET scanning should also be considered. In some cases of seminoma, a PET scan may detect nodal and extranodal disease that is not evident on CT scans.
- CT scan or PET scans for evaluating the response to chemotherapy in seminoma should be performed 3-4 weeks after the last course of chemotherapy. If the CT or PET scan is negative, surveillance is recommended. Options for patients with a positive CT or PET scan include surgery with biopsy, or biopsy and salvage chemotherapy or radiation therapy.
- If a PET scan cannot be done and the residual mass is 3 cm or less in size, surveillance is recommended. When the mass is larger than 3 cm in size, surveillance could be considered but surgery and radiation therapy are options and should be discussed with the patient.
- Patients who experience progressive disease with a growing mass or rising

marker levels should receive salvage chemotherapy.

Nonseminoma stage IA, IB, IS

- After radical inguinal orchiectomy, treatment options are active surveillance or chemotherapy. Retroperitoneal lymph node dissection (RPLND) is used to guide chemotherapy; the number of positive nodes present in the sample determines the number of chemotherapy cycles given.
- The majority of stage I nonseminoma germ cell tumors can be safely managed without subjecting the patient to chemotherapy or RPLND; orchiectomy and follow up surveillance is recommended. The small subset of patients at high risk for systemic recurrence may considered for adjuvant chemotherapy.

Nonseminoma stage IA

Active surveillance can be used in compliant patients. The surveillance should include an abdominal and pelvic CT scan every 3 months for the first year and every 6 months in the second year.

History and physical examination, chest x-ray, and tumor marker assays should be done every 3 months for the first year and every 4 months during the second year. The cure rate is 95%.

Nonseminoma stage IB

Options are open nerve-sparing RPLND; chemotherapy with BEP for 2 cycles; or active surveillance for compliant patients who have T2 disease without any vascular invasion.

Nonseminoma stage IS

If persistent tumor marker elevation is present but no abnormality is visible on imaging studies, chemotherapy with EP for 4 cycles or BEP for 3 cycles is recommended.

Nonseminoma stage IIA, IIB

- Treatment varies according to the stage and the results of tumor marker assays and CT scan. Chemotherapy consists of either EP for four cycles or BEP for three cycles.

Treat recommendations are as follows:

- Nonseminoma stage IIA with normal tumor markers: open nerve-sparing RPLND or chemotherapy
- Nonseminoma stage IIA with persistent elevation of tumor markers: chemotherapy
- Nonseminoma stage IIB with normal tumor markers and lymph node metastasis within lymphatic drainage site by CT scan: open nerve-sparing RPLND or chemotherapy
- Nonseminoma stage IIB normal tumor markers and multifocal symptomatic lymph node metastases with aberrant lymphatic drainage by CT scan: chemotherapy
- Nonseminoma stage IIB with persistent elevation of tumor markers: chemotherapy

Nonseminoma stage IIC, IIIA, IIIB, IIIC and brain metastases
Good risk.

Patients with stage IIC and III are treated with chemotherapy, either EP for four cycles or BEP for three cycles; the cure rate is 95%.

Intermediate risk

In nonseminoma stage IIIB: BEP for four cycles .

Poor risk

- With nonseminoma stage IIIB: BEP four cycles
- In patients who cannot tolerate BEP because of pneumonitis from the bleomycin component, VIP (etoposide, ifosfamide, mesna, cisplatin) is recommended.
- Patients with brain metastases should receive primary chemotherapy plus radiation. Surgery should be performed if clinically indicated.
- In nonseminoma stage IIC, IIIA, IIIB, or IIIC, a CT scan of the abdomen and pelvis and tumor marker assays are indicated after the completion of chemotherapy. With patients in whom these tests indicate a complete response, options are surveillance or open nerve-sparing RPLND.
- If residual disease is present but tumor marker levels are normal, all the residual disease should be resected.

- If the resection specimen shows only necrotic tissue or teratoma, no further therapy is recommended and active surveillance should be done. If residual embryonal, yolk sac, choriocarcinoma, or seminoma elements are present, the patient should receive two cycles of chemotherapy with EP, TIP (paclitaxel, ifosfamide and cisplatin), VIP, or VeIP (vinblastine, ifosfamide, mesna, cisplatin).

6.5.6.2 Recurrent disease and salvage treatment

Patients who do not have a complete response to first-line therapy, or whose disease recurs after complete response, are categorized into favorable and unfavorable prognostic groups.

Salvage treatment for patients with a favorable prognosis; these patients are treated with chemotherapy—VeIP or TIP.

Salvage treatment for patients with an unfavorable prognosis; conventional chemotherapy with either VeIP or TIP, or best supportive care. Third-line chemotherapy with or without cyclophosphamide/ifosfamide can produce a durable complete response in 15-20% of patients and should be considered for patients with good performance scores.

Palliative chemotherapy and radiation; If surgery cannot be done, these patients can be considered for palliative chemotherapy or palliative radiation therapy. Gemcitabine and oxaliplatin (GEMOX) has shown efficacy in relapsed cisplatin-refractory disease and may offer a chance for long-term survival.

Surgical Care; Surgical resection is recommended for patients with residual disease after chemotherapy. Retroperitoneal lymph node dissection (RPLND) should clear the region of residual disease.

6.5.6.4 Radiotherapy

Simulation and field design

Prior to simulation, fertility assessment

Simulate supine

Need IVP or CT to block out kidneys and rule out horseshoe kidney
Place clamshell on uninvolved testicle. Position penis out of field
Borders: PA = T10/T11 superiorly to L5/S1 inferiorly, inferior border is top of obturator foramen. Lateral = tips of transverse processes of lumbar vertebra or 2 cm margin on all nodes (about 10–12 cm wide). For left-sided tumors, widen field to include left renal hilar nodes
If prior inguinal surgery, treat contra lateral inguinal and iliac regions

Dose prescriptions

20 Gy at 2.0 Gy/fraction. Alternatively, 25.5 Gy at 1.5 Gy/fraction
Boost IIA nodes to 30 Gy and IIB nodes to 36 Gy

Dose limitations

50 cGy causes transient azospermia with recovery at 1 year, but only 50% of patients reach their baseline
80–100 cGy causes total azospermia with recovery 1–2 years later for some patients
200 cGy causes sterilization
Clamshell reduces testicle dose by 2–3× (dogleg without shield
~4 cGy/fx, with shield ~1.5 cGy/fx; paraaortic without shield
~2 cGy/fx, with shield ~0.7 cGy/fx)
Kidneys: limit at least 70% <20 Gy

6.5.7 Follow up

After RT for stage I seminoma
H&P, labs (AFP, b-HCG, LDH), and CXR every 3–4 months for year 1, every 6 months for year 2, then annually. Pelvic CT annually for 3 years for patients treated with PA-only RT (not needed if PA and pelvic RT)
Stage I surveillance
H&P, labs every 3–4 months for years 1–3, every 6 months for years 4–7, then annually. CT abdomen and pelvis at each visit. CXR at alternate visits up to 10 years
PET-CT: is indicated for post chemo seminoma stage 2 or 3 to evaluate for resectable metastasis.

6.6 Penile cancer

6.6.1 Introduction

Penile cancer is rare in Western countries (<1% of cancers in men), but accounts for 10–20% of male malignancies in Africa, Asia, and South America.
LN drainage: skin of penis – bilateral superficial inguinal nodes; glans penis – bilateral inguinal or iliac nodes; penis corporal tissue – bilateral deep inguinal and iliac; 20% chance of LN+ at surgery if clinically node negative.
Risk factors: uncircumcised status, phimosis, poor local hygiene, HPV-16, 18.
Pathology: 95% squamous cell; others very rare – melanoma, lymphoma, basal cell, Kaposi's sarcoma.

6.6.2 Work up

History and physical examination with careful palpation and exam; if deep, consider cystourethroscopy with biopsy; bimanual exam under anesthesia.
Laboratory tests: CBC, chemistries, RFT, LFTs including alkaline phosphatase.
Imaging: ultrasound or MRI (penis) , Inguinal ultrasound, pelvic/abdominal USS or CT; CXR, bone scan if advanced/suspicious.
Biopsy of the lesion, FNAC for suspicious nodes
Check HIV / Start ARVs.

6.6.3 Staging

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Penile intraepithelial neoplasia [PeIN])
Ta	Noninvasive localized squamous cell carcinoma
T1	Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade

T1a	Tumor is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid)
T1b	Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)
T2	Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
T3	Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion
T4	Tumor invades into adjacent structures (i.e., scrotum, prostate, pubic bone)

Definition of Regional Lymph Node (N)

Clinical N (cN)

N Category	N Criteria
cNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile ≥ 2 unilateral inguinal nodes or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral

Pathological N (pN)

N Category	N Criteria
pNX	Lymph node metastasis cannot be established
pN0	No lymph node metastasis
pN1	≤ 2 unilateral inguinal metastases, no ENE
pN2	≥ 3 unilateral inguinal metastases or bilateral metastases, no ENE
pN3	ENE of lymph node metastases or pelvic lymph node metastases

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0is
Ta	N0	M0	0a
T1a	N0	M0	I
T1b	N0	M0	IIA
T2	N0	M0	IIA
T3	N0	M0	IIB
T1-3	N1	M0	IIIA
T1-3	N2	M0	IIIB
T4	Any N	M0	IV
Any T	N3	M0	IV
Any T	Any N	M1	IV

6.6.4 Management

6.6.4.1 Treatment of the primary tumor

Complete tumor removal with as much organ preservation as possible while radicality of the treatment should not be compromised.

Treatment of Tis/Ta

Circumcision,
Wide local excision,
Moh's surgery,
Topical 5-FU,
Topical Imiquimod

Treatment of T1G1-2 (Early limited lesions, for RT alone lesions should be T1-2, <4 cm)

Options:
Penectomy
Penis preservation: circumcise first, then EBRT, or chemo-RT EBRT: 40–50 Gy to whole penile shaft ± lymph nodes, then boost to primary lesion + 2 cm margin (total 60–65 Gy)

Consider prophylactic inguinal node RT

- Surgery – from circumcision to local excision to radical penectomy. Recommend >1.5–2 cm margin.
- For clinically node negative, it is recommended to opt prophylactic inguinal node dissection for tumors T2 and above or G3.
- For T1G2, consider dissection depending on other factors (LVI status). If no node dissection, requires very close monitoring. Pelvic dissection if 2+ inguinal nodes, extra capsular extension or + nodes on imaging.
- Post-op RT for LN+ refer vulvar cancer radiotherapy section.

Treatment of T1G3-4 or more advanced lesions

EBRT: Chemo-RT preferred 60 Gy in 2 Gy fractions.
Surgery: save for salvage; partial to radical penectomy; consider prophylactic inguinal node dissection with tumors extending onto shaft of penis/poorly differentiated; if node positive, need inguinal and pelvic LND;

Treatment of T4 with invasion of other adjacent structures

Neoadjuvant chemotherapy followed by surgery in responders (Paclitaxel, Ifosfomide, Cisplatin).
Palliative EBRT.

Local recurrence after conservative treatment

Salvage surgery

6.6.5 Follow up

History and physical examination every 1–2 months for 1 year, every 3 months for second year, every 6 months for third to fifth years, then annually.
Need close follow-up, especially if no prophylactic nodal treatment in cN0 patients.

7 GYNAE-COLOGICAL CANCERS

7.1 Ovarian Cancer

7.1.1 Introduction

Epithelial tumors comprise 90% of all ovarian cancers; most patients present with advanced disease due to anatomical location.

7.1.2 Work up

History and General Physical Examination
Baseline: FBP, RFT, LFT, CA-125, CEA,AFP
Chest X-ray, Abdominal pelvic Ultrasound, CT-Scan (Abdomen and Pelvis)
Ascitic fluid/peritoneal and pelvic washing cytology
Histology of oophorectomy specimen

7.1.3 Staging

Definition of Primary Tumor (T)

T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to ovaries (one or both) or fallopian tube(s)
T1a	IA	Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1b	IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c	IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
T1c1	IC1	Surgical spill
T1c2	IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c3	IC3	Malignant cells in ascites or peritoneal washings

T2	II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	IIA	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
T2b	IIB	Extension to and/or implants on other pelvic tissues
T3	III	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes
T3a	IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes
T3c	IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

Definition of Regional Lymph Node (N)

N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	IIIA1	Positive retroperitoneal lymph nodes only (histologically confirmed)
N1a	IIIA1i	Metastasis up to and including 10 mm in greatest dimension
N1b	IIIA1ii	Metastasis more than 10 mm in greatest dimension

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	FIGO Stage	M Criteria
cM0		No distant metastasis
cM1	IV	Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine
cM1a	IVA	Pleural effusion with positive cytology
cM1b	IVB	Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine
pM1	IV	Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine, microscopically confirmed
pM1a	IVA	Pleural effusion with positive cytology, microscopically confirmed
pM1b	IVB	Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine, microscopically confirmed

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T1c	N0	M0	IC
T2	N0	M0	II
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T1/T2	N1	M0	IIIA1
T3a	NX, N0, N1	M0	IIIA2
T3b	NX, N0, N1	M0	IIIB
T3c	NX, N0, N1	M0	IIIC
Any T	Any N	M1	IV
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB

7.1.4 Management

Treatment recommendations
Stage 1A/B Grade 1&2: Cytoreductive surgery > Observation
Stage IB- Grade 3: Cytoreductive surgery > Adjuvant chemotherapy
Stage IC/II: Cytoreductive surgery > Adjuvant chemotherapy
Stage III: Neoadjuvant chemotherapy > Surgery > Adjuvant chemotherapy
Stage IV: Manage abdominal disease as stage III +/- Palliation

7.1.4.2 Chemotherapy

Choice of regimen:

Carboplatin/Cisplatin and paclitaxel

7.1.4.3 Recurrent Ovarian Cancer

The choice of a second-line regimen depends on the disease-free interval.

Disease-Free Interval ≥6 months (platinum-sensitive disease): remission from completion of primary treatment - retreatment with: carboplatin,paclitaxel and bevacizumab
Carboplatin,Gemcitabine with or without bevacizumab
Carboplatin and Pegylated liposomal doxorubicin
Etoposide, topotecan and gemcitabine.

Disease-Free Interval < 6 months
Single Agent: Liposomal doxorubicin, gemcitabine, topotecan, etoposide and bevacizumab.
Endocrine therapy - Tamoxifen,letrozole and goserelin.

7.1.4.3 Follow up
First and second years: 3 monthly check:
Physical Examination
Laboratory investigations: FBP, RFT, LFT, CA-125, CEA
Imaging investigations: Chest XRay, Ultrasound (abdomen and pelvis), CT-Scan (abdomen and pelvis)
Year 3 and onward: 6 monthly follow-up - same details

7.2 Cervical cancer

7.2.1 Introduction
The disease is associated with a persistent HPV infection. Screening, early detection and vaccination have proved to be successful prevention methods.

Clinical presentation
Asymptomatic in Early stage of the disease
Majority present with abnormal vaginal bleeding (post-coital, inter-menstrual, post-menopausal)
Foul smelling discharge and incontinence (VVF or RVF) - symptoms of late disease

FIGO Staging

Definition of Primary Tumor (T)

T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Cervical carcinoma confined to the uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2.Includes all macroscopically visible lesions, even those with superficial invasion.
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney

T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or non functioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)

*The pelvic sidewall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis. On rectal examination,there is no cancer-free space between the tumor and pelvic sidewall.

Definition of Regional Lymph Node (N)

N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1		Regional lymph node metastasis

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	FIGO Stage	M Criteria
cM0		No distant metastasis
cM1	IVB	Distant metastasis (including peritoneal spread or involvement of the supraclavicular,mediastinal, or distant lymph nodes; lung; liver; or bone)
pM1	IVB	Distant metastasis (including peritoneal spread or involvement of the supraclavicular,mediastinal, or distant lymph nodes; lung; liver; or bone), microscopically confirmed

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1	Any N	M0	I
T1a	Any N	M0	IA
T1a1	Any N	M0	IA1
T1a2	Any N	M0	IA2
T1b	Any N	M0	IB
T1b1	Any N	M0	IB1
T1b2	Any N	M0	IB2
T2	Any N	M0	II
T2a	Any N	M0	IIA
T2a1	Any N	M0	IIA1
T2a2	Any N	M0	IIA2
T2b	Any N	M0	IIB
T3	Any N	M0	III
T3a	Any N	M0	IIIA
T3b	Any N	M0	IIIB
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Treatment recommendations.

STAGE	RECOMMENDATIONS
Pre-invasive	Fertility Sparing methods: Conization, Loop Electrosurgical Excisional Procedure (LEEP), laser, Cryotherapy Hysterectomy
IA1	Simple Hysterectomy or consider conization if patient desires fertility
IA2-IB1	Wertheim Hysterectomy plus Bilateral Pelvic lymph node dissection - RT may be given in the post-operative setting or alone
IB2 – IVA	Concurrent EBRT + Chemotherapy then Brachytherapy
IV B	Combination Chemotherapy

Field Arrangement
AP field:
Superior border:Between L4/L5 vertebra
Inferior border: below ischial tuberosity, or inferior obturator foramen - if any vaginal involvement: 3cms below the most inferior disease in the vagina as palpated or seen by MRI
Lateral Border: 1.5 -2cms beyond bony pelvis

Lateral Field
Superior border:Between L4/L5 vertebra
Inferior border: below ischial tuberosity, or inferior obturator foramen.
Anterior border at the anterior edge of pubic symphysis while ensuring at least a 2.5-cm margin from the anterior aspect of the L5 vertebral body.
Posterior border covered the sacral hollow.

Dose prescription
Concern: Hypofractionation EBRT+ ICT?
Stages IIIA, IIIB - Good PS, receive 3 insertions after 50 in 25#
Stage IIIA/B - poor PS - Hypofractionation (40/2.5Gy/#) - ICT will be 9 Gys x 2

7.3 Vulva Cancer

7.3.1 Clinical Presentation
Lump or vulva mass
Presence of leukoplakia and other dystrophic changes
Itching is a common manifestation and may become ulcerative

Investigation
FBP, RFT, LFTs
Ca-125
Chest Xray
CT scan (Abdomen and Pelvis) +/- MRI
NOTE:Colposcopy to exclude presence of other lesions in the vagina and cervix

FIGO STAGING

Definition of Primary Tumor (T)

T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the vulva and/or perineum.Multifocal lesions should be designated as such. The largest lesion or the lesion with the greatest depth of invasion will be the target lesion identified to address the highest pT stage. Depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
T1a	IA	Lesions 2 cm or less, confined to the vulva and/or perineum, and with stromal invasion of 1.0 mm or less
T1b	IB	Lesions more than 2 cm, or any size with stromal invasion of more than 1.0 mm, confined to the vulva and/or perineum
T2	II	Tumor of any size with extension to adjacent perineal structures (lower/distal third of the urethra,lower/distal third of the vagina, anal involvement)
T3	IVA	Tumor of any size with extension to any of the following—upper/proximal two thirds of the urethra, upper/proximal two thirds of the vagina, bladder mucosa, or rectal mucosa—or fixed to pelvic bone

Definition of Regional Lymph Node (N)

N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	III	Regional lymph node metastasis with one or two lymph node metastases each less than 5 mm, or one lymph node metastasis ≥5 mm

N1a*	IIIA	One or two lymph node metastases each less than 5 mm
N1b	IIIA	One lymph node metastasis ≥5 mm
N2		Regional lymph node metastasis with three or more lymph node metastases each less than 5 mm, or two or more lymph node metastases ≥5 mm, or lymph node(s) with extranodal extension
N2a*	IIIB	Three or more lymph node metastases each less than 5 mm
N2b	IIIB	Two or more lymph node metastases ≥5 mm
N2c	IIIC	Lymph node(s) with extranodal extension
N3	IVA	Fixed or ulcerated regional lymph node metastasis
*Includes micrometastasis, N1mi and N2mi. Note: The site, size, and laterality of lymph node metastases should be recorded.		

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	FIGO Stage	M Criteria
cM0		No distant metastasis (no pathological M0; use clinical M to complete stage group)
cM1	IVB	Distant metastasis (including pelvic lymph node metastasis)
pM1	IVB	Distant metastasis (including pelvic lymph node metastasis), microscopically confirmed

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II

T1-T2	N1-N2c	M0	III
T1-T2	N1	M0	IIIA
T1-T2	N2a, N2b	M0	IIIB
T1-T2	N2c	M0	IIIC
T1-T3	N3	M0-M1	IV
T1-T2	N3	M0	IVA
T3	Any N	M0	IVA
Any T	Any N	M1	IVB

Treatment recommendations

Stage	Recommendations
Cis	Local Excision/CO2 laser
IA	Wide local excision (WLE). Post-op RT (50 Gy) to vulva for + margin, margin <8 mm, LVSI, or depth >5 mm. [Sample lymph nodes for lesion with >1 mm depth of invasion]
IB/II	WLE + Lymph Node Dissection - Unilateral: Lateralized lesions Bilateral: Centralized lesions, lesions > 5mm deep, LVSI, High Grade RT indications are the same Pre-op chemo-RT to be considered if involvement of urethra, clitoris or rectum as margins might be difficult to obtain If Complete Response to pre-op chemoRT, consider biopsy and observe If no complete Response - resect and preserve functional outcomes
III/IVA	Pre-op chemorad or Surgery to start depending on nodal status
IVB	Palliative

SURGERY

Vulvectomy:

First choice for early stage disease. Wide Local Excision (Radical Vulvectomy) preferred for FIGO stage If involvement of adjacent structures - modified radical vulvectomy

Tumor Free Margin > 1cm is required, smaller margins correlate with higher rates of recurrence

Tumor at or close to the surgical margins < 8mm identified at final pathologic analysis - re-excision is suggested to ensure complete resection

Recurrent Disease
EBRT: 45 Gy in 25 daily fractions of 1.8 Gy in 5 weeks.
Electron Therapy if available for individualized boost: 15-20 Gy in 8-11 daily fractions of 1.8Gy
Total Dose: 60-65 Gy in 33 to 36 daily fractions.

Palliative Treatment
Photon or Electron Therapy
20 Gy in 5 daily fractions given in 1 week
30 Gy in 10 daily fractions given in 2 weeks
8-10 Gy in a single fraction for haemostasis

7.4 Endometrial Carcinoma

7.4.1 Introduction
This is predominantly a disease of old women, typically for women above 60-65 years of age. Adenocarcinoma is the commonest histological type. Risk factors for endometrial carcinoma include obesity, diabetes, high fat diet, early age at menarche, nulliparity and late age at menopause, old age and use of tamoxifen

Clinical presentation
Abnormal Uterine Bleeding for women in the post-menopausal period.

Investigations
FBP, RFT, LFTs
Ca-125
Chest Xray
CT scan (Abdomen and Pelvis) +/- MRI
Endometrial Biopsy to confirm diagnosis

STAGING
Definition of Primary Tumor (T)

T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor

T1	I	Tumor confined to the corpus uteri, including endocervical glandular involvement
T1a	IA	Tumor limited to the endometrium or invading less than half the myometrium
T1b	IB	Tumor invading one half or more of the myometrium
T2	II	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus. Does NOT include endocervical glandular involvement.
T3	III	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	IIIA	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

Definition of Regional Lymph Node (N)

N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes
N1mi	IIIC1	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to pelvic lymph nodes
N1a	IIIC1	Regional lymph node metastasis (greater than 2.0 mm in diameter) to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2mi	IIIC2	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes

N2a	IIIC2	Regional lymph node metastasis (greater than 2.0 mm in diameter) to para-aortic lymph nodes,with or without positive pelvic lymph nodes
Suffix (sn) is added to the N category when metastasis is identified only by sentinel lymph node biopsy.		

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	FIGO Stage	M Criteria
cM0		No distant metastasis
cM1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease,lung, liver, or bone) (It excludes metastasis to pelvic or para-aortic lymph nodes, vagina, uterine serosa, or adnexa.)
pM1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone), microscopically confirmed (It excludes metastasis to pelvic or para-aortic lymph nodes, vagina, uterine serosa, or adnexa.)

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	III
T3a	N0	M0	IIIA
T3b	N0	M0	IIIB
T1-T3	N1/N1mi/N1a	M0	IIIC1
T1-T3	N2/N2mi/N2a	M0	IIIC2

T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Management recommendatios.

Stage	Recommendations
All Patients	Medically operable patients should undergo Surgery. Perform TAH/BSO or radical hysterectomy if cervical stromal involvement and obtain peritoneal cytology Consider selective pelvic and paraaortic LN dissection for myometrial invasion or if grade 2–3, and include nodes from paraaortic, common iliac, external iliac, internal iliac, and obturator chains.
IA, IB	Grade 1 - Observation; Grade 2-3 or presence of other adverse features: Offer Vaginal Brachytherapy
IA, IB, II clear cell or serous carcinoma, IB High Grade	Offer Adjuvant Chemotherapy + Vaginal Brachytherapy Or Pelvic External Beam Radiation Therapy alone
III	Adjuvant Chemotherapy + RT (High Risk Disease: EBRT + VBT)
IV	Chemotherapy

Chemotherapy Regimen

Cytotoxic therapy for High Risk Disease inoperable, metastatic or recurrent disease is given with palliative intent and responses are generally of short duration.

The most active medicines are the platinum agents, taxanes and anthraccyclines. Combined regimens recommended for high-risk disease, inoperable, recurrent or metastatic disease include:

Doxorubicin and cisplatin +/- Paclitaxel

Carboplatin plus paclitaxel

Radiation Therapy

EBRT

Given as an adjuvant therapy or as a definitive therapy for inoperable disease, and palliative radiotherapy.

Pelvic radiation therapy should target the lower common iliacs, external iliacs, internal iliacs, parametria, upper vaginal, para-vaginal tissues, and pre-sacral

lymph nodes.
Adjuvant Radiation Therapy:
45-50.4 Gy in 25-28 daily fractions of 1.8 Gy given in 5-5½ weeks.

Primary Radiation Therapy:
45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks followed by Intracavitary Irradiation

Extended Field Radiation Therapy (involvement of Para-Aortic Nodes):
45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks

Brachytherapy
Vaginal Cuff (Cylinder) alone: 6Gy x 5 to vaginal surface, 7Gy x 3 or 5.5 Gy x 4 prescribed to 5mm below vaginal surface (HDR);
Vaginal Cuff (Cylinder) boost: 4-6 Gy x 2-3 fractions prescribed to vaginal mucosa

Palliative Radiation Therapy
20 Gy in 5 daily fractions
30 Gy in 10 daily fractions given in 2 weeks
8-10 Gys in a single fraction for haemostasis

7.5 Vaginal Cancer

7.5.1 Introduction
Majority are Squamous Cell Carcinoma, and are located in the upper posterior 1/3 of the vagina.
Risk factors: carcinoma in situ, HPV, chronic vaginal irritation, previous abnormal Pap smears, early hysterectomy, multiple lifetime sex partners, early age at first intercourse, current smoker, in utero exposure to DES, partner with penile cancer.

Clinical presentation
Irregular vaginal bleeding or discharge (often postcoital), followed by vaginal discharge or dysuria.

Investigations

CBC, electrolytes, BUN, Cr, LFTs
Bimanual and rectal exam, speculum and Pap smear
Colposcopy
FNA or excision of suspected inguinal nodes
Imaging: CXR, CT ± PET, and/or MRI depending on extent (but not to be used for FIGO clinical staging

STAGING

Definition of Primary Tumor (T)

T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the vagina
T1a	I	Tumor confined to the vagina, measuring ≤2.0 cm
T1b	I	Tumor confined to the vagina, measuring >2.0 cm
T2	II	Tumor invading paravaginal tissues but not to pelvic sidewall
T2a	II	Tumor invading paravaginal tissues but not to pelvic wall, measuring ≤2.0 cm
T2b	II	Tumor invading paravaginal tissues but not to pelvic wall, measuring >2.0 cm
T3	III	Tumor extending to the pelvic sidewall* and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)

*Pelvic sidewall is defined as the muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall.

Definition of Regional Lymph Node (N)

N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	III	Pelvic or inguinal lymph node metastasis

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	FIGO Stage	M Criteria
cM0		No distant metastasis
cM1	IVB	Distant metastasis
pM1	IVB	Distant metastasis, microscopically confirmed

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the stage group is…
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T1-T3	N1	M0	III
T3	N0	M0	III
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

Treatment recommendations.

Stage	Recommendations
CIS	CO2 laser or topical 5-FU or wide local excision. Close follow-up required because of multifocality and frequent progression. For recurrent cases, intracavitary (IC) brachytherapy 60–70 Gy to the entire vaginal mucosa
I (<0.5 cm thick and < 2cm, low grade	Surgery: Wide Local Excision or Total Vaginectomy with vaginal reconstruction Post-op RT for close or Positive Margins Alternative: Intra-Cavitary (IC); Treat entire vagina with 65 Gy (60-70) to surface; Boost to 90Gy with 2 cm radial margin with IC
I (>0.5 cm thick and > 2cm, high grade	Surgery: Radical Vaginectomy with Pelvic Lymphadenectomy (if upper 2/3 tumor) or inguinal lymphadenectomy (if lower 1/3 tumor) Alternative: EBRT to whole pelvis +/- inguinal node to 45 Gy. Boost to 75-80Gy with 2 cm radial margin with IC
II	EBRT to whole pelvis ± inguinal LN to 45 Gy (± midline block after 20 Gy, for non-IMRT plans).
III	EBRT to whole pelvis to 45–50 Gy (for non-IMRT plans, consider midline block after 40 Gy). If lower 1/3 involvement, treat inguinal nodes to 45–50 Gy Boost to 75-80 Gy with 2 cm radial margin with IC For parametrial and paravaginal extension, EBRT or IS boost to 65–70 Gy For parametrial and paravaginal extension, EBRT or IS boost to 65–70 Gy If fistula or high risk of fistula, options include total vaginectomy, exenteration, and repair of fistula, if possible. LND generally performed. Avoid primary RT, especially brachytherapy
Metastasis	Palliative RT +/- Chemotherapy
Recurrence	Pelvic Exenteration if no invasion of the side walls; Intracavitary Brachytherapy +/- EBRT can salvage a vaginal recurrence

Radiation therapy.

Techniques.

Simulate the patient supine with tumor and introitus markers.

Bolus on inguinal nodes may be needed (correlate with CT scan). If treating the inguinal nodes, treat patient in the frog leg position**.**

AP/PA field borders:
Superior = L5/S1 interspace (node negative patients);
Inferior = cover entire vagina and 3 cm below lowest extent of disease as marked with a radiopaque marker; - Lateral = 2 cm lateral to the pelvic brim.
If distal 1/3 vaginal involvement, lateral borders widened to include the inguinofemoral nodes (lateral = greater trochanter;
Inferior = inguinal crease or 2.5 cm below ischium;
Superolateral = anterior superior iliac spine).

NOTE:If treating inguinal nodes, techniques may be used to protect the femoral heads as described for vulvar and anal cancer.
A midline block is optional to decrease the dose to the bladder and rectum. If a midline block is not used, the brachytherapy dose must be reduced.
HDR boost dose after 45 Gy EBRT = 6 Gy × 3

Follow up
First and second years: 3 monthly check: Physical Examination
Laboratory investigations: FBP, RFT, LFT.
Imaging investigations: Chest XRay, Ultrasound (abdomen and pelvis), CT-Scan (abdomen and pelvis)
Year 3 and onward: 6 monthly follow-up - same details

7.6 Gestational trophoblastic disease

7.6.1 Introduction
It is a group of malignancies consisting of abnormal proliferation of trophoblastic tissues.

Histologic types:
Invasive mole
Choriocarcinoma
Placental site trophoblastic tumor (PSTT)
Epithelioid trophoblastic tumor (ETT)

Investigation
Serum β-hCG level

LFT, RFT, TSH, T3, T3
CXR and or CT Scan
Abdominal and Pelvic USS or CT Scan
Brain MRI
Tissue sample for histology
CSF hCG level

Clinical presentation:
Persistently raising or plateau BhCG postmolar pregnancy .

STAGING:
Definition of Primary Tumor (T)

T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to uterus
T2	II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension

Definition of Regional Lymph Node (N)
Nodal involvement in gestational trophoblastic neoplasia is uncommon (0.5%), but reportedly occurs in 6-16% of PSTTs.

Definition of Distant Metastasis (M)
The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	FIGO Stage	M Criteria
cM0		No distant metastasis
cM1		Distant metastasis
cM1a	III	Lung metastasis
cM1b	IV	All other distant metastases
pM1		Distant metastasis, microscopically confirmed

pM1a	III	Lung metastasis, microscopically confirmed
pM1b	IV	All other distant metastases, microscopically confirmed

Prognostic Factors Required for Stage Grouping
Risk Score

	Risk Score				
Prognostic Factor	0	1	2	4	Factor score
Age (years)	<40	≥40			
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy		
Interval months from index Pregnancy	<4	4-6	7-12	>12	
Pretreatment hCG (IU/mL)	$<10^3$	10^3 to $<10^4$	10^4 to $<10^5$	$\geq 10^5$	
Largest tumor size, including uterus (cm)	<3	3-5	>5		
Site of metastases	Lung	Spleen, kidney	Gastroin-testinal tract	Brain, liver	
Number of metas-tases identified		1-4	5-8	>8	
Previous failed chemotherapy			Single medicine	Two or more medicines	
Total Risk Score					

FIGO staging

Stage I – Persistently elevated human chorionic gonadotropin (hCG) levels; tumor confined to the uterine corpus

Stage II – Tumors extending to the adnexa or to the vagina, but limited to the genital structures

Stage III – Pulmonary metastases on chest radiograph, with or without uterine,

pelvic, or vaginal involvement
Stage IV – Metastatic disease outside of the lungs and pelvis and/or vagina

Risk stratification:
(FIGO)
Treatment recommendation

Stage/Score	Recommendations
Low risk :Stage I and II and III with WHO risk score below VI	Single agent: Methotrexate or Actinomycin D
High risk:Stage IV or II and III with WHO risk score above VI	Combination therapy: I.EMACO(Etoposide ,Methotrexate,actinomycinD ,Cyclophosphamide ,vincristine II.APE:Actinomicyn D,Cisplatin ,etoposide

Chemotherpy Dosages:
I.**Low risk,single Agents**
Actinomycin D or Methotrexate or .Etoposide

NOTE: Consider consolidation therapy after complete remission to prevent relapse. Use two three courses of the last effective treatment.

II.High risk , combination therapy
EMA-CO or EMA-EP

Monitoring and Follow up
Do serial measurement of BhCG at start of treatment and weekly during therapy.

Brain Metastatisis
Methotrexate,dexamethasone and prophylactic anti epileptic to control seizures Or High dose EMACO plus intrathecal methotrexate and leucovorin.
Concomitant whole brain radiation: 20-30 Gy in 2Gy daily fraction concurrently with high dose chemotherapy(MTX)

8 HAEMATOLOGICAL NEOPLASMS

Hematological malignancies is a general term referring to cancers of the hematopoietic and lymphoid tissues, such as the leukemias, lymphomas, and multiple myeloma.

Due to the wide range of hematological malignancies, there are also many modalities of treatment. The treatment of a hematologic malignancy may involve one or more of chemotherapy, radiotherapy targeted therapy, immunotherapy, and bone marrow transplantation. This section covers the following subtopics:

8.1. Hodgkin Lymphoma (HL)
8.2. Non- Hodgkin Lymphoma (NHL)
8.3. Acute Myelogenous Leukemia (AML)
8.4. Acute Lymphoblastic Leukemia (ALL)
8.5. Chronic Myelogenous Leukemia (CML)
8.6. Chronic Lymphocytic Leukemia (CLL)
8.7. Multiple Myeloma (MM)

8.1 Hodgkin lymphoma

8.1.1 Introduction

Hodgkin Lymphoma comprises about 30% of all lymphomas. The disease is characterized by scattered large multinucleated Reed-Sternberg or mononuclear Hodgkin's cells in an inflammatory background of a lymph node biopsy section.

WHO Classification 2008

Nodular Lymphocyte Predominant Hodgkin's (NLPHL) makes up 5% of all Hodgkin Lymphoma (HL) and occurs mostly in 30-50 year old males
Lymphocyte predominant (LP) cells are CD20, CD79a, CD75, bcl6 and CD45 positive. They are CD15 and CD30 negative
This is an indolent malignancy with frequent relapses. In early stage disease 10 year overall survival is >80%

Classical Hodgkin lymphoma: There are 4 morphological subtypes

Nodular Sclerosing
Lymphocyte-rich
Mixed Cellularity
Lymphocyte-depleted

Incidence peaks at 15-35 years and again in the elderly. Etiology: possibly related to Ebstein-Barr virus, particularly in HIV-positive group. Always CD30 positive and mostly CD15 positive (75-85%); can be CD20 positive in 30-40% (but usually very weakly so)

8.1.2 Work up

8.1.2.1 Baseline

CBC,
CRP/ESR,
RFT,
LFT,
LDH,
HIV,
Coagulation profile
Hepatitis panel

8.1.2.2 Diagnostic

Excision biopsy of a lymph node, if not possible, truecut biopsy for Histopathology and Immunohistochemistry.
FNAC can be used but if does not give definitive diagnosis then do excision.
Image -guided FNAC/biopsy

8.1.2.3 Additional tests

Bone marrow aspiration (BMA) +/- trephine biopsy for staging
PET-scan (If not available Gallium scan)
CT scan of neck, chest, abdomen and pelvis (Staging CT), if not available neck USS, CXR and Abdominal pelvic USS .
MUGA or Echocardiogram to assess cardiac function.

8.1.3 Staging

Lugano Classification for Hodgkin and Non-Hodgkin Lymphoma[1]

Stage	Stage description
Limited stage	
I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen)
IE	Single extralymphatic site in the absence of nodal involvement (rare in HL)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
IIE	Contiguous extralymphatic extension from a nodal site with or without involvement of other lymph node regions on the same side of the diaphragm
II bulky	Stage II with disease bulk
Advanced stage	
III	Involvement of lymph node regions on both sides of the diaphragm; nodes above the diaphragm with spleen involvement
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement or noncontiguous extralymphatic organ involvement in conjunction with nodal Stage II disease or any extralymphatic organ involvement in nodal Stage III disease Stage IV includes any involvement of the CSF, bone marrow, liver, or multiple lung lesions (other than by direct extension in IIE disease).
*Stage II bulky may be considered either early- or advanced-stage disease based on lymphoma histology and prognostic factors (see discussion of HL prognostic factors).	
**The definition of disease bulk varies according to the lymphoma histology. In the Lugano classification,bulk in HL is defined as a mass greater than one third of the thoracic diameter on CT of the chest or a mass >10 cm. For NHL, the recommended definitions of bulk vary by lymphoma histology. In follicular lymphoma, 6 cm has been suggested based on the FLIPI-2 and its validation. In DLBCL, cutoffs ranging from 5 to 10 cm have been used, although 10 cm is recommended.	
NOTE: A/B is no longer used in NHL.	

8.1.4 Prognostic factors

Unfavorable risk factors for stage 1-2 HL
Age >50 years, ESR >50mm/hr or 30mm/hr with B symptoms, Four or more separate nodal sites involved, Mediastinal mass ratio >1/3

Unfavorable risk factors for Stage 3-4 HL
Age >45 years, Male sex, Stage IV, Haemoglobin <10.5g/dl, Albumin <40 g/dl, Lymphocytes <0.6 x 10^9/l or <8%, White blood count > 15 x 10^9/l.

8.1.5 Management

8.1.5.1 NLPHL
Stage1A: involved field radiotherapy (IFRT) .
RT dose: 1.8Gy X 17 Fractions = 30.6 Gy if node excised
1.8Gy X 20 Fractions = 36Gy if disease present
More extensive and Relapse disease: manage as Classic HL
Adriamycin,Bleomycin,Vincristine and Dacarbazine(ABVD)

8.1.5.2 CLASSIC HL

Stage 1 and 2 HL Good risk
Adriamycin,Bleomycin,Vincristine and Dacarbazine(ABVD) chemotherapy if complete response (CR) for radiotherapy (RT).
If no CR give 2 more cycles and restage.

Stage 1 and 2 Poor risk
- These are patients with one or more risk factors.
- ABVD - 4 cycles then restage
- If complete response (CR) then IFRT to initially bulky areas.
- If >50% partial response (PR) give 2 more cycles, when CR achieved then IFRT to initially bulky areas
- If <50% PR or no response (NR) patient is indicated for salvage chemotherapy followed by autologous stem cell transplant.
- Patients not qualifying for ASCT: radiotherapy to residual disease and/or palliative chemotherapy.

Stage 3 and 4

ABVD X 6 cycles

If <50% PR or no response (NR), high-dose chemotherapy (DHAP: dexamethasone + high dose cytarabine + cisplatin) and autologous stem cell transplant (ASCT).

Patients not qualifying for ASCT: radiotherapy to residual disease and/or palliative chemotherapy

Patients with LVEF <50%

LVEF can be affected by cytokines released due to lymphoma ;so if no evidence of pre-existing cardiac disease one can give ABVD and recheck LVEF after 1st cycle

Substitute Epirubicin for Doxirubicin

8.1.5.2 Relapsed Classic HL (Consider bone marrow transplant, if not then palliative)

DHAP as first-line salvage – restage after 2 cycles – if CR add 2 more cycles.

DHAC as the second line.

IGEV chemotherapy as third line

Can also use other chemotherapy regimens such as ICE or MINE-ESHAP (in NHL protocol) for salvage if medicine intolerances

8.1.5.2 HL In HIV-Positive patients

Patients must be started on ARVs before initiating chemotherapy.

They need PCP prophylaxis (co-trimoxazole) even if CD4 count >200.

They are managed in the same way as HIV-negative patients.

8.1.5.3 Chemotherapy regimens

Adriamycin,Bleomycin,Vincristine and Dacarbazine(ABVD)

Salvage Chemotherapy regimens

DHAP, DHAC and IGEV , if medicine intolerance ICE and MINE-ESHAP can be used.

NOTE: Rituximab can be added to any salvage regimen.

8.1.6 Follow up

3 monthly in 1st 2 years, then 6 monthly for 3 years and annually thereafter.
FBC, LDH at each visit. TSH annually if patients had RT to neck and/or mediastinum.
CXR annually if mediastinal mass.
If relapse is suspected patients need lymph node biopsy and staging.

8.2 Non Hodgkins Lymphoma

8.2.2 Work up

History and physical examination.

8.2.3 Investigations

Blood: FBC/ RFTs / LFTs / Serum electrolytes / LDH / HIV serolog / Hepatitis B&C
Bilateral bone marrow, trephine biopsies and Immunohistochemistry:
Nodal or true-cut biopsy.
FNAC or bone marrow biopsy with flow cytometry may be sufficient to make a diagnosis in a selected few patients

Imaging :
Contrasted CT scan of neck, chest, abdomen and pelvis and if indicated, head and nasopharynx (if there is disease in these sites). If CT not available, use CXR and USS as appropriate.
PET CT can be used for initial staging and monitoring of response of NHL .
MUGA Scan or echocardiogram to assess cardiac function
Lumbar puncture and CSF cytology if CNS involvement is suspected or in NHL associated with a high risk of CNS relapse -(testicular, paranasal sinuses, breast, extradural/paraspinal mass)

8.2.4 Staging

Lugano Classification for Hodgkin and Non-Hodgkin Lymphoma[1]

Stage description	
Limited stage	
I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen)
IE	Single extralymphatic site in the absence of nodal involvement (rare in HL)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
IIE	Contiguous extralymphatic extension from a nodal site with or without involvement of other lymph node regions on the same side of the diaphragm
II bulky*	Stage II with disease bulk**
Advanced stage	
III	Involvement of lymph node regions on both sides of the diaphragm; nodes above the diaphragm with spleen involvement
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement or noncontiguous extralymphatic organ involvement in conjunction with nodal Stage II disease or any extralymphatic organ involvement in nodal Stage III disease Stage IV includes any involvement of the CSF, bone marrow, liver, or multiple lung lesions (other than by direct extension in IIE disease).
*Stage II bulky may be considered either early- or advanced-stage disease based on lymphoma histology and prognostic factors (see discussion of HL prognostic factors).	
**The definition of disease bulk varies according to the lymphoma histology. In the Lugano classification, bulk in HL is defined as a mass greater than one third of the thoracic diameter on CT of the chest or a mass >10 cm. For NHL, the recommended definitions of bulk vary by lymphoma histology. In follicular lymphoma, 6 cm has been suggested based on the FLIPI-2 and its validation. In DLBCL, cutoffs ranging from 5 to 10 cm have been used, although 10 cm is recommended.	
Note: A/B is no longer used in NHL.	

8.2.5 General Management

If bulky tumor, anticipate tumour lysis syndrome and admit the patient for first dose of chemotherapy for active hydration and diuresis, alkalinization of the urine and careful monitoring. Start allopurinol a few days before initiation of chemotherapy.

Chemotherapy +/- Immunotherapy is the mainstay of treatment of NHL

8.2.5.1 Indolent lymphomas

Follicular lymphomas

It predominantly involves lymph nodes and generally presents with advanced disease. (Male: Female ratio is 1:1.7).The bone marrow is involved in 40-70%. Patients can be relatively asymptomatic despite widespread disease. Although this is an indolent lymphoma; transformation to diffuse large B-cell lymphoma can occur; in which case the prognosis is very poor.

FLIPI - Follicular Lymphoma International Prognostic index

Poor prognostic factors :

Age >60

Stage III-IV

Number of nodal areas >4

Elevated LDH

Hb <12g/dl

Management

Grade 3 follicular lymphoma is treated like diffuse large B-cell lymphoma(DLBCL)

Asymptomatic patients with grade 1 and 2 FL can be eligble for watchful waiting. Single-agent Rituximab is an option.

Stage 1 and 2: can be treated with involved node radiotherapy or R-CHOP/ R-CVP followed by RT

Symptomatic patients, those with masses which threaten to cause obstruction, and those with extensive bone marrow involvement require systemic treatment. (R-CHOP X6 cycles).

Poor response, progressive disease on chemotherapy or relapse may need rebiospy

Non-responders

Palliative chemotherapy with CMV/ steroids/ chlorambucil
Palliative radiotherapy as required
Early relapse within 2 years: Fludarabine
Relapse more than 2 years: repeat R-CHOP

MALT lymphoma

It comprises 7-8% of B-cell lymphomas. The GI tract is the commonest site of involvement with the stomach being the most common location. Usually it is associated with chronic inflammation due to Helicobacter pylori.
Most patients present with stage 1 or 2 disease. 2-20% have bone marrow involvement (more common in lung and ocular Malt).

Management

Helicobacter eradication essential in gastric Malt
Repeat endoscopy 3-6months.
Radiotherapy: It is a radiosensitive tumor. radiotherapy post chemo for orbital or gastric malt especially if residual disease after chemo (30-36Gy)
For RT failures , Chemotherapy is an option: R-CHOP.
Relapsed or refractory disease is managed like low grade follicular lymphoma

Other Indolent B- cell Lymphomas

These include small lymphocytic lymphoma (SLL), nodal marginal zone and splenic marginal zone lymphoma
They are generally managed like low grade follicular lymphomas except for splenic marginal zone lymphoma where splenectomy is recommennded.

Indolent T-cell Lymphomas: Mycosis fungoides

This is a primary cutaneous T-cell lymphoma (CTCL), accounting for 50% of all CTCL.
Mycosis Fungoides (MF) tends to run an indolent clinical course with slow progression over years or decades.

Clinical presentation.

Longstanding history of skin lesions which tend to be extensive and consist of patches, plaques and/or nodules . In advanced stages other organ involvement may occur including lymph nodes, spleen, liver, lung or blood. Bone marrow

involvement is very rare.

Workup

Physical examination including whole skin and lymph nodes, document extent of skin involvement

FBP/RFT/LFT/LDH.

Sezary screen in peripheral smear

Imaging: CXR in stage T1 or limited T2. CT neck, chest, abdomen, pelvis for ≥T2

Bone marrow biopsy not required for staging unless suspected due to blood involvement

Biopsy of suspicious lymph nodes may be indicated

Mycosis Fungoides Staging

Treatment

Topical corticosteroids: for localised or generalised skin involvement (stage IA, IB, IIA, IIB and III except if blood involved),

Systemic therapies for skin involvement not responding to skin-directed therapy and for systemic disease including Sezary syndrome.**Options include**:

Retinoids

Interferons

Methotrexate (low dose)

Systemic therapies for aggressive/advanced disease options include:

Gemcitabine

Liposomal doxorubicin

Second line :

Chlorambucil

Etoposide

Cyclophosfamide

Methotrexate (>100mg/week)

8.2.5.1 Aggressive lymphomas

Diffuse Large B-Cell Lymphoma

This is a neoplasm of large B lymphoid cells that has a diffuse growth pattern. Typical immunohistochemical profile is CD20+, CD45+ and CD3- with a relatively high Ki67.

Prognosis

International Prognostic Index

Based on number of the following risk factors:
Age > 60 years
Stage III and IV disease
>1 Extranodal sites
ECOG performance status >2
Elevated serum lactic dehydrogenase

Management

The initial treatment of DLBCL depends on the extent of disease, generally classified as having either limited stage disease or advanced stage disease based upon whether or not the tumor can be contained within one irradiation field:

Stage 1 and 2 with normal cardiac function

Patients with IPI of 0 with no bulky disease: R-CHOP alone OR R-CHOP followed by radiotherapy.
Patients with IPI>0 and/or bulky disease: R-CHOP followed by involved feld radiotherapy (IFRT).
Stem cell transplation is a subsequent option in some patients.

Stage 3 and 4 with good performance status and normal cardiac function

- R-CHOP in CD 20 positive DLBCL.
- Patients with testicular , sinus,BM, or epidural involvement should receive concomitant IT methotrexate and/or cytarabine.
- Consider RT to any site of bulk disease at diagnosis.
- Restage after 4 cycles with CT Scan and BMA if BM was initially involved.
- If CR after 4-5 cycles go to 8 cycles
- If >50% PR go to 8 cycles and repeat CT-scan and/or BMB
- If <50% PR for salvage therapy if patient qualifies for stem cell transplant(SCT)
- If not eligible for SCT consider palliative chemotherapy with CMV and palliative radiotherapy to residual disease

NOTE: If poor cardiac function omit anthracycline and treat with Etoposide (VP16), Cyatarabine and Methyprednisolone.

Radiotherapy

Involved field radiotherapy

Patients with stage 1 and 2 should be considered for IFRT after attaining CR.
Dose is 36Gy in 1.8Gy fractions
3D planning: tumour volume consists of previously involved sites of disease + 1-2cm margin

Palliative radiotherapy

Consider "radical palliation" if patient has a good performance status and limited residual disease but is not for transplant or has failed salvage chemotherapy
For "radical palliation" can do 3D planning to 36-40Gy
Patients with poor PS and disease not responding to or growing on chemotherapy for 2D planning and 3GyX10Fractions or 4GyX5 Fractions
Can also give a single fraction of 8Gy if very poor PS

Primary DLBCL of CNS

<1% of NHL and 2-3% of all brain tumours
Includes all primary CNS or intraocular DLBCL and excludes immunodeficiency-associated CNS lymphomas.
Are usually EBV-negative (but positive in HIV-associated CNS lymphomas)
Median age 60 years, mostly males
60% are located supratentorially and 20-40% have multiple lesions.
Dissemination to extraneural sites is very rare
Previously had a very poor prognosis, but this has improved with the use of high-dose methotrexate

Management of CNS lymphoma

- No patient should be treated for primary CNS lymphoma without definitive cytologic proof of diagnosis(csf cytology,brain biopsy or vitrectomy)
- HIV test, full lymphoma workup to exclude systemic disease and testicular involvement, and a complete neurological examination including a mini-mental test if possible
- >40% have leptomeningeal involvement occurs at diagnosis, so if no

contraindications, do LP and send CSF for flow cytometry as well as cell count, protein and glucose levels. Intratechal chemotherapy at the same time of LP for cytology.

- Do not do LP within a week of biopsy to avoid false positives.
- Primary CNS lymphoma is staged as 1E according to Anne Arbor but prognosis can be assessed according to the International Extranodal Lymphoma Study Group using the following prognostic features:

Age>60 years, ECOG PS>1, Elevated LDH, High CSF protein concentration and tumour located within deep regions of brain (periventricular, basal ganglia, brainstem, cerebellum)

- Standard chemotherapy regimens like CHOP are not effective possibly due to poor penetration of the blood-brain-barrier (BBB).
- Methotrexate is the single most effective chemotherapy for primary CNS lymphoma.
- Radiatherapy alone is effective but with a low median survival of 18 months.
- Combination of chemotherapy and radiotherapy give a longer survival benefit but at the expense of severe toxicities, particularly dementia.
- Corticosteroids should be used carefully at first because they might make biopsy difficult and also reduce penetration of chemotherapeutic agents across the BBB.

Primary CNS lymphoma in HIV-positive patients

Require ARVs
Manage in the same way as HIV-negative patients
CNS involvement together with systemic disease CHOP plus IT methotrexate

Adult Burkitt Lymphoma

This generally has poor prognosis, unlike BL in children.
The standard of care for BL has yet to be defined
Some of the regimens used include (plus Rituximab in some centers) :
CODOX-M plus IVAC(Magrath regimen)
CALGB 9251
HyperCVAD
Dose-Adjusted EPOCH

Mantle cell lymphoma

B-cell neoplasm with monomorphic small to medium sized lymphoid cells
CD5, BCL2 and cyclin D1 positive; CD10 and BCL6 negative
The t(11;14)(q13;q32) translocation is seen in nearly all cases and many other mutations are commonly
present particularly in the more aggressive variants
3-10% of all NHL
Median age 60, male predominance
Patients generally present with advanced disease
Lymphadenopathy, hepato-splenomegally and bone marrow involvement
Extranodal sites include GIT and Waldeyer ring
Patients often have peripheral blood spill and sometimes lymphocytosis mimicking prolymphocytic
leukaemia at presentation
Median survival 3-5 years
Is incurable, so patients are offered allogeneic stem cell transplant in first remission
High Ki67 is an adverse prognostic factor
Treat with R- CHOP / R-CVP
Restage after 4 cycles – if responding treat until clear or consider SCT once minimal residual disease
remaining particularly in blastoid variety

Aggressive T-Cell Lymphomas

This heterogeneous group of rare lymphomas is generally more aggressive than DLBCL. Patients require the standard lymphoma workup with the provision that they receive treatment relatively urgently. With a few exceptions, first-line therapy is CHOP with Etoposide (CHEOP).

Lymphomas in HIV

All subtypes of NHL occur more commonly in the HIV-positive population (60-200 times more);
although the incidence has declined dramatically since the widespread use of HAART

These aggressive B-cell lymphomas are considered AIDS-defining according to the WHO:
Lymphomas which also occur in immunocompetent patients:
DLBCL
Burkitts lymphoma
Primary CNS lymphoma
Lymphomas occurring more specifically in HIV-positive patients:
Plasmoblastic lymphoma
Lymphoma arising in HHV8-associated Multicentric Castleman Disease
Primary Effusion lymphoma
NOTE: Hodgkins and other lymphomas are not considered AIDS-defining but HL has become the commonest
non AIDS-defining malignancy

Chemotherapy
Recommended Chemotherapy Regimens in Lymphoma
Cyclophosphamide,Vincristine and Prednisolone(CVP)
Cyclophosphamide,Adriamycin,Vincristine and Prednisolone (CHOP)
CHOEP **-** Etoposide used for aggressive T-cell lymphomas
Rituximab in either of the above regimen if CD 20 positive.

Intrathecal Chemotherapy
Methotrexate
Ara C

CMV
Palliative regime for indolent and aggressive NHL

FC (Fludarabine and Cclophosphamide).
Used as second-line for indolent B-cell lymphomas

High dose Methotrexate for CNS Lymphomas
Maintain urine output and alkalinisation during and after methotrexate infusion
Start leucovorin rescue at 24 hours after methotrexate infusion

DHAP + rituximab if CD 20 positive.
This is our most commonly used salvage regimen for patients with relapsed or refractory disease
(aggressive or indolent B-cell lymphomas as well as aggressive T-cell lymphomas) being considered for
stem cell transplant.

ICE- Ifosfamide, Carboplatin, Etoposide, Mesna.
For patients not responding to DHAP

ESHAP - Etoposide ,Methylprednisolone , Cisplatinum, Cytarabine
If complete remission with MINE consolidate with ESHAP.

Tumor Lysis Syndrome
Lymphoblastic lymphoma/leukaemia and Burkitts lymphoma are at greatest risk of TLS
DLBCL with bulk and CLL with high WBC count are at moderate risk
It occurs with the first cycle of chemotherapy but it may occur when patients start salvage chemotherapy as well
Biochemical features of TLS:

- Hyperuricaemia
- Hyperkalaemia
- Hyperphosphateamia
- Hypocalcaemia

Management
Anticipate and prevent TLS
Start Allopurinol
Do baseline bloods – RFT, urate, Ca, Mg, Ph, K
Prehydrate, give citrosoda
Monitor labs 6 hourly for high risk patients and 12 hourly for moderate risk.

8.2.6 Follow up
3 monthly for 2 years then 6 monthly for 2 more years followed by annual evaluation.

FBC and LDH at each visit. Other blood tests as required. TSH annually if patients had RT to neck and/or mediastinum
CXR annually if initial disease in mediastinum. Or Chest CT-Scan
Abdominal Pelvic uss or CT-Scan
If relapse is suspected patients need a lymph node biopsy and full staging on relapse

8.3 Acute Myeloid Leukemia (AML)

It is primarily a disease of later adulthood with an increasing incidence with age. The median age at diagnosis is 65 years with a slight male preponderance. Outcome varies greatly according to age at diagnosis due to disease and patient features. Untreated AML is a uniformly fatal disease with a median survival of 11-20 weeks.

8.3.1. Diagnosis and Work-up

All patients suspected of leukemia should do peripheral blood film and undergo bone marrow studies incorporating morphological assessment, flow cytometry, immunophenotyping, cytogenetic and molecular evaluation.
Ancillary Tests: FBP,liver, kidneys, coagulation and cardiac function.
Blood group and human leukocyte antigen (HLA) typing of patient and family should be done as soon as possible in transplant eligible patients.
+/- Lumbar puncture (LP)

8.3.2. Classification

There are four main groups of AML recognized by the WHO classification system[3,4.]:
AML with recurrent genetic abnormalities (11% of cases),
AML with myelodysplasia-related features (6% of cases),
Therapy-related AML and myelodysplastic syndrome (MDS) (2% of cases)
AML, not otherwise specified (81% of cases)
Acute Myeloid Leukemia-Prognostic Factors.

Age, Zubrod performance status (PS)

PS	Definition
0 or 1	Minimal symptoms
2	Between 1 & 3
3	In bed 50-100% of time
4	Bed ridden

Hematopoietic cell transplantation comorbidity index (HCT-CI):

Cytogenetics (20 metaphase):

Description
Favorable
Intermediate
Adverse

Status of NPM, FLT3 and CEBPA genes:

Status
NPM1 mutation in absence FLT3 internal tandem duplication
Bi allelic CEBPA mutation
FLT3 internal tandem duplication

8.3.3. Treatment Approaches in AML

The initial goal of therapy for AML is to achieve a complete remission, given that a complete remission with currently available therapy is requisite, although not sufficient for a cure. It is the sole outcome currently associated with improved survival.

Chemotherapy is the mainstay of treatment. Poor performance status and comorbid medical conditions, in addition to age, are factors which influence the ability of an individual to tolerate induction therapy.

Induction phase

(CYTARABINE + DAUNORUBICIN)) Regimen:

Consolidation phase (if in remission i.e. BMA with blast cells ≤ 2%)
HiDAC Regimen
Thereafter: Consider consolidation or Stem Cell Transplant (SCT)

Relapsed AML
FLAG-IDA Regimen

Others:
Palliative single-dose regimen
Low-dose cytarabine (LD-AraC)

Azaticidine
-also an analogue of cytidine used in AML

Management of APML

- APML represents a medical emergency.
- Treatment should be started as soon as the diagnosis is suspected based on cytologic criteria, and before definitive genetic, cytogenetic, or immunostaining confirmation of the diagnosis has been made.
- The treatment of APL is also comprised of Remission induction, Consolidation and Maintenance.
- ATRA is an important agent in all three phases of APL treatment. Achievement of complete hematologic and molecular remission requires the addition of ATO or chemotherapy (anthracyclines, hydroxyurea etc.)
- Risk stratification based on WBC count:
- Low- or intermediate risk : WBC $\leq 10 \times 10^9$/L)
- High risk : WBC > 10×10^9/L

N.B. Disseminated coagulation and differentiation syndrome are of particular concern in APML.

1. Disseminated intravascular coagulation
   Transfusions of platelets and cryoprecipitate to maintain the platelet count above 30,000 to 50,000/microL or higher and the plasma fibrinogen concentration above 150 mg/dL.
   Immediate initiation of treatment with ATRA followed quickly by

chemotherapy.

2. Differentiation syndrome
   Treatment with dexamethasone (10 mg intravenously every 12 hours for three or more days), along with temporary cessation of ATRA if severe symptoms were present

8.4. Acute Lymphoblastic Leukemia (ALL)

Acute Lymphoblastic Leukemia (ALL) is a highly aggressive hematological - malignancy resulting from the proliferation and expansion of lymphoid blasts in the blood, bone marrow and other .

It has a bimodal distribution with an early peak in children 4 – 5 years old followed by a second peak at ~ 50 years of age (Fullmer, et al 2010) with the worldwide incidence being ~ 1 – 4.75/100,000 individuals with a male:female prevalence of roughly 1·3:1.

It is the most common childhood acute leukemia accounting for ~ 80% of the pediatric leukemias but contributing to only 20% of adult leukemias. Although significant progress has been made in treating adult ALL the overall survival amongst adults 18 to 60 years old is only 35% in contrast to childhood ALL in which overall survival at five years is more than 80%.

8.4.1. Diagnosis and Work-up

- Peripheral blood film, bone marrow studies incorporating morphological assessment, immunophenotyping, cytogenetic +/- FISH and molecular evaluation.
- For B-cell ALL, results of BCR-ABL by PCR or t(9;22) by cytogenetics/FISH should be available within 5 days as this will influence the induction treatment regimen used.
- Patients with failed cytogenetics for B-cell ALL should have molecular/FISH testing for BCR-ABL (if not yet done) and MLL rearrangement.
- Patients for whom anthracycline based treatment is contemplated should receive a cardiac evaluations e.g. MUGA scan or echocardiogram or cardiac MRI.
- Transplant – eligible patients and their siblings should be HLA typed.

8.4.2. Classification and Prognostication

Patients should be classified as having B-cell or T-cell ALL based upon immunophenotyping results.

Pre-treatment risk stratification should be ascertained for all patients using age, WBC and cytogenetics/FISH and/or molecular studies.

Post-treatment risk stratification should include the outcomes of minimal residual disease assessment using either flow cytometry or PCR.

8.4.3. Treatment approaches in ALL

In general, the treatment of ALL is complex consisting of several different chemotherapy cycles and, for some patients, stem-cell transplantation.

The following is the recommended regimen:

HYPER-CVAD/MTX-ARA-C Regimen:
Cyclophosphamide / Mesna / Vincristine / Doxorubicin / Dexamethasone
Methotrexate / Cytarabine / Leucovorin

8.5. Chronic Myelogenous Leukemia (CML)

Diagnosis and Work up:

FBP/ RFT/LFT/ Peripheral smear/ BMA cytology/ FISH or RT qPCR
CXR
Abd Pelvic USS

Treatment:

Hydroxyurea if BCR/ABL gene mutation negative.
Imatinib Mesylate is the first line for BCR/ABL gene positive.
Other lines of treatment include: Dasatinib/ Bosutinib/ Nilotinib and Ponatinib.

8.6. Chronic Lymphocytic Leukemia (CLL)

CLL is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent but mature lymphocytes.

Onset is insidious, and sometimes diagnosed incidentally after a blood cell count done for another purpose. About 25-50% of patients will be asymptomatic on presentation.

8.6.1. Diagnosis

CBC and peripheral smear

Peripheral blood flow cytometry is the most valuable test to confirm a diagnosis of CLL.

Other helpful tests include bone marrow biopsy and ultrasonography of the liver and spleen.

Immunoglobulin testing may be indicated for patients in recurrent infections.

8.6.2. Staging

Two staging systems are used for CLL.

a).The Rai-Sawitsky staging system

Low risk (formerly stage 0) – Lymphocytosis in the blood and marrow only

Intermediate risk (formerly stages I and II) – Lymphocytosis with enlarged nodes in any site or splenomegaly or hepatomegaly.

High risk (formerly stages III and IV) – Lymphocytosis with disease-related anemia (hemoglobin < 11 g/dL) or thrombocytopenia (platelets < 100 x 10^9/L)

b).The Binet staging system :based on the number of lymph node groups involved:

Stage A – Hemoglobin 10 g/dL or higher, platelets 100 × 10^9/L or higher, and fewer than three lymph node areas involved.

Stage B – Hemoglobin and platelet levels as in stage A and three or more lymph node areas involved

Stage C – Hemoglobin less than 10 g/dL or platelets less than 100 × 10^9/L, or both

8.6.3. Management

Patients with early-stage CLL are not treated with chemotherapy until they become symptomatic or evidence of rapid progression of disease.

Fludarabine is the most commonly used first-line therapy in CLL. In our setup,single agent chlorambucil is an alternative.

Combination regimens have shown improved response rates in several clinical trials and include the following:

Fludarabine, cyclophosphamide, and rituximab (FCR)

Pentostatin, cyclophosphamide, and rituximab (PCR)

Fludarabine, cyclophosphamide, and mitoxantrone (FCM)
Cyclophosphamide, vincristine, and prednisone (CVP)
Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
In some cases, most often for relapsed disease, targeted therapies such as Ibrutinib and Obinutuzumab are used.

8.7 Multiple Myeloma (MM)

MM is a progressive plasma cell tumor in which an initially stable clone becomes malignant via a multistep process
MM should be differentiated from other plasma cell disorders including Monoclonal Gammopathy of Undetermined significance (MGUS) and Smoldering MM , both of which do not require treatment.
Solitary plasmacytoma is a rare disorder that is similar to multiple myeloma. People with solitary plasmacytoma do not have myeloma cells in the bone marrow or throughout the body. Instead, they have a tumor composed of plasma cells that is restricted to a single area of the body.
Older age is the primary risk factor for MM, but obesity also increases risk.
MM is incurable, but treatment advances in the past decade have more than doubled the duration of survival

8.7.1. Indications for Treatment

Patients who have any of the following end-organ damage attributable to the underlying plasma cell disorder have MM and require therapy:(CRAB criteria)
anemia (i.e., hemoglobin <10 g/dL),hypercalcemia (ie, serum calcium >11 mg/dL [>2.75 mmol/liter]),renal insufficiency (ie, creatinine clearance <40 mL/min or serum creatinine >2 mg/dL) or bone lesions (ie, one or more osteolytic lesions on skeletal radiography, CT, or PET]/CT.

Otherwise asymptomatic patients with one of the following biomarkers are also considered to have MM and require therapy:
≥60 percent clonal plasma cells in the marrow involved/uninvolved free light chain (FLC) ratio of 100 or more; or more than one focal bone lesion on MRI.

8.7.2. Work up

FBP with peripheral morphology, creatinine, serum calcium, albumin, LDH, beta-2 microglobulin, and C-reactive protein, serum free monoclonal light chain (FLC) measurement, serum protein electrophoresis (SPEP) with immunofixation and quantitation of immunoglobulins, urinalysis and urine electrophoresis
Bone marrow aspiration and biopsy (with immunophenotyping, conventional cytogenetics, and FISH.) Repeat bone marrow could be necessary to monitor response or disease progression.
Plain radiographs(skeletal survey), CT/PET CT/MRI

Revised International Staging System (RISS) Adopted by the International Myeloma Working Group

RISS stage group	Factors
Stage I	Serum β2-microglobulin <3.5 mg/L And serum albumin ≥3.5 g/Dl and no high-risk cytogenetics*and Normal LDH
Stage II	Not stage I or III
Stage III	Serum β2-microglobulin ≥5.5 mg/L And high-risk cytogenetics* and/or high LDH

*High-risk cytogenetics consist of one or more of the following: del17p, t(4;14), or t(14;16).

Note: The following variables must be collected at the time of diagnosis for staging of multiple myeloma according to the RISS: serum β2-microglobulin, serum albumin, serum LDH, and FISH results from the bone marrow specimen for t(4;14), t(14;16), and del17p.

8.7.3. Management

In resourceful setup, chemotherapy followed by autologous hematopoietic cell transplantation (HCT) is the standard of care for most patients. Patients should be risk-stratified whenever possible.

Chemotherapy:

Patients with active myeloma or asymptomatic ones meeting the aforementioned criteria are often given a combination of 2 or 3 medicines. The medicines chosen depend on the patient's health (including their kidney

function) and whether a stem cell transplantation is planned.
Refer the table below for the commonly used regimens.

Radiation therapy

Pain control of lytic lesions that are refractory to systemic therapy, treatment of spinal cord compression from plasmacytoma and primary treatment of solitary plasmacytoma.

Palliation of lytic bone lesions : 20 to 30 Gy in 5 to 10 fractions while higher doses are required for the treatment of solitary plasmacytoma or spinal cord compression

For solitary plasmacytoma of bone radiation(curative) dose of > 45 Gy in 2 Gy/# with 2-3cm margin.

For spine radiotherapy include one vertebra above and one below the involved vertebrae

Bisphosphonates therapy and supportive care

Patients with one or more lesions on skeletal radiographs and those with osteopenia should be given bisphosphonate therapy.(E.g. Zoledronic acid 4mg IV 4-weekly usually for two years).An oral alternative is Alendronic acid 70 mg weekly.

Beware of for toxicities of bisphosphonates ,in particular renal insufficiency and osteonecrosis.

Ensure adequate hydration and analgesia

Transfusion and antibiotics when indicated

Some of the major treatment regimens in MM		
Regimen	Commonly used regimen	Remark
Melphalan-prednisone (4-day schedule) ± lenalidomide	Melphalan 0.18 mg/kg/day oral days 1 -4 Prednisone 2mg/kg /day oral days 1-4 Repeated every 4- 6 week for 6 -9 months	-Avoid Melphalan based regimen in candidates for HCT -Melphalan dose should be adjusted in renal insufficiency
Thalidomide-Dexamethasone	Thalidomide 200mg oral days 1-28 Dexamethasone 40mg oral days 1,8,15,22 Repeated every 4 week	High risk of thrombosis(among others) with thalidomide
Lenalidomide-Dexamethasone	Lenalidomide 25mg oral days 1-21 every 28 days Dexamethasone 40mg oral days 1,8,15,22 Repeated every 4 week	
Bortezomib-Dexamethasone	Bortezomib 1.3mg/m^2 IV days 1,8,15,22 Dexamethasone 20mg on day of and day after Bortezomib(or 40mg day 1,8,15,22) Repeated every 4 week	(Bortezomib-Melphalan Prednisone) / (Bortezomib- Thalidomide Dexa) are also used
Melphalan-Prednisone-Thalidomide	Melphalan 0.25mg/kg oral days 1-4(use 0.20mg/kg/day oral days 1-4 in patients above 75 years) Prednisone 2mg/kg oral days 1-4 Thalidomide 100-200mg oral days 1-28(use 100mg dose in patients > 75) Repeated every 6 week	
Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD)	Cyclophosphamide300mg/m^2 orally on days on days1,8,15,22 Bortezomib 1.3mg/m^2 IV days 1,8,15,22 Dexamethasone 40mg day 1,8,15,22 Repeated every 4 week	Omit day 22 if counts are low or when the regimen is used as a maintenance therapy
Rarely used(less effective, more toxic)		

9 HEAD AND NECK CANCERS

9.1 Introduction

Cancer of the Head and neck include the following; the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, salivary glands, and thyroid. This document contains guidelines for the management of head and neck cancer by site, as well as guidelines for management of an occult primary.

9.1.2 Epidemiology

- Worldwide, head and neck cancer accounts for more than 550,000 cases and 380,000 deaths annually.
- In Tanzania there is no national data about Head and neck cancers but data at Ocean Road Cancer Institute reports that Head and neck cancer contribute about 7% of all cancers.
- In 2005 Ocean Road Cancer Institute received around 174 cases, which kept increasing to 483 in 2016.

9.1.3 Approach to Neck mass

Head and neck cancer may present with a neck mass due to lymph node metastases, with or without findings from the primary disease site. However, the differential diagnosis of a neck mass is broad and includes other malignancies, such as lymphomas, as well as infectious or inflammatory etiologies.

The preferred initial diagnostic approach for a suspicious neck mass is fine-needle aspiration (FNA) which provides a useful guide on the next line of management. Open biopsies are reserved for FNA reported as likely lymphoma, in ulcerative lesions, or if repeated FNA is not conclusive. Open biopsy for metastatic disease is not recommended.

Nasopharyngeal Cancer

9.2.1 Introduction

Nasopharyngeal carcinoma is the predominant tumor type arising in the epithelium of the nasopharynx, a narrow tubular passage behind the nasal

cavity. Frequently it originates from the pharyngeal recess, the fossa of Rosenmuller. It differs from other head and neck squamous cell carcinomas in epidemiology, histology, natural history, and response to treatment.

Nasopharyngeal carcinoma has a bimodal distribution, with the first peak in late adolescence or early adulthood (ages 15-24 years) and the second peak later in life (4^{th}-5^{th} decade). Patients are more likely to present with a neck mass than symptoms from the primary site. It is strongly associated with EBV, smoking and alcohol. This document addresses the most common histology-Squamous Cell Carcinoma, other rare histologies (eg lymphoma) will be addressed elsewhere.

9.2.2 Work up

Clinical Presentation: Neck mass, unilateral hearing loss, tinnitus, nasal obstruction, epistaxis and cranial nerve palsies.

Diagnosis: History and Physical exam: A thorough history and physical examination is paramount in diagnosis of nasopharyngeal carcinoma.

Imaging:
Chest X-ray
Abdo/pelvic Ultrasound (Liver metastasis)
Head and neck CT scan and/or MRI
Nasopharyngoscopy
Bone scan

Pathology: Definitive diagnosis is confirmed by endoscopic guided biopsy of the primary tumor. Immunohistochemistry may be needed to further confirm the diagnosis.

9.2.3 Staging and Risk Assessment

Staging is based on the clinical presentation and Physical examination
Imaging reports (Endoscopy, CT Scan/MRI etc)

TNM Staging system:

AJCC TNM Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Tumor 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

N Category	N Criteria
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

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

9.2.4 Management

9.2.4.1 Surgery

Due to deep location of nasopharynx, and anatomic proximity to critical structures, radical surgery is typically not used.
Role of surgery is initially for biopsy for histological confirmation
It may also be used for management of the neck for persistently enlarged lymph nodes

9.2.4.2 Radiotherapy and Chemotherapy

Mainly treated by Radiotherapy either alone or in combination with chemotherapy.

Stage I: Radiotherapy alone to primary disease and neck

Stage II-IVB: Concurrent chemotherapy and radiation to the primary disease and neck. Adjuvant chemotherapy with Cisplatin/5FU or Carboplatin/5FU.

Stage IVC: Palliative care (which may include chemotherapy and radiotherapy)
Induction chemotherapy can be considered for stage III-IVB if delays are anticipated in initiation of concurrent chemotherapy and radiation or where there is a bulky disease that needs downstaging.

Note: If induction chemo not given, adjuvant chemotherapy should be given if can be tolerated by the patient.
Local Recurrence: Chemotherapy, surgery or re-irradiation.

9.2.4.3 Radiotherapy details

Radiation therapy (RT) is the mainstay of first-line local treatment for early stage nasopharyngeal carcinoma. For more advanced disease, concurrent chemoradiation reduces the rate of distant metastasis, and improves local control and overall survival compared with RT alone.
Dental review and clearance (2 weeks) prior to RT.

Simulation (3D)

Set up the patient in supine position with the head extended.

The immobilization device should include at least the head and neck mask on S-frame.

If possible, shoulders should also be immobilized to ensure accurate patient setup on a daily basis.

A bite block can be placed during simulation and throughout radiation to push the tongue away from the high-dose nasopharynx region.

CT simulation using 3 mm thickness with IV contrast should be performed to help guide the GTV target and nodes. Where no CT scan, conventional simulator can be used.

3D Conformal Radiotherapy

Suggested target volumes at the gross disease region

Suggested target volumes at the high-risk subclinical region

Radiation dose for 3D — External beam RT typically is given to a total dose of 70 to 72 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks. A similar dosing schedule is used for more advanced disease, with 66 to 70 Gy to involved lymph nodes.

In patients with N0 neck, it may be safe to cover the upper neck down to level III and to omit level IV and supraclavicular nodes.

Target Volume for 2D RT

In places where 3DCRT is not available, 2D can be use but the entire prescription dose used in 3D cannot be applied without exceeding tissue tolerances.

Conventional Radiation Fields (2D)

Fields arrangement

Two lateral opposing fields with conedowns off the spinal cord at 42-45 Gy

Matched to lower direct anterior neck field with spinal cord blocking

Lateral fields borders

Superior: generously cover sphenoid sinus and base of skull.
Inferior: match at plane above true vocal cords (to block larynx in AP field).
Posterior: spinous processes. At 42-45 Gy field is truncated off spinal cord and electrons are used on posterior neck.
Anterior: 2–3 cm anterior to tumor (and include pterygoid plates and posterior 1/3 of maxillary sinuses).

Direct anterior neck field border

Superior border: Is the inferior border of the lateral fields – start with small cheater block on spinal cord then at 42-45 Gy use full midline cord block.
Inferior border: Is the head of clavicle
Lateral border: outer 2/3 of the clavicle OR could use: where ribs cross the clavicle
Note: If supraclavicular nodes are involved add a mediastinal 8 cm wide T field with inferior border 5 cm below the head of the clavicle.

Radiation dose 2D — External beam RT typically is given to a total dose of 60 to 66 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks.

Chemotherapy details:
Concurrent chemotherapy:
Platinum based mostly Cisplatin

Induction Chemotherap

For patients with advanced nasopharyngeal carcinoma - PF or TPF (Taxane, Platinum and 5 FU)

Adjuvant Chemotherapy:

In curative intent concurrent chemorad is indicated with Cisplatin / 5FU
If induction chemotherapy was not given then adjuvant chemotherapy is recommended.

Post treatment Follow up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow-up includes periodic examination of the nasopharynx and neck, assessment of cranial nerve function, and evaluation of systemic complaints.

Nasopharyngeal carcinoma has a greater propensity to recur later than head and neck cancers arising in other sites.

Bone is the most frequent site for first distant metastases, followed by liver and then lung.

Patients to be followed every three months for the first two years, every six months for years 3 to 5, and annually thereafter. An annual chest radiograph is indicated, although other experts suggest reimaging only as indicated by signs and symptoms

Treatment of Recurrent or Metastatic disease:

The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy). Unless otherwise specified, regimens listed below can be used.

Combination therapy

Cisplatin or Carboplatin/Docetaxel or Paclitaxel.

Paclitaxel/ Cisplatin/ 5-FU
Cisplatin/ gemcitabine, Gemcitabine/ vinorelbine

Single agents

Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5-FU, Methotrexate, Gemcitabine and Capecitabine.

Supportive care

Nutritional management including assessment, counseling and supplementary

feeding (eg gastrostomy) is very important in nasopharyngeal cancer.
This assessment should be done before any treatment as many patients will lose weight as a result of their disease, and treatment related toxicities.
Dental care: Dental clearance and tooth extraction if indicated should be done 2 weeks prior to radiotherapy.
Fungal infections should be managed accordingly using Fluconazole/ nystatin etc.
Oral care: using NaHCO3 and Mucaine gel (for pain) should be done during radiotherapy.
Speech and swallowing therapy should be arrange

9.3 Laryngeal Cancer

9.3.1 Introduction

Laryngeal cancer is one of the most common cancers of head and neck. World wide laryngeal cancer cases are estimated to be around 238,000 and around 106,000 die annually. Laryngeal cancer is predominately found in men and mostly in those with history of tobacco smoking and alcohol intake.
Larynx is divided into three major anatomic regions; Supraglottis, Glottis and Subglottis.Tumors from these sub-regions are staged differently and management in terms of radiation slightly differ. There is no screening for Laryngeal cancer.

9.3.2 Clinical Presentation

- Hoarseness
- Stridor
- Difficulty in breathing
- Neck mass
- Odynophagia
- Cough

9.3.3 Diagnosis

History and Physical exam: A thorough history and physical examination is paramount in diagnosis of Laryngeal carcinoma. The physical exam includes Laryngoscopy.

Imaging:
Chest X-ray
CT scan and/or MRI of the head and neck.
Laryngoscopy

Pathology: Definitive diagnosis is confirmed by laryngoscopy-guided biopsy of the primary tumor. Fine needle aspiration of a neck mass may also be used.

Staging and Risk Assessment
Staging is based on the following;
The clinical presentation and Physical examination
Imaging reports (Laryngoscopy, CT Scan/MRI etc)

Table AJCC TNM staging;
T stage for supraglottis.

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area,preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g.,trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

T stage for Glottis.

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g.,trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

T stage for Subglottis.

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced

T4a	Moderately advanced local disease Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–);or metastasis in any lymph node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

9.3.5 Management

9.3.5.1 Supraglottic

Stage I and II

Primary site: Where surgery capacities are available open partial laryngectomy or trans oral laser excision. Otherwise these patients will be treated with radiotherapy alone.

Neck: Radiotherapy or surgery depending on treatment of primary site.

Stage III-IVB

Concurrent Chemoradiation

Total Laryngectomy and neck dissection. Adjuvant radiotherapy or chemo radiotherapy is considered depending on the surgical adverse effects.

9.3.5.2 Glottic

Stage I and II

Primary site: Where surgery capacities are available open partial laryngectomy or trans oral laser excision. Otherwise these patients will be treated with radiotherapy alone.

Neck: Radiotherapy or surgery depending on treatment of primary sit

Stage III-IVB

Concurrent Chemoradiation

Total Laryngectomy and neck dissection. Adjuvant radiotherapy or chemo radiotherapy is considered depending on the surgical adverse effects.

9.3.5.3 Subglottic

Stage I and II

Primary site: Where surgery capacities are available open partial laryngectomy or trans oral laser excision. Otherwise these patients will be treated with

radiotherapy alone.

Neck: Radiotherapy or surgery depending on treatment of primary site.

Stage III-IVB

Concurrent Chemoradiation

Total Laryngectomy and neck dissection. Adjuvant radiotherapy or chemo radiotherapy is considered depending on the surgical adverse effects.

Stage IVC for all sub sites:

Palliative chemotherapy should be the option. Radiation may be used for bleeding or pain.

9.3.5.4 Radiation details

Radiation therapy (RT) is the mainstay of first-line local treatment for early stage laryngeal. For more advanced disease, concurrent chemoradiation reduces the rate of distant metastasis, and improves local control and overall survival compared with RT alone.

Simulation (2D & 3D)

Set up the patient in supine position with the head hyperextended.

Wire scars and tracheostomy (if present)

The immobilization device should include at least the head and neck.

If possible, shoulders should also be immobilized to ensure accurate patient set up on a daily basis.

Bolus may be needed for anterior commissure tumors and over the tracheostomy (if involved by cancer)

CT simulation using 3 mm thickness with IV contrast should be performed to help guide the GTV target. Where no CT scans, conventional simulator can be used.

Target Volume for 3D Conformal RT

Suggested target volumes at the gross disease region

Suggested target volumes at the high-risk subclinical region

Radiation dose for 3D — External beam RT typically is given to a total dose of 70 to 72 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks. Treat

the lateral fields to 42-45Gy with a small cord block, then move the posterior border off-cord and use an electron (if available) boost to treat the elective posterior neck to 50Gy.

Target Volume for 2D RT

In places where 3DCRT is not available, 2D can be used but the entire prescription dose used in 3D cannot be applied without exceeding tissue tolerances.

Conventional Radiation Fields (2D)

Glottic

Fields arrangement

Two lateral opposing fields
Direct anterior neck field
Two lateral opposing fields with cone downs off the spinal cord at 42-45 Gy
Matched to lower direct anterior neck field with spinal cord blocking

For early stage disease, opposed lateral 5 cm fields covering all of the thyroid cartilage : A 15° or 30° wedge is used to compensate for changes in the contour of the neck. If the anterior commissure is involved 15° wedges or open fields are used to increase the doses by 5 to 10 percent anteriorly or bolus may be applied to the front of the larynx.

Fields borders

T1N0: Use a 5x5 cm field with the superior border at the thyroid cartilage, the inferior border at the bottom of the cricoid, a 1-cm skin flash anteriorly and a 2 cm margin posteriorly or the anterior border of the vertebral body.
T2N0: The field size is increased to 6 x6 with the inferior border on tracheal ring below the cricoid.
T3-4N0: Extend the superior border to 2 cm above the angle of mandible, the posterior border behind the spinous processes and the inferior border to include 1.5-2cm margins on the subglottic extent of the tumor. After 42-45Gy move the posterior border off-cord.
Match the lateral fields to the lower neck AP field

Radiation dose 2D — External beam RT typically is given to a total dose of 60-

70 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five-days per week over six to seven weeks. Treat the lateral fields to 42-44Gy with a small cord block, and then move the posterior border off-cord. The anterior field should be treated to 50Gy to both uninvolved and involved nodes at a specified depth. Additional anterior or electron boost fields can be delivered to involved nodal regions in the low neck.

Chemotherapy details:

- Concurrent chemo radiotherapy, induction chemotherapy followed by radiation therapy (RT) alone, and sequential therapy are all used as functional organ-preservation techniques.
- Concurrent chemoradiotherapy may be preferable for patients with N0, N1, and N2a presentations, while induction therapy may offer advantages for patients with a relatively high risk of distant metastases.
- Induction therapy may be particularly useful in patients with large primary tumors (bulky T3 and select T4) and/or advanced nodal presentations (large N2a, N2b, N2c, and N3) who are at high-risk for distant metastases.
- For concurrent chemoradiotherapy using Cisplatin/ Carboplatin or TPF (Taxane,Platinum and 5 FU) used for induction therapy and/or sequential therapy.

Post treatment Follow up

Patients should be followed by ENT every 3 months in the first two years for clinical examination and laryngoscopy. Every 6 months for three additional years, and then yearly thereafter.

TSH every 6 months (if radiotherapy to the neck) and annual chest x-ray.

Treatment of Recurrent or very advanced:

Radiotherapy

Palliative radiation should be considered in the advanced cancer setting when curative-intent treatment is not appropriate. The following regimens are recommended:

50Gy in 20 Fractions OR 30 Gy in 10 Fractions OR 20 Gy in 5 fractions

3.7 Gy given twice a day for four fractions over 2 days, repeated every 1-2 weeks for 3 cycles (total of 12 fractions)

Chemotherapy
The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy)
Unless otherwise specified, regimens listed below can be used.

Combination therapy
Cisplatin or carboplatin/Docetaxel or paclitaxel
Cisplatin/5-FU, Carboplatin/cetuximab
Cisplatin/gemcitabine, Gemcitabine/vinorelbine

Single agents
Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5-FU, Methotrexate, Gemcitabine , Capecitabine

Supportive care
Nutritional management including assessment, counseling and supplementary feeding (eg gastrostomy) is very important in laryngeal cancer.
This assessment should be done before any treatment as many patients will lose weight as a result of their disease, and treatment related toxicities.
Speech rehabilitation services (electrolarynx, tracheoesophageal puncture) should be emphasized for patients who have laryngectomy.

9.4 Hypopharyngeal cancers

9.4.1 Introduction
Hypopharyngeal cancer includes tumors arising from the pyriform sinus, posterior pharyngeal wall, postcricoid region. It is associated with tobacco use, alcohol consumption, and Plummer-Vinson syndrome. It is mostly seen in patients above 40 years. There is no screening for Hypopharyngeal cancer

9.4.2 Clinical Presentation
- Dysphagia
- Odynophagia
- Change in speech(dysarthria)
- Neck mass
- Referred otalgia

- Throat pain
- Weight loss
- Sensation of mass in throat
- Hoarseness

9.4.3 Diagnosis

History and Physical examination: A thorough history and physical examination is paramount in diagnosis of hypopharyngeal carcinoma. The physical exam includes esophagoscopy and biopsy.

Imaging:

Chest X-ray

CT scan and/or MRI of the neck

Pathology: Definitive diagnosis is confirmed by endoscopy-guided biopsy of the primary tumor. Fine needle aspiration of a neck mass may also be used.

9.4.4 Staging and Risk Assessment

Staging is based on the following;

The clinical presentation and Physical examination

Imaging reports (Laryngoscopy. Esophagoscopy, CT Scan/MRI etc)

Table AJCC TNM staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophageal mucosa
T4	Moderately advanced and very advanced local disease

T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland,esophageal muscle or central compartment soft tissue*
T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–);or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

9.4.5 Management

Radiation details

Radiation therapy (RT) is the mainstay of first-line local treatment for early stage Hypopharyngeal carcinoma. For more advanced disease, concurrent chemoradiation reduces the rate of distant metastasis, and improves local control and overall survival compared with RT alone.

Simulation (2D & 3D)

Set up the patient in supine position with the head hyperextended.
Wire scars and tracheostomy (if present)
The immobilization device should include at least the head and neck.
If possible, shoulders should also be immobilized to ensure accurate patient setup on a daily basis.
CT simulation using 3 mm thickness with IV contrast should be performed to help guide the GTV target. Where no CT scans, conventional simulator can be used.

Target Volume for 3D Conformal RT

Treat primary and levels II-V and retropharyngeal nodes in all cases.
With traditional field design:
Superior border is the skull base and mastoid.
Inferior border is 1cm below the inferior extent of disease or 1cm below cricoid on the lateral and matched to the AP low neck field.
With posterior pharyngeal wall tumors, the anterior border does not need flash skin. A clothespin may be used to spare the skin anteriorly.
Indication for stoma treatment: Emergent tracheostomy, subglottic extension, tumor invasion to soft tissue of neck, extra-nodal extension in level VI, close/+ margin, scar crosses stoma.

Radiation dose for 3D — External beam RT typically is given to a total dose of 70 to 72 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks. Treat the lateral fields to 42-45Gy with a small cord block, then move the posterior

border off-cord and use an electron (if available) boost to treat the elective posterior neck to 50Gy.

Target Volume for 2D RT

In places where 3DCRT is not available, 2D can be used but the entire prescription dose used in 3D cannot be applied without exceeding tissue tolerances.

Pyriform fossa(T1/T2,N0 or minimal lymphadenopathy)

The initial target volume includes the primary tumor and the upper cervical lymph nodes from the angle of the jaw to the lower border of the cricoid cartilage.

The superior and inferior borders are modified if necessary to cover the extension.

The posterior border includes the spinous processes for the first 50Gy and then moved off cord for the remainder of the doses. Cone down includes only the primary tumor and any involved lymph nodes.

Dose

Initial target volume:50 Gy in 25 fractions given in 5 weeks
Cone down:16- 20Gy in 8-10 fractions given in 10 days
Total dose:66-70 Gy in 33-35 fractions given in 6 to 7 weeks.

Pyriform fossa (T3 tumors with extensive lymphadenopathy)

Target volume includes primary tumor and lymph nodes of the involved side of the neck up to the base of the skull.

Large lymph node masses in the neck cannot be treated with opposing lateral fields because tolerance of the underlying spinal cord is limited to about 45Gy in 4.5 weeks. A wedged lateral filed and a contralateral anterior oblique field are used to treat the tumor and ipsilateral nodes while sparing the spinal cord. Alternately is using opposed lateral fields for a first phase treatment and the arrangement described above for the second phase.

Dose same as early stage.

Post cricoid region
Posterior Pharyngeal wall
The target volume includes the whole hypopharynx and adjacent deep cervical lymph nodes bilaterally, including the retropharyngeal space.
A 2cm margin is allowed above and below visible tumor and the posterior border is placed anterior to the spinal cord on the second phase while in the phase the whole spine is included.
Opposing lateral fields are used with a 15° wedge as compensator if necessary. Dose as the rest.

Conventional Radiation Fields (2D)
Radiation dose 2D — External beam RT typically is given to a total dose of 66-70 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks.

Chemotherapy details
Concurrent: Cisplatin, Cetuximab

Induction therapy and sequential therapy
Taxane,Platinum and 5 FU chemotherapy are typically used.

Recurrent and metastatic disease
Radiotherapy
Palliative radiation should be considered in the advanced cancer setting when curative-intent treatment is not appropriate. RT regimens should be tailored individually; severe RT toxicities should be avoided when treatment is for palliation. The following regimens are recommended

- 50Gy in 20 Fractions
- 30 Gy in 10 Fractions
- 20 Gy in 5 fractions
- 3.7 Gy given twice a day for four fractions over 2 days, repeated every 1-2 weeks for 3 cycles (total of 12 fractions)

Chemotherapy
The choice of systemic therapy should be individualized based on patient

characteristics (PS, goals of therapy).
Unless otherwise specified, regimens listed below can be used .

Combination therapy
Cisplatin or carboplatin/Docetaxel or paclitaxel
Cisplatin/5-FU, Carboplatin/cetuximab
Cisplatin/gemcitabine, Gemcitabine/vinorelbine

Single agents
Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5-FU, Methotrexate, Gemcitabine or Capecitabine

Follow-Up
Patients should be followed every 3 months in the first two years for clinical examination. After two years, they should be seen every 4-6 months for three additional years, and once a year thereafter.
CT Scan 3 months post radiotherapy, then no more CT only when is indicated.
TSH after 6 months (if radiotherapy to the neck), then as indicated and annual chest x-ray

9.5 Salivary gland

9.5.1 Introduction
Salivary gland cancers arise from major or minor salivary glands in the head and neck region. The most common malignant salivary gland tumors are mucoepidermoid carcinoma and adenoid cystic carcinoma. There is no screening for salivary gland cancer

Clinical Presentation
Clinical findings depend on primary site involved.
Mass
Pain
Nerve palsies
Neck mass

Diagnosis

History and Physical examination: A thorough history and physical examination is paramount in diagnosis of salivary gland cancers.

Imaging:

Chest X-ray

Abdominal pelvic USS

CT scan and/or MRI of head and neck

Pathology: Definitive diagnosis is confirmed by endoscopy-guided biopsy of the primary tumor. Fine needle aspiration of a neck mass may also be used.

Staging and Risk Assessment

Staging is based on the following;

The clinical presentation and Physical examination

Imaging reports (CT Scan/MRI of head and neck)

Table AJCC/TNM staging.

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension without extraparenchymal extension*
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor larger than 4 cm and/or tumor having extraparenchymal extension*
T4	Moderately advanced or very advanced disease
T4a	Moderately advanced disease Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

* Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

cN Category	cN Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–);or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); or metastasis in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) with clinically overt ENE(+)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Management

Treatment

Primary site:

Complete surgical resection with adjuvant radiotherapy if adverse features are present (see appendix)

If disease is unresectable, definitive radiotherapy or concurrent chemoradiotherapy is indicated.

Neck dissection is indicated for high-grade tumors or clinically positive neck disease

Radiation Details

Preferably 3DCRT

Simulation and Daily Localization

The patient is typically set up in a supine position with head extended. The immobilization shell would encompass the head and neck down to the shoulders. Surgical scars are wired if present.

Radiation Fields

Post Operative volume includes operative bed with at least 2 cm margin

Radiation dose

Post-Operative RT: Negative margins: 60-63 Gy at 1.8-2Gy/fraction

Post-Operative RT: Positive margins: 66 Gy at 1.8-2Gy/fraction

RT alone or Post-Operative RT for gross residual disease: 70Gy at 1.8-2Gy/fraction

Elective neck RT: 50-54Gy at 1.8-2Gy

Recurrent and metastatic disease

For select patients with small locoregional recurrences, we suggest an aggressive approach, using surgical salvage and radiation therapy.

In some cases, radiation or reirradiation, with or without concurrent chemotherapy, may be used in place of surgery

For most patients with metastatic disease, the goal of treatment is palliation or prevention of symptoms

For patients who are very symptomatic and for whom the goal is to maximize the likelihood of a response, we suggest initial treatment with a combination such as platinum, doxorubicin, and cyclophosphamide (CAP).
Single agent chemotherapy is an alternative.
Targeted therapy with trastuzumab may be appropriate for select patients with over expression or amplification of HER2, especially those with mucoepidermoid carcinoma, adenocarcinoma, or salivary duct carcinoma.

9.6 Nasal cavity and Paranasal sinus Cancer

9.6.1 Introduction

The paranasal sinuses are composed of seven bones (ethmoid,maxilla, palatine, lacrimal, pterygoid plate of sphenoid,nasal, and inferior turbinate), four paired sinuses (frontal, ethmoid, maxillary, and sphenoid), and complex networks of nervous, vascular, and lymphatic structures.

The nasal cavity anteriorly begins from the limen nasi, the line of transition from skin to mucous membrane. The nasopharynx is situated directly behind the nasal cavity and communicates with it by the posterior nasal aperture. Inferiorly, the floor is composed of the hard palate. Superiorly, the nasal cavity borders the base of the skull (frontal sinuses, cribriform plate of the ethmoid bone, and ethmoid air cells). The medial walls of the maxillary sinuses define the lateral extent of the nasal cavity. The midline septum divides the nasal cavity into two halves.

Clinical Presentation

- Nasal obstruction
- Epistaxis
- Proptosis
- Double vision
- Cheek mass
- Loss of sensation of the cheek
- Loosening or pain of the teeth

Diagnosis

History and Physical exam: A thorough history and physical examination is very important.

Imaging:

Chest X-ray
Abdominalpelvic USS
CT scan and/or MRI of the para nasal sinuses and neck
Direct fibre-optic endoscopy

Pathology: diagnosis is confirmed by endoscopic guided biopsy of the primary tumor.

Staging and Risk Assessment

Staging is based on the following;
The clinical presentation and Physical examination
Imaging reports (Endoscopy, CT Scan/MRI etc)
TNM Staging system: provides guidance for choosing the appropriate treatment of patients with this type of carcinoma.

Table AJCC /TNM Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses

T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); or metastasis in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) with clinically overt ENE (ENEc)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Management

Surgery

Surgery can be done for biopsy for histological confirmation

For early stage tumor plus neck dissection followed by radiotherapy

It may also be used for management of the neck for persistently enlarged lymph nodes

It can also be done in persistent or recurrent disease

- Stage I-IINO: complete surgical resection followed by radiotherapy alternatively definitive radiotherapy
- Stage III-IVNO (resectable) :Complete surgical resection with adjuvant radiotherapy If unresectable, radiation or chemoradiotherapy is indicated.

Radiotherapy and Chemotherapy

Nasal and para-nasal carcinoma is treated by Radiotherapy either alone or in combination with chemotherapy.

- Stage I: radiotherapy alone to primary disease and neck
- Stage II-IVB: concurrent chemotherapy and radiation to the primary disease and neck
- Stage IVC: palliative care (which may include chemotherapy and radiotherapy)

Induction chemotherapy can be considered for stage III-IVB if delays are anticipated in initiation of concurrent chemotherapy and radiation.

Local Recurrence: Chemotherapy, surgery or re-irradiation.

Radiotherapy details

Radiation therapy (RT) can be used as a first-line local treatment for early stage nasal cavity and para-nasal carcinoma. For more advanced disease, concurrent chemoradiation reduces the rate of distant metastasis, and improves local control and overall survival compared with RT alone.

For Paranasal sinus cancers, 3DCRT is mandatory.

Simulation (3D)

Set up the patient in supine position with the head extended.

Eyes open, straight ahead to keep posterior pole away from high dose region.

The immobilization device should include at least the head and neck (thermoplastic devise).
If possible, shoulders should also be immobilized to ensure accurate patient setup on a daily basis.
Tongue blade/cork to depress tongue out of fields. A bite block can be placed during simulation and throughout radiation to push the tongue away from the high-dose nasopharynx region.
Fill surgical defects with tissue equivalents.
CT simulation using 3 mm thickness with IV contrast should be performed to help guide the GTV target.

Target Volume for 3D Conformal RT

Target volumes for gross disease

Target volumes	Definition and description
GTV70	All gross disease on physical examination and imaging (CT and MRI). PET can help further define the tumor extent
CTV 70	Usually same as GTV 70. If a margin is needed due to uncertainness during gross disease delineation, add 3–5 mm so that GTV 70 + 3–5 mm = CTV 70
PTV 70	CTV 70 + 3–5 mm depending on comfort level and can be as small as 1 mm when near critical normal structures.

Radiation dose for 3D — External beam RT typically is given to a total dose of 66 to 70 Gray (Gy) to the primary tumor.
Concurrent chemotherapy: Chemotherapy are used concurrently with Radiotherapy. The current standard of care for concurrent chemotherapy is either Cisplatin 100 mg/m^2 on days 1, 22, and 43. A weekly dose of Cisplatin 30 to 40 mg/m^2 is a good alternative option. Cetuximab not recommended for paranasal sinus cancers.

Follow up

Follow-up includes periodic physical examination and investigations to rule out disease recurrrence or metastatic.
We follow patients every three months for the first two years, every four to six months for years 3 to 5, and annually thereafter. We suggest an annual chest

radiograph, although other experts suggest reimaging only as indicated by signs and symptoms

Supportive care

Nutritional management including assessment, counseling and supplementary feeding is very important in nasopharyngeal cancer as it is in all head and neck cancer patients many of who lose weight as a result of their disease, health behaviors and treatment related toxicities.

9.7 Oral cavity Cancer

Introduction

Oral cavity consists of the upper and lower lips, gingivobuccal sulcus, buccal mucosa, upper and lower gingiva (including alveolar ridge), retromolar trigone, hard palate, floor of mouth, and anterior two-third of the tongue. Risk factors include smoking, excessive consumption of alcohol, poor oral hygiene, prolonged focal denture irritation, betel nut chewing, and syphilis. There is no routine screening for oral cavity cancer

Clinical Presentation

- Nonhealing painful ulcer
- Speech difficulty
- Hypersalivation
- Neck mass
- Dysphagia
- Otalgia

Diagnosis

History and Physical examination: History and physical examination is necessary in diagnosis of oral cavity carcinoma including complete head and neck examination

Imaging:

Chest X-ray
CT scan and/or MRI of the primary and neck
Mirror and fibre-optic endoscopic examination

Pathology:

Histologic confirmation (fine-needle aspiration [FNA] of a suspected lymph node or open biopsy of the primary disease is sufficient and critical in determining the histopathology.

Staging and Risk Assessment

Staging is based on the following;
The clinical presentation and Physical examination
Imaging reports (Endoscopy, CT Scan/MRI etc)

Table : AJCC /TNM staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm with depth of invasion (DOI)* ≤ 5 mm
T2	Tumor ≤ 2 cm with DOI* > 5 mm or tumor > 2 cm and ≤ 4 cm with DOI* ≤ 10 mm
T3	Tumor > 2 cm and ≤ 4 cm with DOI* > 10 mm or tumor > 4 cm with DOI* ≤ 10 mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor > 4 cm with DOI* > 10 mm or tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

cN Category	cN Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(–)

N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

9.7.5 Management

9.7.5.1 Surgery

Surgery is the mainstay treatment modality for cancer of the oral cavity. Single modality treatment with surgery or radiation therapy is preferred for early-stage oral cavity cancer. Surgery followed by adjuvant therapy or combined chemoradiation is needed for more advanced disease.

It may also be used for management of the neck for persistently enlarged lymph nodes

There may be role in residual or recurrent disease

Stage I-II: Radical resection and selective neck dissection as single modality

Stage III-IV (nonmetastatic): Surgery is the primary treatment modality followed by adjuvant therapy

9.7.5.2 Radiotherapy and Chemotherapy

Radiation is much less preferred and surgery should be given whenever possible.

Radiotherapy as adjuvant treatment after complete resection for high-risk patients can be given, with or without chemotherapy

Definitive radiation with concurrent chemotherapy is the current standard for unresectable locally advanced disease .Also radiotherapy can be given as palliative treatment to primary or metastatic area.

Stage II-IVB: concurrent chemotherapy and radiation to the primary disease and neck

Stage IVC: palliative care (which may include chemotherapy and radiotherapy)

Induction chemotherapy can be considered for stage III-IVB if delays are anticipated in initiation of concurrent chemotherapy and radiation.

Local Recurrence: Chemotherapy, surgery or re-irradiation.

Radiotherapy details

Radiation therapy (RT) is the mainstay of first-line local treatment for early stage oral cavity carcinoma. For more advanced disease, concurrent chemoradiation reduces the rate of distant metastasis, and improves local control and overall survival compared with RT alone.

Simulation(2D & 3D)

Set up the patient in supine position with the neck in slight hyperextension

The immobilization device should include the head, neck and shoulders. .

A bite block can be placed during simulation and throughout radiation.

CT simulation using 3 mm thickness with IV contrast should be performed to help guide the GTV target. Where no CT scan, conventional simulator can be used.

Target Volume for 3D Conformal RT

Target volumes for pre-operative treatment of oral cavity cancers

Target volumes	Definition and description
GTV 70 Primary	all gross disease on physical examination and imaging
CTV 70	Same as GTV 70 , although a 5 mm margin can be added if uncertainty exists regarding the extent of gross disease
CTV 59.4 Primary	encompass the entire CTV 70 with an additional margin of up to 10 mm
Neck nodes	nodal levels with pathologic involvement and adjacent ipsilateral or contralateral nodal regions at high risk for subclinical disease
CTV 54 Nodal	Ipsilateral and/or contralateral uninvolved nodal levels at low risk for subclinical disease

Target volumes for postoperative treatment of oral cavity cancers,

Target volumes	Definition and description
CTV 66 Primary	Preoperative tumor volume can guide the targeting of CTV66. Regions of soft tissue invasion, bone invasion, or microscopically positive margins should be included in this volume
CTV 60 Primary	Preoperative gross disease and the entire operative bed
Neck nodes	Preoperative gross disease and adjacent ipsilateral or contralateral nodal regions at high risk for subclinical disease
CTV 54	Ipsilateral and/or contralateral uninvolved nodal levels at low risk for subclinical disease.

Radiation dose for 3D — External beam RT typically is given to a total dose of 66 gray to 70Gray (Gy) to the primary tumor and 50 Gy to 54 Gy the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks

Target Volume for 2D RT
In places where 3DCRT is not available, 2D can be use but the entire prescription dose used in 3D cannot be applied without exceeding tissue tolerances.

Conventional Radiation Fields(2D)
Fields arrangement

- Two lateral opposing fields
- Direct anterior neck field

Lateral fields borders

- Superior: skull bases.
- Inferior: bottom of hyoid bone and match with lower anterior neck field (half-beam block)
- Posterior: spinous processes.
- Anterior: mentum for oral cavity

Direct anterior neck field border

- Superior border: Is the inferior border of the lateral fields
- Inferior border: Is the head of clavicle
- Lateral border: outer 2/3 of the clavicle

NOTE: If supraclavicular nodes involved a mediastinal 8 cm wide T field with inferior border 5 cm below the head of the clavicle.
Radiation dose 2D — External beam RT typically is given to a total dose of 60 to 66 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks.
Concurrent chemotherapy: Chemotherapy are used concurrently with Radiotherapy. The current standard of care for concurrent chemotherapy is either 100 mg/m^2 on days 1, 22, and 43. A weekly dose of 30 to 40 mg/m^2 is a good alternative option.
Induction Chemotherapy: The addition of Taxotere to cisplatin and fluorouracil in neoadjuvant regimen further improves treatment outcome compared to PF neoadjuvant regimen

Follow up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow-up includes history and physical examination ,Flexible endoscopy, Indirect mirror examination ,TSH yearly for the first 3 years, then annually, CT of the neck every 3–6 months, then CXR annually.

Prognosis

Prognosis for oral cavity cancer depends on the location of the primary tumor and the stage at presentation.

Treatment of Recurrent or Metastatic disease

Small local recurrences should be treated using the following options: Surgery is the first choice. Combination of surgery and RT, with or without concurrent chemotherapy is an alternative option.

In metastatic setting, palliative chemotherapy should be considered for patients with adequate performance status.

Supportive care

Nutritional management including assessment, counseling and supplementary feeding is very important as many of who lose weight as a result of their disease, health behaviors and treatment related toxicities.

9.8 Oropharyngeal Cancer

Introduction

Oropharynx is located between the soft palate superiorly and the hyoid bone inferiorly. The oropharynx has four walls; soft palate, tonsillar region , base of tongue, and pharyngeal wall. It is associated with tobacco use and alcohol consumption and HPV, and mostly seen in patients above 40 years.

HPV-related cancers appear to occur at a slightly younger age and have better survival rates when treated with radiotherapy and chemotherapy as compared to non-HPV-related cancers. Cancers arising in the pharyngeal tongue may be clinically silent until extensive. The lesion may be entirely submucosal and recognizable only by induration. Tonsillar and pharyngeal tongue tumors frequently are initially recognized by nodal metastases.There is no screening for oropharyngeal cancer

According to the UICC/AJCC 8th edition staging system, oropharyngeal cancer cannot be staged without knowledge of p16 immunohistochemical status (or HPV DNA status if p16 is equivocal). Knowledge of p16 or HPV DNA status is mandatory for staging oropharyngeal cancer.

Clinical Presentation

- Sore throat,
- Non healing oropharyngeal ulcers

- Dysphagia,
- Referred otalgia,
- Hoarseness(with larynx invasion),
- Odynophagia,
- Hot potato voice
- Impaired tongue movement, including protrusion.

Diagnosis

History and Physical exam: A thorough history and physical examination including a complete head and neck examination with addition of Indirect mirror examination, fibreoptic endoscopy and fine needle aspiration of neck mass.

Imaging:

Chest X-ray
Ultrasound
CT scan and/or MRI of the primary and neck

Pathology: Diagnosis is confirmed by biopsy of the primary tumor .
Immunohistochemistry testing may also be done for HPV infection

Staging and Risk Assessment

Staging is based on the following;
The clinical presentation and Physical examination
Imaging reports (Endoscopy, CT Scan/MRI etc)

Table AJCC /TNM Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis

T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–);or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Management

Surgery

Surgery can be used in very selected early stage cases.

Definitive radiotherapy is usual or surgery (composite resection with neck dissection) with post-op radiotherapy can be given. Locoregionally advanced oropharynx (large size of primary tumor or multiple nodes or large nodes) usually requires combined chemoradiation therapy.

Radiotherapy and Chemotherapy

Oropharyngeal is mainly treated by Radiotherapy in combination with chemotherapy. Indications for radiotherapy are;

Adjuvant treatment after complete resection for high-risk patients, with or without chemotherapy

Definitive radiation with concurrent chemotherapy is the current standard for unresectable locally advanced disease

Palliative treatment to primary or metastatic foci

T1-2 tumor with no nodes or one small lymph node: Definitive radiotherapy or surgery (composite resection with neck dissection) with post-op radiotherapy

Locoregionally advanced: Concurrent chemoradiotherapy is preferred to the primary disease and neck. However, in cases where concurrent chemoradiation alone may be suboptimal for very advanced primary or nodal disease, induction chemotherapy may be considered. Surgical resection if possible with neck dissection followed by adjuvant chemoradiation or radiotherapy alone.

Local Recurrence: Chemotherapy, surgery or re-irradiation.

Radiotherapy details

Radiation therapy (RT) is the mainstay of treatment for early stage oropharyngeal carcinoma. For more advanced disease, concurrent chemoradiation reduces the rate of distant metastasis, and improves local control and overall survival compared with RT alone.

Simulation(2D & 3D)

Set up the patient in supine position with the head hyperextended. Wire neck scars.

The immobilization device should provide adequate shoulder immobilization to ensure accurate patient setup

Bite block can be placed during simulation and throughout radiation
CT simulation using 3 mm thickness with IV contrast should be performed to help guide the GTV target.
Isocenter is typically placed just above the arytenoid cartilages. Where no CT scan, conventional simulator can be used.

Target Volume for 3D Conformal RT

Taget volumes for gross disease;

Target volumes	Definition and description
GTV 70 Primary	All gross disease as defined by clinical examination (e.g., base of tongue tumors that are superficial and not apparent on imaging) and imaging.
Neck nodes:	all suspicious (>1 cm, necrotic, enhancing, or FDG avid) lymph nodes. Borderline suspicious lymph nodes may be treated to an intermediate dose (66 Gy in 33 fractions).
CTV 70	Typically same as GTV 70 (no added margin). Margin of 5 mm may be added if there is uncertainty in extent of gross tumor so that GTV 70 + 5 mm = CTV 70
PTV 70	CTV 70 + 3–5 mm, depending on accuracy of daily patient positioning and image guidance.

Target volume for subclinical disease; general guidelines

Target volumes	Definition and description
CTV 59.4 Primary	Generally the primary CTV59.4 should encompass GTV + minimum 1 cm margin while respecting anatomical barriers to spread, including bone, air, and skin
Neck nodes	Should include the at-risk lymphatic areas in the node-positive neck: Levels II–IV Lateral retropharyngeal lymph nodes up to skull base/jugular foramen High level II/retrostyloid space Although sparing of ipsilateral IB is controversial, it is routinely spared unless there is gross involvement or extension of the primary GTV into the oral cavity
CTV 54	Neck nodes – should include the at-risk lymphatic areas in the node-negative neck: Levels II–IV Lateral retropharyngeal lymph nodes up to C1High level II/retrostyloid space is excluded

Radiation dose for 3D — External beam RT typically is given to a total dose of 70Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks. A similar dosing schedule is used for more advanced disease, with 66 Gy to involved lymph nodes.
Target Volume for 2D RT
In places where 3DCRT is not available, 2D can be use but the entire prescription dose used in 3D can not be applied without exceeding tissue tolerances.

Conventional Radiation Fields(2D)
Fields arrangement

- Two lateral opposing fields
- Direct anterior neck field

Lateral fields borders

- Superior: base of skull and mastoid(retropharyngeal lymphnodes should be covered)
- Inferior: bottom of hyoid bone match with anterior neck field at plane above true vocal cords (to block larynx in AP field).
- Posterior: spinous processes.
- Anterior: 2cm anterior to tumor
- Beam-split above larynx at thyroid notch, if possible, to allow laryngeal sparing.

Direct anterior neck field border

- Superior border: Is the inferior border of the lateral fields
- Inferior border: inferior edge of clavicular head
- Lateral border: two thirds of the clavicle or 2cm lateral to adenopathy

Note: If supraclavicular nodes involved a mediastinal 8 cm wide T field with inferior border 5 cm below the head of the clavicle.
Radiation dose 2D — External beam RT typically is given to a total dose of 60 to 66 Gray (Gy) to the primary tumor and 50 Gy to the uninvolved neck in single daily fractions of 2 Gy, five days per week over six to seven weeks.

Concurrent chemotherapy:

- Chemotherapy are used concurrently with Radiotherapy. The current standard of care for concurrent chemotherapy is either 100 mg/m^2 on days 1, 22, and 43. A weekly dose of 30 to 40 mg/m^2 is a good alternative option.

Induction Chemotherapy**:**

- Induction chemotherapy followed by concurrent chemo-radiotherapy cannot be considered as a standard therapy for most patients with advanced oropharyngeal carcinoma. When used PF or TPF (Taxane, Platinum and 5 FU) regimen has been used.

Follow up

- Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring of toxicity. Follow-up includes periodic examination of the oropharynx and neck, assessment of cranial nerve function, and evaluation of systemic complaints. Post treatment imaging of the primary and neck recommended within 6 months of treatment.
- We follow patients every three months for the first two years, every six months for years 3 to 5, and annually thereafter. We suggest TSH every 6 months and annual chest radiograph, although other experts suggest reimaging only as indicated by signs and symptoms

Treatment of Recurrent or Metastatic disease

- Small local recurrences should be treated using the following options: brachytherapy, radiosurgery, IMRT or a combination of surgery and RT, with or without concurrent chemotherapy.
- Regional recurrence is managed by radical neck dissection if resectable and the primary is controlled.
- In metastatic, palliative chemotherapy should be considered for patients with adequate performance status.

Supportive care

- Nutritional management including assessment, counseling and supplementary feeding is very important as many of who lose weight as a result of their disease, health behaviors and treatment related toxicities.

10 THORACIC MALIGNANCIES

Introduction

Lung cancer is the most common cancer worldwide and accounts for the most cancer-related deaths. Smoking is the highest risk factor, along with second-hand smoking, radon gas, asbestos, air pollution, environmental and occupational chemical exposure among nonsmokers.

There are two types of primary lung cancer; small cell carcinoma SCLC (oat cell, polygonal cell, lymphocytic, and spindle cell) and non-small cell carcinoma (adenocarcinoma, squamous cell, neuroendocrine, bronchoalveolar and large cell)

Non–small cell lung cancers (NSCLC) account for over 85% of all cases; the rates of small cell lung cancers (SCLC) fall with the reduction in smoking rates. Paraneoplastic syndromes are commonly seen in SCLC. Prophylactic cranial irradiation (PCI) is indicated for all stages of SCLC after response to primary therapy.

PCI is not routinely recommended for NSCLC.

Epidemiology

Worldwide, lung cancer is the commonest cancer with an estimate of 1.8 million new cases by 2012 data (Globocan). In Tanzania there is no national data for lung cancer ..

10.1 Small cell lung cancer (SCLC).

Introduction.

Small cell lung cancer is the aggressive form of lung cancer, which most commonly occurs in smokers.

Usually starts in bronchioles and it grows very quickly, resulting into a large mass and eventually spread throughout the body (metastasizing).

Risk factors for SCLC.

- Smoking cigarettes, pipes, or cigars is the major risk for small cell lung cancer.

- Second hand smoke exposure.
- Exposure to asbestos, arsenic, chromium, beryllium, nickel, soot, or tar in the workplace.
- Family history of lung cancer
- HIV infection.
- Being exposed to radiation from any of the following:
- Radiation therapy to the breast or chest.
- Radon in the home or workplace.
- Imaging tests such as CT scans.
- Atomic bomb radiation.

Symptoms.
- Bloody phlegm,
- cough,
- chest pain, and
- Shortness of breath.

Diagnosis.
- History and Physical examination including performance status and weight loss documentation

Imaging:
- Chest X-ray
- Abdominal Ultrasound
- CT scan of chest and abdomen
- MRI brain
- Bone scan

Pathology: investigations to confirm the disease include sputum for cytology, bronchial lavage, image guided transthoracic FNAC, mediastinoscopy, thoracentesis and bronchoscopy with biopsy.

Staging.
The role of staging is for treatment purposes. There are two types of staging used for SCLC which are, limited stage and extensive stage.

Limited stage:
The disease is only on one side of the chest and can be treated with a single radiation field. This generally includes cancers that are only in one lung (unless tumors are widespread throughout the lung), and that might have also reached the lymph nodes on the same side of the chest.

Extensive disease
The disease has spread widely throughout the lung, to the other lung, to lymph nodes on the other side of the chest, or to other parts of the body (including the bone marrow).

The TNM staging system
Table AJCC /TNM staging.

T Category	T Criteria
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension

T2	Tumor >3 cm but ≤5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
cM1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
cM1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
cM1c	Multiple extrathoracic metastases in a single organ or in multiple organs

Treatment

The treatment includes surgery (for small tumors) as well as chemotherapy, sometimes in combination with radiation therapy.

Treatment recommendations for limited-stage SCLC

Radiotherapy for limited stage:

Dose for gross disease in chest is 45 Gy in 30 fractions given twice daily over 3 weeks of treatment, or patient can be given 66 Gy in 33 fractions given once daily.

Ideally start radiation before cycle 2 of chemotherapy. Prophylactic cranial Irradiation (PCI) for limited stage is recommended after completion of chemoradiation

Dose for PCI is 25 Gy in 10 fractions.

Stages I-III disease:

Concurrent chemotherapy: Cisplatin/Carboplatin,Etoposide

Chemotherapy as first-line therapy: Patients with limited-stage (stages I–III) disease who are not able to tolerate chemotherapy and radiation concurrently. Chemotherapy medicines as above.

NOTE:Sequential therapy can also be given for limited-stage disease for patients unable to tolerate concurrent chemoradiation; chemotherapy is given first, followed by radiation therapy because of the high rate of responsiveness to chemotherapy for SCLC.
T3-4 tumors due to multiple ipsilateral lung nodules are treated as extensive-stage disease.

Treatment recommendation for Extensive stage (IV)
First-line chemotherapy for extensive-stage disease
Stage IV disease:

- Cisplatin/ Carboplatin Etoposide or Cisplatin/ Carboplatin plus Irinotecan
- Cyclophosphamide,doxorubicin,vincristine

Second-line chemotherapy for relapsed or refractory disease (Stage IV disease).
Etoposide/Topotecan/Paclitaxel

Combination Chemotherapy:Carboplatin/Cisplatin,irinotecan

Radiotherapy for Extensive stage.
For any patient who shows response to the full course of chemotherapy, radiation to the residual disease in the chest is recommended and also prophylactic cranial irradiation (PCI) to the brain is recommended.
Dose: 25 Gy in 10 fractions.

10.2 Non small cell lung Cancer

Introduction
Non-small cell lung cancer (NSCLC) is the most common type of lung cancer with the following subtypes; Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma are all subtypes of NSCLC.

Screening
Chest CT scan screening for non small cell lung cancer is recommended for 40 Pack – years smoking.

Clinical Presentation

- Cough
- Hemoptysis
- Chest pain
- Wheezing
- Dyspnoea

Diagnosis:

History and Physical examination including performance status and weight loss documentation

Imaging:

- Chest X-ray
- Abdominal Ultrasound
- CT scan of chest and abdomen for staging.
- MRI brain for patients with neurological symptoms to rule out brain metastasis.
- Bone scan for individuals with bone pain to rule out bone metastasis.

Pathology:

investigations to confirm the disease include sputum for cytology, bronchial lavage, image guided transthoracic FNAC, mediastinoscopy, thoracentesis and bronchoscopy with biopsy.

Staging and Risk Assessment:

Staging is based on the following;
The clinical presentation and Physical examination
Imaging reports (CT Scan/MRI etc)

TNM Staging system: This staging system provides important guidance for choosing the appropriate treatment of patients with non small cell lung carcinoma.(**TNM Staging refer to SCLC)**

Management

Surgery

Surgery is the mainstay for curative treatment of NSCLC.

It is the treatment of choice for early-stage NSCLC, and it is often incorporated for early locally advanced patients as well.

Surgical resection may be either lobectomy, wedge resection or pneumonectomy with node resection.

At least nodal sampling should be performed, if not complete lymphadenectomy.

Adjuvant chemotherapy for completely resected T(1-2)N1, T2N0 especially > 4cm and completely resected T3N0 or T3N1-3 give adjuvant chemo.

For close/+margin, re-resect or consider post-op RT.

Radiotherapy and Chemotherapy:

Locally advanced NSCLC where a complete surgical resection cannot be obtained is often managed with concurrent chemotherapy and radiation therapy.

Other options include concurrent chemo-radiotherapy followed by→adjuvant chemo or induction chemo for down-staging followed by concurrent chemo radiation.

Postoperative chemotherapy (Cisplatin based) is recommended for stages IB, II and IIIA after an initial surgery.

Radiotherapy may be offered to operable patients who are not medically fit for surgery.

Postoperative radiation after surgical resection for patients with pathologic N2 disease, T4 disease except for separate nodules in the same lobe, close/positive surgical margins, gross residual disease.

Radiotherapy as palliation for pain, bleeding, SVC syndrome, brain metastasis, cord compression.

Systemic agents (chemotherapy, targeted agents) are given in the adjuvant setting after surgical resection for stage Ib (tumors >4 cm) to IIIA patients, or palliatively for stage IV patients

Radiotherapy details

Simulation(2D & 3D)

Patients are typically immobilized with their arms over their head to maximize the number of potential beam angles.

The upper body cradle extends inferiorly to provide immobilization through the thorax.

Wedges and/or compensating filters may be needed.

CT simulations are performed with a slice thickness of 2.5–3 mm. Intravenous contrast can be considered when necessary to differentiate tumor involvement from mediastinal structures such as the vasculature.

Radiation dose for 3D

Definitive dose for primary and involved LN: generally, 60Gy in 30 fractions with chemotherapy or 66Gy in 33 fractions without chemotherapy.

For treating patients in unresectable disease with radiation, at least 60 Gy should be administered

Concurrent chemoradiation improve outcomes

CT can be performed at the end of natural inhalation, exhalation, or under free-breathing conditions to gauge the extent of motion of the tumors and include all of the areas into which they move.

GTV + 5mm = CTV, CTV + 3-5 mm = PTV, or ITV + 3-5 mm = PTV.

NOTE: There is no role for prophylactic cranial irradiation for patients with NSCLC.

Target Volume for 2D RT

In places where 3DCRT is not available, 2D can be used but the entire prescription dose used in 3D cannot be applied without exceeding tissue tolerances hence can be used on physician decision.

A margin of 2 cm around any gross tumor and 1cm margin around regional lymph node groups should be applied.

Upper lobe tumor; Include ipsilateral supraclavicular and subcarinal in treatment field.

Middle and lower lobe tumor: Cover entire mediastinum (from thoracic inlet to 8cm below carina)

Postoperative chemotherapy:
Cisplatin and etoposide/vinorelbine
Cisplatin and gemcitabine/docetaxel
Carboplatin and Paclitaxel

Concurrent with RT:
Cisplatin and etoposide
Cisplatin,vinblastine.Carboplatin and paclitaxel.

Sequential chemo → RT:
Cisplatin and vinblastine
Alternative: carboplatin and paclitaxel

NOTE: Consider Crizotinib for ALK/ROS1 positive locally advanced or metastatic non small cell lung cancer, dose 250mg PO q12hr.

Post treatment Follow up
We follow patients every three months for the first two years, every four to six months for years 3 to 5, and annually thereafter.
It is suggested to do CXR every 3–4 months for 2 years, then every 6 months for 3 years, then annually.
CT chest annually.

Treatment of Recurrent or Metastatic disease: radiotherapy is recommended for local palliation or prevention of symptoms as pain and obstruction.
The dose and fractionation of palliative radiotherapy should be personalized.
Commonly used dose is 30Gy in 10 fractions and 20Gy in 5 fractions.
Other palliative doses are 40Gy/20 fractions and 20Gy/10 fractions.
When higher doses are used, technologies to reduce normal tissue irradiation should be used.
For patients with advanced lung cancer with extensive metastases systemic chemotherapy is recommended where platinum based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.

10.3 Thymic tumors

Introduction

Thymoma and thymic cancer are relatively rare neoplasm and have an indolent, locally invasive pattern but can metastasize.

They usually occur in patients aged 40-60 years with a median age of 52; It is uncommon in children.

Clinical Presentation

Thymoma patients are normally asymptomatic. Common signs and symptoms are caused by local invasion of the disease or paraneoplastic syndrome especially myasthenia gravis. Some of the symptoms includes: fatique, cough, chest pain, hoarseness, dysphagia, symptoms of superior vena cava syndrome(swelling of the neck, chest and face, swelling of the visible veins in the upper body, headache and dizziness).

Diagnosis:

- Complete history and physical examination
- Imaging:
- Chest X-ray
- CT scan/MRI of chest
- Pathology: tissue diagnosis by core or open biopsy to confirm the disease.

Staging and Risk Assessment:

Staging is based on the following;

On the extent of either macroscopic or microscopic invasion into mediastinal structures at the time of surgery

Modified Masaoka clinical Staging of Thymoma or TNM staging:

This staging system provides important guidance for choosing the appropriate treatment of patients with thymoma.

Table AJCC/ TNM Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
T1a	Tumor with no mediastinal pleura involvement
T1b	Tumor with direct invasion of mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in anterior (perithymic) lymph nodes
N2	Metastasis in deep intrathoracic or cervical lymph nodes

M Category	M Criteria
cM0	No pleural, pericardial, or distant metastasis
cM1	Pleural, pericardial, or distant metastasis
cM1a	Separate pleural or pericardial nodule(s)
cM1b	Pulmonary intraparenchymal nodule or distant organ metastasis

Management

Surgery:

Surgery is the main treatment modality for thymoma.

- Stage I: complete resection
- Stage II: complete resection ± post-op radiotherapy (depending on the

risk of LR based on pathology). Favor post-op radiotherapy for close or involved margins, thymic carcinoma, and thymic carcinoid.

- Stage III: Complete resection (if possible) → post-op radiotherapy. If not a surgical candidate or unresectable: chemo-RT or definitive RT.
- Stage IV: Induction combination chemo → radiotherapy and/or surgery depending on response

Radiotherapy and Chemotherapy:

Radiotherapy reduces recurrence rates and improves outcomes for incompletely resected stage II–IV thymoma.

The role of post-op RT for completely resected stage II–III thymoma is controversial.

Radiotherapy is mainstay treatment for unresectable disease (concurrent with chemotherapy)

Induction radiation can be considered if chemotherapy is contraindicated in unresectable cases.

Neoadjuvant chemotherapy can be used to improve respectability.

Combined chemoradiation therapy for unresectable cases may be considered.

Radiotherapy

Simulation (2D & 3D)

Simulate patient supine with arms overhead and adequate immobilization.

Surgical clips denoting the extent of surgical resection and/or regions of residual disease are important for design of post-op fields.

Radiation dose for 3D

Doses of adjuvant radiotherapy for thymoma depend on the status of surgical margin

50 Gy for clear/close margins,

54 Gy for microscopically positive margins, and

60 Gy for grossly positive margins using conventional fractionation.

Doses of 60–70 Gy may be needed for gross residual disease or unresected cases.

Chemotherapy medications include; cisplatin, doxorubicin, cyclophosphamide.

Follow up

Follow up is every 3 months for the first two years, every 6 months for three to five years, and annually thereafter.CXR every 3–4 months for 2 years, then every 6 months for 3 years, then annually.
CT of the chest annually

10.4 Thyroid carcinoma

Introduction

Thyroid cancer is a commonest endocrine malignancy in Tanzania. It accounts approximately 0.8-1% of all malignancies seen at Ocean Road cancer institute annually.Histological types are medullary, anaplastic and well differentiated thyroid cancer. Majority of these cases are differentiated thyroid cancer, the commonest being follicular subtype followed by papillary subtype and rare ones being Hurthle cell, follicular variant of papillary thyroid carcinoma, tall cell, columnar, solid and clear cell.
Female are mostly affected, the male to female ratio being 3:1

Clinical Presentation

- Anterior neck swelling (the commonest)
- Obstructive symptoms stridor, hoarseness,
- Metastatic symptoms such as weight loss, difficulty in breathing, bone pain/pathological fractures

Diagnosis

- History and physical examination
- Laboratory (Thyroid function tests, CBC, Serum calcium, Vitamin D level if available)
- Imaging:
- Radiology: CXR (If clinically indicated), Neck USS
- Nuclear Medicine: Thyroid scan, Bone scan
- Pathology: FNAC, tissue biopsy

Staging

Table AJCC /TNM Staging for Thyroid Cancer

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤1 cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3	Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension beyond the strap muscles
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/ Delphian, or upper mediastinal) lymphnodes. This can be unilateral or bilateral disease.
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis

Treatment

Surgery

Patients with indeterminate thyroid nodules (follicular neoplasm, suspicious for follicular neoplasm, atypia of unknown significance, follicular lesion of unknown significance) should undergo initial diagnostic lobectomy and isthmusectomy.
Consideration for initial total thyroidectomy: patient preference, history of radiation exposure, +/- size >=4cm, +/- family history of thyroid cancer, contralateral nodules
Patients who underwent initial lobectomy should be referred for total thyroidectomy if radiation exposure, patient preference, extrathyroidal extension, positive tumor margins, incidental positive lymph nodes, vascular invasion, aggressive tumor subtype (tall cell, insular, columnar), +/- family history
Total thyroidectomy should be performed on all patients with Hurthle cell carcinoma

Radioactive Iodine Therapy of Differentiated Thyroid carcinoma

Radioactive Iodine therapy is defined as the systemic administration of I-131 sodium or potassium Iodide for selective irradiation of thyroid remnants, microscopic DTC or other non-resectable or incomplete resectable DTC or both purpose.
Based on the primary goal of RAIT, there are 2 main forms of procedure:

Radioiodine ablation

Is a post-surgical adjuvant modality seeking to eliminate thyroid remnants to increase sensitivity and specificity of follow up testing for persistent or recurrence by serum thyroglobulin (Tg) assay as a tumour marker and of diagnostic whole body scintigraphy (WBS).
Ablation also allow sensitive post therapy whole body scintigraphy (WBS) that may depict occult metastases and serve to treat any microscopic tumour deposits.

I -131 ablation is indicated for certain patients following total thyroidectomy. It decreases local recurrence, may have a survival benefit. Ablation may reduce long-term morbidity and possibly mortality.
131-I is not recommended for multi-focal tumours if all foci are <1cm provided: there are no other high risk features. Ablative I- 131 should be planned for three to four weeks post- surgery.
NOTE: Breast feeding should stop at least 6-8 weeks prior to RAI treatment.

Indications for repeat diagnostic scan following I-131 Ablation

- "DxWBS, either following thyroid hormone withdrawal (THW) or rhTSH., 6–12 months after remnant ablation may be of value in the follow-up of patients with high or intermediate risk of persistent disease but should be done with 123-I or low activity 131-I
- If this scan shows no abnormal uptake and the patient is low risk no further routine diagnostic scans are required
- Repeat 123-I diagnostic scans in intermediate or high risk patients in the following situations
  - o Persistently raised thyroglobulin antibodies
  - o Rising thyroglobulin level
  - o High risk patients with persistent abnormal uptake of 123-I requiring treatment

Ablation success criteria

On follow up dxWBS, negative thyroid bed uptake or thyroid bed uptake beneath an arbitrarily set, low threshold, e.g. 0.1%
Absence of detectable TSH-stimulated Tg antibodies has been excluded.
Absence of suspicious findings on neck Ultrasonography (US).

Follow up

Patients are followed up 3 monthly for first 2 years following initial treatment, then 6 monthly for 3 years then annually
TSH, T4, thyroglobulin and thyroglobulin antibody levels in 6 weeks
Ultrasound of the neck to be requested in all remaining patients 6-12 months after
Women must be advised against pregnancy for 6-12 months after treatment with 131-I

TSH Suppression

TSH suppression with Eltroxin (Thyroxine) is indicated in all patients post-ablation and post- lobectomy.
Aim to keep TSH <0,1mU/L.

Tumour recurrence/ metastases

Local recurrence in the thyroid bed or neck nodes should be managed surgically. Local recurrence or distant metastases not suitable for surgery that are iodine avid are treated with I-131. External beam radiation is reserved for disease that is not amenable to either of the above and for palliation of bone or brain metastases.

Treatment of Persistent with 131- Iodine.

Persistent abnormal uptake of 123/131-I after ablation generally requires repeat administration of 131-I with a higher dose.

Potential early and late sequelae of RAIT

Sequelae	Approx. incidence	Comment	Potential intervention (s)
Early/Short term			
Radiation thyroiditis (pain, swelling discomfort)	10-20%	More frequent with large remnants	Steroids for several days after RAI administration
Tumour swelling	10-20%	May cause compressive symptoms, pain or both	Steroids as above
Gastritis	30%	Transient and self-limiting	Use of H2 blockersfollowing RAI administration
Sialadenitis	30%	Transient and self- limiting	Liberal hydration, use of lemon juice, sour candy and chewing gum in the 24+h after RAI administration
Bone marrow depression (thrombocytopenia/ leucopenia	Depends on administered activity	Mostly transient decrease in cell counts; incidence of severe bone marrow depression increases with multiple bone metastases and large cumulative radioiodine activity	

Xerostomia/caries		Rare after single ablation procedure	
Abnormalities of taste and smell		Transient and self- limited	
Nausea/vomiting			Ant-emetics
Hypospermia		Usually transient	Gonadal radiation exposure can be minimized by liberal hydration and frequent urination, consider sperm banking in case of high activities

Long Term			
Radiation pulmonary fibrosis	<1% of patients with lung metastases	Affects patients with diffuse Iodine –avid pulmonary metastases who receive multiple RAITs in a short time and treated with high activities or both	Ensure appropriate interval between RAITs and consider their cumulative absorbed dose
Secondary primary malignancy	<1%	Latency period of > or equal 5 years. Cases most frequently observed when cumulative radioiodine activities exceed 20-30GBq	Limit RAIT above these cumulative activities to patients in whom a clear therapeutic benefit may be expected
Permanent bone marrow depression	Rare		
Chronic hypospermia or azoospermia	Rare when cumulative activity<14GBq		Consider sperm banking in case of high activitites
Early onset of menopause			
Chronic sialadenitis with xerostomia, abnormality with taste and smell	10-20% after RAI ablation, more frequent after multiple RAITs		Liberal hydration, use of lemon juice, sour candy and chewing gum in the 24+h after RAI administration
Chronic dry eye	Rare		

Palliative Chemotherapy

Patients with visceral metastatic disease not responding to 131-Iodine may be offered palliative chemotherapy.

Regimen: Adriamycin..

External Beam Radiation

- Adjuvant radiation to the thyroid bed and neck nodes should be considered in the following situations:
- -Macroscopic residual disease
- -Microscopic/unresectable and local recurrence disease that does not take up I-131
- -pT4 disease and extra-nodal spread in patients over 60 years
- Palliation of metastases
- Palliative doses include: 20Gy in 5 Fractions or 30Gy in 10 fractions or 8Gy single Fraction.
- Anaplastic carcinoma: 50Gy in 20 Fractions or 60Gy in 30 Fractions.

Medullary Thyroid Cancer (MTC)

Diagnosis

History - All patients with a personal medical history of primary C cell hyperplasia, MTC, or MEN 2; patients with intestinal ganglioneuromatosis; family history consistent with MEN 2 or FMTC, and at risk for autosomal dominant inheritance

Investigation:

FBP, Blood chemistry evaluation, PTH, CEA, Thyroid function tests, calcitonin levels, (albumin-corrected calcium or ionized calcium, plasma free metanephrines and normetanephrines, or 24-hour urine metanephrines and normetanephrines,

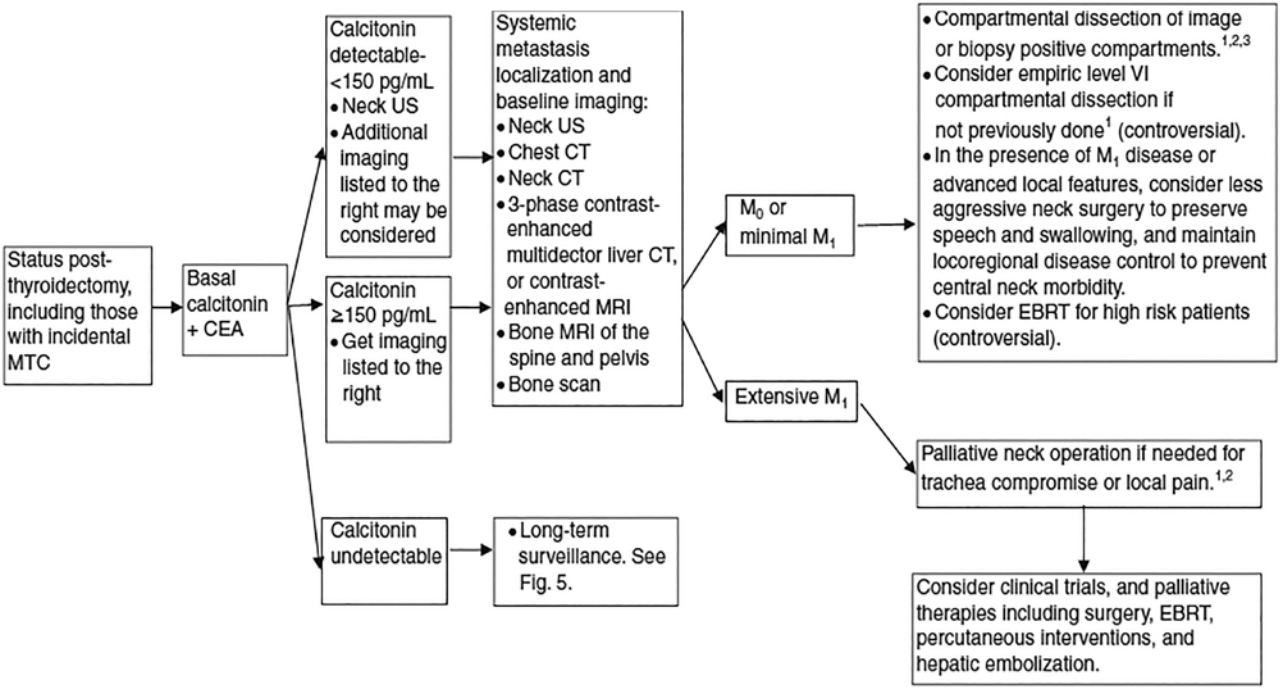
Neck ultrasound, neck CT, abdominal USS and CT, MRI, Preoperative chest CT, neck CT, and three-phase contrastenhanced multidector liver CT or contrast-enhanced MRI and somatostatin receptor imaging

FNAC

Management of Local Regional disease MTC

Surgery

A total thyroidectomy with or without Bilateral level 6 prophylactic Cervical node dissection
Replacement rather than suppressive T4 therapy with target serum TSH levels between 0.5 and 2.5 ml/UL



Management of Metastatic MTC
Surgery, EBRT, percutaneous interventions, and hepatic embolization.
Somatostatin analogs and cytotoxic chemotherapy have limited role

Follow up
Calcitonin and CEA levels obtained approximately every 6 months, Neck USS should be performed

Anaplastic Thyroid Cancer (ATC)
Diagnosis
History taking and physical examinations
FBP,LFT, RFT, TSH, Calcium and phosphorus levels, Coagulation profile.
Radiological: Neck USS, for disease extension - CXR, Neck CT, MRI and PET/CT
Pathological: Cytology, histology,
Laryngoscope; to evaluate vocal cords and larynx

Treatment
Locoregional disease
Surgery
Surgery type - A total thyroidectomy with a therapeutic lymph node dissection should be performed in patients with intrathyroidal ATC
In patients with extrathyroidal invasion, an en bloc resection should be considered.

Radiotherapy
Following an R0 or R1 resection - definitive radiation therapy (with or without concurrent chemotherapy)
Patients who have undergone R2 resection or have unresected disease with good performance status should be offered definitive radiation (with or without concurrent chemotherapy)
Palliative radiotherapy for unresectable disease.

Chemotherapy
Combination of Paclitaxel /Docetaxel, and/or Doxorubicin and/or Cisplatin/ Carboplatin

Follow up:
3-month in the first 2 years then 6 months for 3 years, followe by yearly visits.

11 SARCOMA

11.1 Soft tissue sarcoma

Introduction

Median age 40–60 years.
Slight male predominance, more frequent among African- Americans.

Risks factor

Genetics: NF-1, Retinoblastoma, Gardner's syndrome, Li-Fraumeni syndrome.
Environmental exposures: ionizing radiation, herbicides, thorotrast, chlorophenols, vinyl chloride, arsenic.

Clinical Presentation

Painless mass,chronic lymphedema of upper extremity → lymphangiosarcoma.

Work up

- History & Physical examination
- FNAC for disease confirmation or to R/o recurrence.
- Core biopsy
- CBC, BUN/Cr, ESR & LDH
- Molecular tests
- Ultrasound
- Plain X-ray of primary and all patients get CT chest.
- If myxoid liposarcoma, include CT abdomen because it frequently metastasizes to retroperitoneum.
- CT/MRI of primary.
- PET scan.

TNM Staging

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor

T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension

Definition of Regional Lymph Node (N)

N Category	N Criteria
N0	No regional lymph node metastases or unknown lymph node status
N1	Regional lymph node metastasis

Definition of Distant Metastasis (M)
Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Treatment recommendations

Surgery
Includes wide en bloc resection,radical resection,wide excision,Excisional biopsy,Intralesional biopsy.

Chemotherapy
Consider neoadjuvant chemo → surgery for high-grade or unresectable tumors
Ifosfamide
Doxorubicin/ ifosfamide or epirubicin/ifosfamide.

Treatment recommendations for low-grade soft tissue sarcoma

Stage I:

Surgery is the primary treatment.

Adjuvant external beam radiation therapy (XRT) is recommended to prevent local recurrence.Definitive radiation therapy is recommended for patients who are not surgical candidates; radiation doses range from 70-80 Gy

Treatment recommendations for high-grade soft tissue sarcoma

Stages II-III:

Resectable disease, surgery followed by radiation therapy with or without adjuvant chemotherapy or surgery alone is recommended; preoperative radiation therapy, chemotherapy, or chemoradiation prior to surgery are alternatives.

Unresectable disease: preoperative radiation therapy, chemotherapy or chemoradiation with doxorubicin-based regimens.

Preoperative XRT:

Dose for XRT is 50 Gy

Treatment recommendations for metastatic disease

Stage IV:

Limited metastasis: Resection, radiofrequency ablation (RFA), embolization, or radiation therapy with curative intent.

Disseminated metastases:observation or palliative therapy (radiation, chemotherapy, or surgery)

Chemotherapy recommendations for metastatic disease

Single agents regimens include the following :

Doxorubicin or Liposomal pegylated Doxorubicin/Epirubicin, Ifosfamide and Mesna; Gemcitabine, Dacarbazine,Methotrexate, Cisplatin, and Taxanes

Combinations agents regimens: doxorubicin, ifosfamide, and mesna; doxorubicin and dacarbazine, doxorubicin, ifosfamide, and dacarbazine including mesna, gemcitabine and docetaxel.

Radiotherapy Techniques

Post op EBRT

- Bolus scar and drain sites for first 50 Gy unless in tangential beam.
- Field = tumor bed, scar, drainage sites + 5–7 cm longitudinal and 2–3 cm perpendicular margin in initial field. After 50 Gy, reduce field to surgical bed (outlined by clips, scar) + 2 cm margin.
- Dose=usually 2 Gy/fraction with negative margins or microscopic residual to 60 Gy, +margins to 66 Gy, gross disease to 75 Gy.

NOTE: Always spare 1.5–2 cm strip of skin. Try to exclude skin over ant tibia, if possible, due to poor vascularity.Never treat whole circumference of extremity to >50 Gy. Delay RT >3 day from doxorubicin.

- Try to spare 1/2 of cross-section of weight-bearing bone, entire or >1/2 of joint cavities, and major tendons (patellar, Achilles).
- Upper inner thigh best treated with frog-leg position.
- Buttock/post thigh best treated in prone position.
- Nodes: Gross nodes should be resected. No elective nodal radiation.
- For distal extremities, patients often have severe reaction with pain, edema, erythema. Usually heals within 1 months.

Pre-op EBRT

Dose = 2 Gy/fx to 50 Gy.
Field = tumor + 5–7 cm longitudinal margin and 2 cm lateral margin. No conedown.
Surgery 3 weeks after RT.
Boost with EBRT: close/+margins to 65–66 Gy, gross disease to 75 Gy.

EBRT alone

50 Gy to large field, conedown to 60 Gy, then to 75 Gy.
Consider decreasing RT dose by 10%, if doxorubicin given.

Treatment Summary

STAGE	RECOMMENDED TREATMENT
I extremity	-Surgery alone (unless close (<1 cm) or + margin → post-op RT).
II–III extremit	-Surgery + post-op RT or pre-op RT → surgery. Consider neoadjuvant/adjuvant chemo for large deep high-grade tumors. For recurrence, amputation salvages
IV	-For controlled primary, with ≤4 lung lesions and/or extended disease free interval, consider surgical resection best supportive care, chemo, and/or palliative surgery or RT.
Retroperitoneal	-Surgery + IORT (12–15 Gy)→ post-op EBRT 45–50 Gy. Alternatively,pre-op RT +/- chemo →resection +/- IORT boost.
GIST	-If resectable, surgery→imatinib (consider observation vs. imatinib if completely resected). If marginally or unresectable, imatinib→consider surgery→imatinib

Follow up

Physical examination, MRI of primary, CT chest every 3 months × 2 year, every 4 months in third year, every 6 months in fourth and fifth years, then annually. Consider bone scan or PET, if clinically indicated

11.3 Kaposi's Sarcoma

Introduction

Kaposi's sarcoma (KS) is a spindle-cell tumor derived from endothelial cell lineage caused by Human herpesvirus-8 (HHV-8). In Tanzania, Kaposis sarcoma is the third commonest malignancy among adults. The incidence of KS at ORCI has been rising from 286 in 2006 to 741 in 2016.

Kaposi's sarcoma can be primarily categorized into 4 types:

- Epidemic of AIDS-related KS
- Immunocompromised KS
- Classic, or sporadic KS
- Endemic (African) KS

Clinical presentation

Lesions in Kapos's sarcoma:

May involve skin, oral mucosa, lymph nodes,visceral organs and mucous membrane(palate, gingiva, conjunctiva)

May present as macular, papular, nodular, or plaquelike appearances.

May be discrete or confluent and typically appear in a linear, symmetrical distribution, following Langer lines.

Diagnosis

Laboratory studies: FBP, RFT, LFT, CD4 lymphocyte counts, plasma HIV viral-load.

Imaging studies: CXR and Abdominal pelvic USS. Regional CT scan for selected patients based on clinicals symptoms.]

Procedures: Punch biopsy,other procedures such as Bronchoscopy, Esophagogastroduodenoscopy (EGD) or colonoscopy can be considered based on symptoms.

Staging

HIV Positive patients (Epidermic KS) staging

ACTG (AIDS Clinical Trials Group) Classification System

Tumor (T)	Extent of tumor
T0 (good risk)	Kaposi sarcoma is confined to skin and/or lymph nodes and/or demonstrates minimal oral disease (roof of mouth); the Kaposi sarcoma lesions in the mouth are flat rather than raised
T1 (poor risk)	Kaposi sarcoma lesions are widespread; one or more of the following is present: Edema (swelling) due to the tumor Extensive oral Kaposi sarcoma: nodular lesions (raised) and/or lesions in areas of the mouth besides the palate Lesions of Kaposi sarcoma are in organs other than the lymph nodes (eg, lungs, intestine, liver)
Immune system (I)	Status of the immune system, as measured by CD4 cell levels
I0 (good risk)	CD4 cell count is ≥200/µL (normal range, 600-1500/µL); more recent studies have used counts of either 150 or 100/µL
I1 (poor risk)	CD4 cell count is <200/µL; more recent studies have used counts of either 150 or 100/µL

Systemic illness (S)	Extent of involvement within the body or systemic illness
S0 (good risk)	No systemic illness present; all of the following are true: No history of opportunistic infections or thrush None of the following B symptoms is present: unexplained fever, night sweats, >10% involuntary weight loss, diarrhea persisting for >2wk Karnofsky performance status score is ≥70 (ie, patient is up and about most of the time and able to take care of him- or herself)
S1 (poor risk)	Systemic illness present; one or more of the following is true: History of opportunistic infections or thrush One or more B symptoms is present Karnofsky performance status score <70 Other HIV-related illness is present (eg, neurologic disease or lymphoma)

HIV Negative patients (Endemic KS) staging

Stage I	Lesions restricted to one anatomical region (eg. lower limbs, upper limbs, back or trunk)
Stage II	Lesions involving 2 or more anatomic regions
Stage III	Cutaneous lesions (Stage I or II) AND generalized lymphadenopathy
Stage IV	Stage III AND visceral involvement (pulmonary or GI tract involvement, including oral lesions).

Treatment

Antiretroviral therapy –first line treatment in Epidermic KS.

- Limited asymptomatic lesions; Observation
- Localized nodular disease; radiotherapy.
- Diffuse involvement of a large portion of an extremity or in widespread, bulky or rapidly progressive disease with visceral involvement; Systemic chemotherapy.

Radiation Therapy

For patients with advanced disease a dose of 8Gy in one fraction (parallel opposed photon portals) is preferable. In case of partial response, this dose can be repeated up to 3 times.

Other recommended options include; 20Gy/5 fractions or 20Gy/10 fractions.

Chemotherapy

ABV (Adriamycin+ Bleomycin + Vinblastine), Pegylated liposomal doxorubicin or Paclitaxel

Bleomycin + Vincristine or Vincristine alone.

Follow up

Physical examination, CXR, Abd Pelvic USS, every 3 months × 2 year, every 4 months in third year, every 6 months in fourth and fifth years, then annually.

12 SKIN CANCERS

12.1 Non-melanoma skin cancers.

Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin are the most common histological types of skin cancer.

Risk Factors.

Pre-malignant conditions: actinic keratoses, keratoacanthoma, lentigo maligna, and nevi.

Past medical history: immunosuppression, ultraviolet light exposure and Geno dermatoses.

Genetic syndromes: such as albinism, xeroderma pigmentosum, Turcot syndrome, Fanconi anemia, and Gorlin or nevoid basal cell syndrome predispose individuals to nonmelanoma skin cancer (and other types of malignancies) formation.

Carcinogens: ultraviolet light, exposure to ionizing radiation, chemicals (inorganic arsenic, soot, polycyclic aromatic carbons), smoking (squamous cell carcinoma only)

Work up

- History and physical examination.
- Biospy
- Laboratory tests: Baseline RFT, LFT and FBC.

NOTE: CT or MRI for suspected Nodal and bone involvement.

Clinical presentation

Basal Cell Skin Cancer (BCC)

Smooth, raised lesions with translucent borders

Lesions can infiltrate deeply and can cause deformity

Occurs mainly in the head and neck region

They rarely metastasize

Squamous Cell Cancer (SCC)

Irregular, nodular, or plaque-like lesions.

Some lesions are covered by a keratotic scale

Invasion is common in larger lesions and may involve the underlying muscle, bone, blood vessels, or lymphatic channels

Staging of Skin Squamous Cell Carcinoma, Basal Cell Carcinoma and Other Skin Carcinomas

Tx	The primary tumor cannot be evaluated.
T0	There is no evidence of a primary tumor.
Tis	The cancer is in situ, meaning it has not invaded into deeper layers.
T1	The tumor is 2 centimeters or less at its largest point. Also, it must have fewer than two high-risk features.
T2	The tumor is more than 2 centimeters at its largest point, OR the tumor can be of any size with two or more high-risk features.
T3	The tumor invades the cheekbone (maxilla), jawbone (mandible), eye socket (orbit) or the bone of the ear (temporal bone).
T4	The tumor invades nerves at the base of the skull.

N stage: spread of cancer to the lymph nodes in the neck

Nx	The neck lymph nodes cannot be assessed.
N0	There is no evidence of any spread to the nodes.
N1	It looks like there is a single node, on the same side of the main tumor, that is 3 centimeters or less in greatest size.
N2a	The cancer has spread to a single node on the same side as the main tumor, and it is more than 3 centimeters but less than or equal to 6 centimeters in greatest dimension.
N2b	More than one lymph node has cancer, on the same side as the main tumor, but none are more than 6 centimeters.
N2c	There are lymph nodes in the neck on either the opposite side as the main cancer or on both sides of the neck, but none are more than 6 centimeters.
N3	There is spread to one or more neck lymph nodes, and the size is more than 6 centimeters.

M stage: spread of cancer outside the head and neck

M0	No evidence of distant spread.		
M1	There is evidence of spread outside of the head and neck (i.e., in the lungs, bone, brain, etc.).		
Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage 2	T2	N0	M0
Stage 3	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage 4	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

Treatment

Squamous and basal cell carcinomas are most commonly treated with surgery, radiation therapy, or a combination of the two. Selection of therapy is based on preservation of function and cosmesis, and patient preference.

Surgery

Surgical excision is indicated for primary curative or palliative.

Radiotherapy

Commonly used in treating lesions on the face >5cm for better cosmetic and functional results.

Radiation therapy dose is; 60 Gy at 2 Gy per fraction or 50 Gy in 15 fractions over 3 weeks.

For Palliative setting: Consider 30Gy in 10 Fractions.

Follow up

History and physical examination; 3-6 months for 2 years, 6 monthly for 2-5 years, then yearly.

Investigations; To be requested basing on clinical symptoms.

12.2 Melanoma:

Introduction

Suspicious lesions are characterized by **A**symmetry, **B**order irregularities, **C**olour heterogeneity, **D**ynamics, (dynamics or evolution in colours, elevation or size) ('ABCD rule').

The ugly duckling 'concept' helps to identify melanomas, because naevi in the same individual tend to resemble one another and melanomas often do not fit the individual's naevus pattern.

Risk factor: skin exposure to ultraviolet (UV) light.

Work up

History and physical examination.

Laboratory studies - FBP, RFT, LFT and LDH

Biopsy – Excisional biopsy, Incisional biopsy etc

Imaging studies – Chest Xray, Abdominal pelvic USS, Bone scanning, CT scanning, MRI and PET scanning.

Staging

AJCC TNM staging.

Definition of Primary Tumor (T)

T Category	Criteria/Thickness	Criteria/Ulceration Status
TX	Primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable
T0	No evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable
Tis	Melanoma in situ	Not applicable
T1	≤1.0 mm	Unknown or unspecified

T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
T1b	0.8-1.0 mm	With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Definition of Regional Lymph Node (N)

N Category	Extent of regional lymph node and/or lymphatic metastasis	
	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) Exception: pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node

N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases.	Four or more tumor-involved nodes or in transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

M Category	M Criteria	
	Anatomic Site	LDH Level
cM0	No evidence of distant metastasis	Not applicable
cM1	Evidence of distant metastasis	Any
cM1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
cM1a(0)	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not elevated
cM1a(1)	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Elevated
cM1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified

cM1b(0)	Distant metastasis to lung with or without M1a sites of disease	Not elevated
cM1b(1)	Distant metastasis to lung with or without M1a sites of disease	Elevated
cM1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
cM1c(0)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not elevated
cM1c(1)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Elevated
cM1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
cM1d(0)	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not elevated
cM1d(1)	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Elevated
pM1	Evidence of distant metastasis, microscopically proven	Any
pM1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node, microscopically proven	Not recorded or unspecified
pM1a(0)	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node, microscopically proven	Not elevated
pM1a(1)	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node, microscopically proven	Elevated
pM1b	Distant metastasis to lung with or without M1a sites of disease, microscopically proven	Not recorded or unspecified
pM1b(0)	Distant metastasis to lung with or without M1a sites of disease, microscopically proven	Not elevated
pM1b(1)	Distant metastasis to lung with or without M1a sites of disease, microscopically proven	Elevated
pM1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease, microscopically proven	Not recorded or unspecified
pM1c(0)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease, microscopically proven	Not elevated
pM1c(1)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease, microscopically proven	Elevated

pM1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease, microscopically proven	Not recorded or unspecified
pM1d(0)	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease, microscopically proven	Not elevated
pM1d(1)	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease,microscopically proven	Elevated

Clinical (cTNM)

Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

Pathological (pTNM)

Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b/c, N3b/c	M0	IIIC
T1a/b, T2a	N1a, N2a	M0	IIIA
T1a/b, T2a	N1b/c, N2b	M0	IIIB
T2b, T3a	N1a/b/c, N2a/b	M0	IIIB
T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0	IIIC
T3b, T4a	Any N ≥N1	M0	IIIC
T4b	N1a/b/c, N2a/b/c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

Satellites = within 2 cm of primary tumour.
Breslow depth = microscopically measured vertical thickness (mm) of the primary tumour from the epidermal granular layer (or base of the lesion if the tumour is ulcerated) to the deepest identifiable contiguous melanoma cell.

Clark's staging:

Level	
I	Confined to epidermis
II	Confined to papillary dermis
III	Impinging onto upper part of reticular dermis
IV	Extension into reticular dermis
V	Extension into subcutaneous fat

Treatment

Primary skin

Recommended surgical excision margins:

Breslow Thickness	Margin	5 Yr Survival
In situ	0.5 - 1 cm complete excision	100%
< 1 mm	1 cm	95 - 100%
1 – 2 mm	1 – 2 cm	80 – 96%
2.1 – 4 mm	2 cm (1 – 3 cm)	60 – 75%
> 4 mm	2 – 3 cm	50%

Local Recurrence

Recurrence within 2 cm of the scar generous surgical resection (1-3 cm) is the treatment of choice + down to deep fascia

Distant Metastasis

Surgery

Surgical resection with curative intent for solitary lesions of skin and distant nodal sites as well as isolated lung metastases can result in long disease free survival in carefully selected patients.

Chemotherapy

Standard chemotherapy using single agent DTIC.
Other options Temazolamide – orally
Combination chemotherapy in young, fit patients: Cisplatinum /Vinblastine/ DTIC

Radiotherapy

Radiation can be useful for palliation.

Radiotherapy Techniques

Primary Treatment
Skin or mucosal surfaces involving oral cavity, vagina + anus – 60-70 Gy in 2 Gys/ fraction.

Lentigo maligna (depends on size): 45 Gy in 3 Gys/ fractions or 50-60 Gy in 2 Gys/ fraction.
Adjuvant therapy: 50 Gys in 2 Gys/ fractions.

Metastatic Disease
Soft tissue (Dermal, subcutaneous and lymph nodes): 44 Gys fractionsgiven 2 x/week x 11fractions
Brain Metastases: 30Gys/10#s, If poor PS 20 Gys /5 fractions
Bone Metastasis: 20Gy /5 fractions to total 20 Gy in 1 week Or 3.0 Gy x 10fraction to total 30 Gy in 1 week
Spinal Cord Compression (post decompression if possible): 30 Gys/10 fractions, 45 Gys/18 fractions

Follow up
Educate patient on self skin examination, ABCD changes.
Schedule 3-4 months first 2 years, then 6 monthly for 5 years then yearly to 10 years

PART III

PAEDIATRIC CANCERS

13 BRAIN TUMORS IN CHILDREN

Introduction

13.1 Infratentorial Tumors

Cerebellar astrocytoma-30% Medulloblastoma- 30% Ependymoma-10% Brainstem glioma –15%, Other-15%

Supratentorial tumours include sellar and suprasellar tumours which comprise about 20% of all childhood brain tumours eg: Craniopharyngioma. Other supratentorial tumours include Astrocytoma- low grade, high grade, mixed Oligodedroglioma PNET

Others include:

- Diencephalic tumours i.e. tumours of chiasm, thalamus/hypothalamus Germ cell tumours
- Ependymoma Meningioma (rare in kids) Choroid plexus tumours Pineal tumours- pineoblastoma, pineocytoma, mixed tumour,germ cell tumour Neuronal and mixed neuronal/glial tumours- gangioglioma
- Desmoplastic gangioglioma DNET
- Metastases
- Spinal cord tumours are rare: 1-2% of all childhood CNS tumours 70%= low grade astrocytomas &/or gangiogliomas

Infratentorial Tumors

13.1.1 Cerebellar Astrocytomas

Peak incidence in kids 5-10 years

>80%= JPA and most of the rest are low grade (G2)

Treatment:

Surgery

Mainstay of treatment.Watch carefully and repeat surgery or RT at progression

Chemotherapy

Carboplatin/Vincristine. Not yet standard of care but can be used in younger

children with recurrent disease to delay RT.

Radiotherapy
Dose= 1.80 Gy X 28 Fractions = 50.40 Gy

13.1.2 Medulloblastoma
Generally Commonest malignant CNS tumour of childhood.

Clinical Presentation
Arises in midline of cerebellum growing into and compressing 4th ventricle (V4)
May cause hydrocephalus and associated raised ICP. i.e. headache, nausea, vomiting, papilloeadema, irritability and lethargy. May also cause gait ataxia and dysmetria if cerebellar invasion.

Investigations
- MRI whole brain and spinal cord
- CSF cytology
- Baseline hearing test should be done.
- FBC, RFT and LFT

NOTE: Lumbar Puncture prior to surgery may be dangerous, it is usually done not less than 10-14 days after surgery, to allow post-surgical contamination to clear

Staging
Modified Chang staging system

T Stage	Criteria
T1	tumor <3 cm in diameter
T2	tumor ≥3 cm in diameter
T3	
• T3a	tumor >3 cm and with extension into Aqueduct of Sylvius or foramen of Luschka
• T3b	tumor >3 cm and with unequivocal extension into brainstem
T4	tumor >3 cm with extension past Aqueduct of Sylvius or down past foramen magnum

M Stage	
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	microscopic tumors cells found in CSF
M2	gross nodular seeding intracranially beyond the primary site (in cerebellar/cerebral subarachnoid space or in third or lateral ventricle)
M3	gross nodular seeding in spinal subarachnoid space
M4	metastasis outside cerebrospinal axis

Risk Stratification

Standard (Average) Risk (66%)

- >3 years old
- <1.5 cm^2 residual disease after resection
- M0 by craniospinal MRI and CSF

High Risk (34%)

- <3 years old
- Subtotal resection, >1.5 cm^2 residual tumor
- M+; leptomeningeal seeding
- Location outside of posterior fossa (PNET)

Treatment

Surgery

Resection of the tumor +/- shunt.

Radiotherapy and chemotherapy

Craniospinal irradiation (CSI) to 36 Gy with a boost to the posterior fossa (Total Dose = 50-55 Gy).

Average risk patients

Chemotherapy and lower dose CSI is gold standard.

Radiotherapy Dose: 36 Gy or 23.40 Gy/13 Fractions, Boost = 1.80 X 18 Fractions = 32.40 Gy (tumour bed + 2cm margin) i.e. Total Dose to tumour bed= 55.80 Gy in 31 Fraction

Standard adjuvant chemotherapy consists of Vincriatine / Cisplatin and CCNU. If CCNU is not available then use Carboplatin, vincristine and etoposide.

NOTE: Weekly vincristine is given during RT.

High risk patients
Craniospinal RT+ weekly concurrent Vincristine followed by carboplatin, vincristine, etoposide.
Dose of RT = 1.80 Gy X 20 Fraction =36 Gy (5 times per week) Boost = 1.80 Gy X 11 Fraction = 19.80 Gy
Total Dose to tumour bed = 55.80 Gy
NOTE:Patients < 3 years: They will receive chemotherapy to delay RT until either aged 3yrs, or 6 cycles to be given.

Chemotherapy
Carboplatinum,Vincristine and Etoposide

Follow –up
Brain MRI/CT SCAN

13.1.3 Epedymoma
Classification
- Subependymoma (WHO grade 1)
- Ependymoma (WHO grade 2) Cellular Papillary Epithelial Clear cell Mixed
- Malignant (anaplastic) ependymoma (WHO grade 3)
- Ependymoblastoma (PNET)

Staging: as for medulloblastoma

Management: Surgery - Complete resection

Radiotherapy: Local field RT
If no dissemination: Dose= 1.80Gy X 30 Fractions = 54.00 Gy
For disseminated disease: Craniospinal RT as for medulloblastoma with boosts to bulk disease of 12-14 Gy
Recurrent tumours: Re-resection and/or radiosurgery.

13.1.4 Childhood Brainstem Glioma
Treatment
Are usually not amenable to surgery.
RT is mainstay of treatment

Radiotherapy
Treat patient supine without a cast.
Field Boarders:
Anterior= Posterior clinoid
Superior= Laterial ventricle as determined from midline sagittal MRI
Inferior = Bottom of C2
Posterior = to cover tumour + 2-3cm margin as measured on sag. MRI
Start with parallel opposed fields:
Dose = 2.00 Gy x 15 Fractions= 30 Gy

NOTE: Reassess after 1 week. There is frequently a marked improvement. If no improvement, stop RT at 20-30 Gy. If improved, make cast and consider 3-D plan to treat to Total Dose 56 Gy.

13.2 Supratentorial Tumors

13.2.1 Pineal Tumors
Germ cell tumours- See adult protocol
PNET(Pineoblastoma)-See adult protocol. Treat as for medulloblastoma.

13.2.2 Childhood Malignant Hemispheric Glioma
Grade is predictive of outcome
Outcome may be better than in adults, but still only 30-40% survival at 2 years.

Treatment: Surgery + RT

Radiotherapy
Dose= 1.80Gy X 25 Fractions = 45.00 Gy to large volume (Mass + Oedema as seen on T2 of MRI+ small margin), 1.8Gy X 8 Fractions = 14.4 Gy boost to small volume (Enhancing mass + 2 cm margin as seen on T1 MRI with Gadolinium) (T.D. = 59.40 Gy)- reduce for OAR if required

Adjuvant chemotherapy: (Vincristine , CCNU, prednisolone)

Recurrence: Re-resection +/- chemotherapy if good PS
Temozolomide.

13.2.3 Childhood Visual Pathway Glioma/ Hypothalamic

13.2.3.1 Glioma

Treatment

Observation- in NF1 patients or non-symptomatic non-progressive lesions.
Surgery- In isolated optic nerve lesions with progressive symptoms.
Radiotherapy -Dose = 1.6Gy X 30 Fractions =45.00 Gy
Chemotherapy- Vincristine/ actinomycin D and Vincristine/Carboplatin

13.2.3.2 Craniopharyngiomas

These are histologically benign tumours that may be disabling/ life-threatening because of their position

Presentation is insidious- usually decreasing VA or VF, and/or endocrine abnormalities

Radiotherapy

Dose = 1.80 Gy X 30 Fractions = 54.00Gy

Recurrent disease Local drainage

Drain the cyst via the Omayo at regular intervals if the cyst is smaller, surgery and/or RT may be possible with less morbidity.

Follow up

Follow up should combine neuro-paediatric /endocrine clinic if possible.
Growth monitoring, pituitary function testing , visual assessment and many psychosocial issues are addressed.

13.2.3.3 Spinal Cord Tumors

Very rare in children (<2% of CNS malignancy)
Approximately half are malignant

14 LEUKEMIA IN CHILDREN

14.1 Acute Lymphoblastic Leukemia/ Lymphoma Treatment Scheme

Diagnostic and Treatment Tree:

Assessment of risk factors:

- Age at first symptoms
- Highest WCC pre-treatment (including pre steroids at peripheral hospital)
- T or B cell leukaemia
- Presence of absence of bulky non-marrow disease
- Response to treatment
- Response to pre-phase steroids (D8 peripheral blood or D8/15 BMA)
- Response to Induction chemotherapy – D28 BMA
- Cytogenetics (when available)

Investigation at Diagnosis:
Day 1 Pre-phase

- FBP – result suspects Leukaemia
- Urgent CXR to rule out large mediastinal disease
- Peripheral smear (PS)
- If blasts present in PS, do peripheral flow if ALC is between 1 and 5 take FULL BOTTLE of FBC sample, (If ALC is below 1 do bone marrow flow).
- If no blasts reported or ALC <1, do bone marrow aspirate –4 normal slides for general microscopy and 6 special sticky slides for cytogenetics
- Bone marrow flow cytometry

NOTE: If the aspirate is dry then take bone marrow biopsy.

ALL treatment:
Follow BFM 90 regimen

- Induction Treatment
- Remission Induction
- Consolidation/CNS phase
- Radiotherapy

NOTE; If incomplete remission consider stem cell transplant

14.2 Chronic Myelogenous Leukemia (CML)

Chronic myelogenous leukemia (CML) is a disease characterized by the expression of BCR-ABL, an oncogenic tyrosine kinase that induces bone marrow stem cell proliferation.

Work-up

- CBC and differential
- Bone marrow aspirate and biopsy
- Baseline bone marrow cytogenetics
- Peripheral blood or bone marrow quantitative real-time polymerase chain reaction (Q-RT-PCR).
- Liver function tests, lipase, glucose, urate, cholesterol, fasting glucose, HgbA1c, lipid panel

Staging

WHO Classification

CML PHASE	WHO CLASSIFICATION
Chronic stable phase	Peripheral blood blasts fewer than 10% in the blood and bone marrow
Accelerated phase	Blasts 10-19% of white blood cells in peripheral and/or nucleated bone marrow cells ; persistent thrombocytopenia ($< 100 \times 10^9$/L) unrelated to therapy or persistent thrombocytosis ($> 1000 \times 10^9$/L) unresponsive to therapy; increasing white blood cells and spleen size unresponsive to therapy; cytogenetic evidence of clonal evolution
Blast crisis	Peripheral blood blasts ≥ 20% of peripheral blood white blood cells or nucleated bone marrow cells; extramedullary blast proliferation; and large foci or clusters of blasts on bone marrow biopsy

Treatment

1st Generation - Imatinib (glivec)

2nd Generation - Dasatanib /Nilotinib /Bosutinib.

Clonal progression or advanced-phase disease -stem cell transplantation.

15 LYMPHOMA IN CHILDREN

15.1 Non Hodgkins lymphoma

Types commonly found in children

- Burkitts Lymphoma and Burkittls Like Lymphoma
- Lymophoblastic Lymphoma (Treatment as Acute Lymphoblastic Leukemia)
- Diffuse large B cell Lymphoma
- Anaplastic Large Cell Lymphoma.

International Pediatric Non-Hodgkin Lymphoma Staging System

Stage I	Single tumor with exclusion of mediastinum and abdomen (N; EN; B or S: EN-B, EN-S)
Stage II	Single EN tumor with regional node involvement ≥ Two N areas on same side of diaphragm Primary GI tract tumor (usually in ileocecal area), ± involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of tumor to adjacent organs, it should be regarded as stage III)
Stage III	≥ Two EN tumors (including EN-B or EN-S) above and/or below diaphragm ≥ Two N areas above and below diaphragm Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary GI tract tumor [usually in ileocecal region] ± involvement of associated mesenteric nodes that is completely resectable) Any paraspinal or epidural tumor, regardless of whether other sites are involved Single B lesion with concomitant involvement of EN and/or nonregional N sites
Stage IV	Any of the above findings with initial involvement of CNS (stage IV CNS), BM (stage IV BM), or both (stage IV combined) based on conventional methods

NOTE: For each stage, type of examination and degree of BM and CNS involvement should be specified. Based on classification proposed by Murphy.

15.1.2 Burkitts Lymphoma (BL)

Is a highly aggressive B-cell non hodgkins lymphoma characterised by

translocation and deregulation of the Myc gene on chromosome 8. There are three distinct clinical forms namely;

- Endemic(African)
- Sporadic and
- Immune deficiency associated BL.

Clinical presentations

Endemic BL

Common sites

- Jaw and Facial 50 to 60%
- Abdomen

Less common sites

- Ovary
- Testes
- Kidney
- Mesentery
- Meninges
- Bone marrow involvement

Uncommon sites

- Peripheral Lymph nodes
- Spleen
- Mediastinum

Sporadic BL

Usually has abdominal presentation
Other sites includes Kidney, breast, testes ovaries, Bone marrow and CNS

Immune deficiency BL

Mostly involves Lymph nodes, Bone marrow and CNS

Investigations

Tissue biopsy (excision or tru cut biopsy)
FNA (only for flow cytometry if available)
Bilateral bone marrow aspirate
Abdominal USS and CXR

Lumbar puncture
CT-scan/MRI
FBP, RFT.LFT
Serum electrolytes and chemistry
HIV serology

Staging.
The staging system is as follows:

Group A – Low Risk:
A single facial mass (excluding retro-orbital masses) less than 10cm

Group B – High Risk:
Any disease more than Group A but without CNS disease

Group C – CNS disease present:
Any child with clinical or laboratory evidence of CNS disease associated with any other stage of BL disease; all retro-orbital masses are considered as high risk for CNS disease and therefore included in this group.

Group D – Bone Marrow Involvement:
Any child with laboratory evidence of Bone Marrow involvement associated with any other stage of BL disease.

Treatmnent
First line Chemothearpy: Cyclophosphamide, Vincristine, and Methotrexate (COM)

Group	Number and name of intravenous (IV) cycles of chemotherapy	Number of cycles of intrathecal (IT) chemotherapy
A: Low Risk	3 COM	3
B: High Risk	6 COM	3
C: CNS positive	6 COM	6
D: BM Positive	6 alternating COM/ EMIC	6

Second line Chemotherapy: Etoposide, Mesna, Ifosfamide, Cytarabine (EMIC)

Follow-Up .
Three-monthly for the first year ,then every 6 months for 2 years then yearly.
Growth monitoring (height and weight), CXR /USS, CT scan.

15.1.3 Diffuse Large Cell Lymphoma

Diagnostic workup
Similar to the work up for Burkitts Lymphoma

Treatment Diffuse Large B cell Lymphoma
CHOP (Cyclophosphamide, Adriamycin, Vincristine and Prednisolone)

15.1.4 Anaplastic Large Cell Large Cell Lymphoma

ALCL is a peripheral T-cell that typically presents as painless Lymphadenopathy with or without skin or subcutaneous tissue involvement.
Frequently associated with constitutional symptoms such as Fever, weight loss and Night sweats.

Investigations
ALCL is similar to that in Burkitts Lymphoma depending on tumor site and clinical presentations.
On immuphenotyping most of the ALCLtumors are marked by Anaplastic Lymhoma kinase positivity (ALK) due to chromosomal rearrangement involving the ALK gene.

Treatment
CHOP (Cyclophosphamide, Adriamycin, Vincristine and Prednisolone)

15.2 Hodgkin Lymphoma

Introduction
Hodgkin Lymphoma (HL) also known as Hodgkin Disease, incidence of HL varies considerably by age in children such that it is an extremely rare disease in infants but more common in the second decade of life.

HL is linked with EBV infection.

Types

There are generally two broad groups of HL namely **Classsical** and **Nodular Lymphocyte predominant Hodgkin Lymphoma**. Nodular Lymphocyte predominant HL tends to have better prognosis than the classical Group. The Classical type is further histologically subtyped into four subtypes namely;

- Nodular Sclerosis HL
- Mixed Cellularity HL
- Lymphocyte rich HL
- Lymphocyte depleted HL

Clinical presentations

Lymphadenopathy

B-symptoms (fatigue, anorexia, fever, weight loss and drenching night sweats) and Mediastinal mass.

Other sites involved may include spleen and occasionally Liver, Lung and bone marrow marked by cytopenia

Investigations

CXR, CT scan

Bone marrow aspiration/Biopsy is only indicated for patients advanced stages (III and IV) or in those with features of cytopenia

FBP /ESR,RFT,LFT,Serum LDH

Serology for HIV and Hepatitis B and C

Staging for HL by Ann Arbor System

- **Stage I:** Disease confined to single node or group of 'lymphoid structures'
- **Stage II:** Disease involves two or more groups of lymphoid structures on the same side of the diaphragm
- **Stage III:** Disease involves lymphoid structures above and below the diaphragm
- **Stage IV:** Diffuse or disseminated involvement of one or more organs or tissues outside the lymphoid structures with or without associated lymph

node enlargement.

Lymphoid Structures

Lymphoid structures are defined as lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patch.

Substages

Substage A **indicates "asymptomatic" disease.**

Substage B **includes unexplained weight loss of 10%+ within last 6 months and/or drenching night sweats and/or unexplained fever exceeding 38oC**

Substage E **indicates** limited direct extension from an extranodal site or discrete single extranodal deposit consistent with extension from regionally involved node (ie could be encompassed by a single radiotherapy field). Multiple extranodal disease or bilateral lung extension is defined as Stage IV disease.

Treatment for HL

Chemotherapy Summary for First line

Adriamycin, Bleomycin, Vinblastine, Darcabazine (ABVD).

If good response →ABVD +/- radiotherapy if localized disease

Chemotherapy Summary for Second line

If poor response→EPIC(Etoposide, ifosfamide, prednisone, Cisplatin) +/- radiotherapy if localized disease

Follow up

Three-monthly for the first year ,then every 6 months for 2 years then yearly.

Growth monitoring (height and weight), CXR /USS, CT scan.

16 NEUROBLASTOMA

Introduction

The term neuroblastoma also known as ganglioneuroblastomas, and ganglioneuromas.

Investigations

- FBP, RFT, LFT, Serum electrolytes, LDH , ferritin, IgG, TSH, T4
- Coagulation profile
- Urine catecholamine metabolites, vanillilmandelic acid (VMA) and homovanillic acid (HVA)
- CXR, USS
- CT or MRI of primary tumour.
- Bone radiographs or (and scans) of any symptomatic bone areas.
- Bone marrow aspirates
- Biopsy.
- Echocardiography

Staging by the INRGSS

- L1 - Localized tumor not involving vital structures, as defined by the list of image-defined risk factors and confined to one body component
- L2 - Locoregional tumor with presence of one or more image-defined risk factors
- M - Distant metastatic disease
- MS - Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Management

The decision for curative treatment approach for any child with NBL should be made after rsik stratification of the patient.

Low risk disease

Age less 18 months
Localized diasease
MYCN negative tumor (if available)

Infantile Neuroblastoma (widely metastatic (stage 4S)

Intermediate risk Disease

Children above 18months with localized disease without MYCN amplification
Children with completely resected tumor with MYCN amplification
Children less than 12 months of age with widely metastatic disease without MYCN amplification

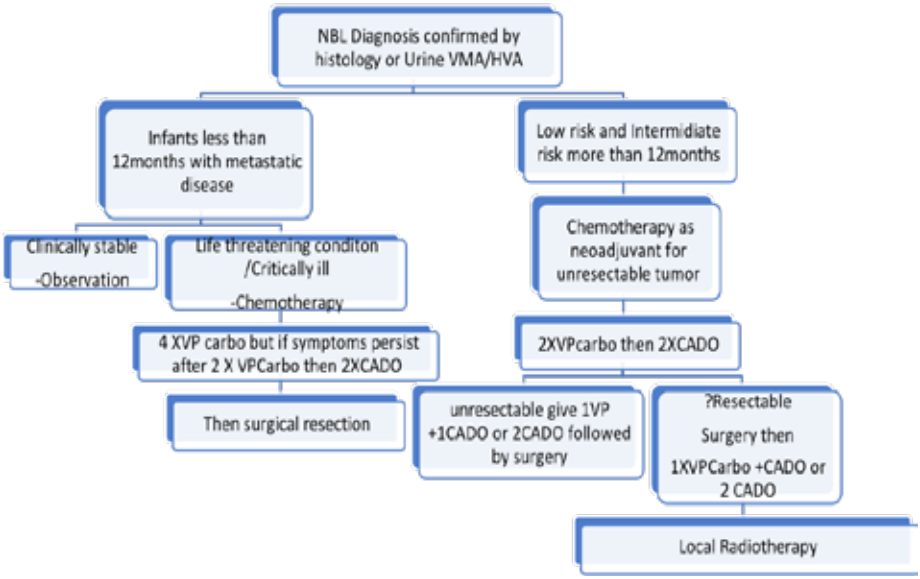
NOTE: All other patients not falling in the above categories should be considered high risk and sent for palliative care.

Surgery

Complete tumor excision for resectable tumors.
Un-resectable tumors should be treated with preoperative neoadjuvant chemotherapy.

Chemotherapy

Chemotherapy Scheme



Chemotherapy

- VPCARBO Regimen: VP16 (Etoposide), Carboplatin
- CADO Regimen: Cyclophosphamide, Doxorubicin, Vincristine

NOTE: For infants less than 5 kg should get dose reduction by 33%

Radiotherapy

Doses of 30–36 Gy in high-risk neuroblastoma.

17 WILMS TUMOUR

Introduction

Wilms tumour is a relatively common and treatable kidney tumour.Wilms tumour is primarly a sporadic disease and only 1 to 2 percent of individual have a relative with the disease. In approximately 10 percent of cases, wilms tumour occurs as part of a multiple malformation syndrome, including WAGR (A syndrome involving Wilm's tumour,Aniridia, Genitourinary malformations and mental Retardation), Denys-Drash and Beckwith-Wiedemann syndrome.

Diagnosis

The diagnosis can be made with reasonable certainty based on history, physical examination and CT scan of the abdomen. Usually most patients present with asymptomatic abdominal mass. Others may present with abdominal pain, fever, or severe general malaise. Hypertension and haematuria may be present.

Investigations

CBC, RFT, LFT, Serum electrolytes and calcium, Urinalysis, Coagulation studies,Cytogenetics studies (1p and 16q deletion).
Elisa antibody test for HIV
Renal USS
4 field Chest X-rays, postero-anterior (and if available lateral) are made to detect lung metastases.
Abd & chest CT/ MRI
Biopsy

Staging

There are two major systems currently in use :

- National Wilms Tumor Study (NWTS) – The NWTS system is based upon surgical evaluation **prior** to the administration of chemotherapy. It is used throughout the United States and Canada.
- International Society of Pediatric Oncology (SIOP) – The SIOP system is based upon **post**-chemotherapy surgical evaluation and is used extensively in Europe.

Stage	NWTSG (before chemotherapy)	SIOP (after chemotherapy)
I	Tumor is limited to the kidney and completely excised	Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal ontours of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and is completely resected (resection margins "clear")
	The tumor was not ruptured before or during removal	The tumor may be protruding into the pelvic system and "dipping" into the ureter (but it is not infiltrating their walls)
	The vessels of the renal sinus are not involved beyond 2 mm	The vessels of the renal sinus are not involved
	There is no residual tumor apparent beyond the margins of excision	Intrarenal vessel involvement may be present
II	Tumor extends beyond the kidney but is completely excised	The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins "clear")
	No residual tumor is apparent at or beyond the margins of excision	The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected
	Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor.	The tumor infiltrates adjacent organs or vena cava but is completely resected
	Although tumor biopsy or local spillage confined to the flank were considered stage II by NWTSG in the past, such events will be considered stage III in upcoming COG studies.	

III	Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain tumor	Incomplete excision of the tumor, which extends beyond resection margins (gross or microscopical tumor remains postoperatively)
	Diffuse peritoneal contamination by the tumor	Any abdominal lymph nodes are involved
	Implants are found on the peritoneal surfaces	Tumor rupture before or intraoperatively (irrespective of other criteria for staging)
	Tumor extends beyond the surgical margins either microscopically or grossly	The tumor has penetrated through the peritoneal surface
	Tumor is not completely resectable because of local infiltration into vital structures	Tumor thrombi present at resection margins of vessels or ureter, transsected or removed piecemeal by surgeon
		The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery
		Regional lymph node involvement was considered stage II in the previous SIOP staging system.
IV	Presence of hematogenous metastases or metastases to distant lymph nodes	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region
V	Bilateral renal involvement at the time of initial diagnosis	Bilateral renal tumors at diagnosis

COG: Children's Oncology Group; NWTSG: National Wilms Tumor Study Group; SIOP: International Society of Pediatric Oncology.

Management

Stage and Histology	Surgery	Chemotherapy	Radiation Therapy
Stage I or II favorable histology without loss of heterozygosity (LOH) 1p and 16q†	Nephrectomy	Vincristine, dactinomycin	No
Stage I or II favorable histology with LOH 1p and 16q	Nephrectomy	Vincristine, dactinomycin, doxorubicin	No
Stage III and IV favorable histology without LOH 1p and 16q	Nephrectomy	Vincristine, dactinomycin, doxorubicin	Yes
Stage III and IV favorable histology with LOH 1p and 16q	Nephrectomy	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, etoposide	Yes

The current dose for radiation therapy for favorable histology Wilms tumor is approximately 10.80 Gy for the abdomen in unfavourable and 19.5-21Gy for unfavourable and 12Gy for the lungs

NOTE: Doses are reduced to 2/3 of the original dose in patients with a bodyweight < 12kg.

Metastatic disease

Patients with metastatic lung and/or liver disease will be treated with vincristine, actinomycin D and doxorubicin.

18 RHABDOMYOSARCOMA

Introduction

Rhabdomyosarcoma (RMS) is thought to arise from primitive mesenchymal cells committed to develop into striated muscles. It can be found virtually anywhere in the body, including those sites where striated muscles are not normally found.

There are two common subtypes: **embryonal and alveolar**.

Stratification and Risk groups

Patients have been stratified in 8 Subgroups (A through H) that are subsequently grouped in 4 Risk Groups: low, standard, high and very high.

The prognostic factors considered are:

Pathology

Favourable = all embryonal, spindle cells, botryoid RMS

Unfavourable = all alveolar tumours (including the solid-alveolar variant)

Post surgical stage

according to the IRS grouping. Briefly

Group I = primary complete resection (equivalent to SIOP pT1);

Group II = microscopic residual (equivalent to SIOP pT3a) or primary complete resection but node involvement (N1);

Group III = macroscopic residual (equivalent to SIOP pT3b). For more details on IRS grouping system see also appendix A.2.

Site

Favourable = orbit, GU non bladder prostate (i.e. paratesticular and vagina/uterus) and head & neck non PM

Unfavourable = all other sites (parameningeal, extremities, GU bladder-prostate and "other site")

Node stage

According to the TNM classification

N0 = no clinical or pathological node involvementN1 = clinical or pathological nodal involvement

Size & Age

Favourable = Tumour size (maximum dimension) ≤5 cm **and** Age < 10 years
Unfavourable = all others (i.e. Size >5 cm **or** Age ≥ 10 years)

Note: patients with malignant effusion (i.e. tumour cell in peritoneal or pleural fluid) or cells in the spinal fluid should be treated according to the protocol for metastatic RMS

Risk Stratification for EpSSG non metastatic RMS

Risk Group	Sub groups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Low Risk	**A**	Favourable	I	Any	N0	Favourable
Standard Risk	**B**	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High Risk	**E**	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable*	I, II, III	Any	N0	Any
Very High Risk	**H**	Unfavourable	I, II, III	Any	N1	Any

Confirming the diagnosis

This must be established pathologically. Open surgical biopsy is the preferred approach as this maximises the tissue available for diagnostic procedures, biological studies and central pathology review. Open biopsy is essential if initial needle biopsy is non diagnostic or equivocal. On rare occasions diagnosis may be achieved by cytology of a malignant effusion or bone marrow aspirate.

Clinical assessment

Regional lymph node involvement should be assessed and recorded in all cases, including biopsy if involvement is suspected but is clinically/radiologically uncertain - under these circumstances needle biopsy or fine needle aspirate

cytology may be sufficient to confirm tumour infiltration.

Investigations

FBP,RFT,LFT,Serum electrolytes, LDH, Alkaline Phosphatase, Urinalysis
CSF Examination for cytospin and cell count is required only for parameningeal tumours
BMA & Biopsy
Echocardiogram
USS , CXR, CT scan or MRI
Bone Scan

IRS and pTNM grouping system

IRS Group	Definition	pTNM
I	Tumour macroscopically and microscopically removed	
(IA)	Tumour confined to organ or tissue of origin	pT1
(IB)	Tumour not confined to organ or tissue of origin	pT2
II (IIA IIB)	Macroscopic complete resection but microscopic residuals Lymph nodes not affected Lymph nodes affected but removed	pT3a
III	Macroscopic complete resection but microscopic residuals and lymph nodes affected and not removed	pT3a
	Macroscopic residuals after resection or biopsy With malignant effusion	pT3b pT3c
IV	Metastasis present or non-regional lymph nodes involved	pT4

Treatment

Surgery – tumor resection

Chemotherapy - vincristine, actinomycin D, cyclophosphamide (VAC), VACA; VAC plus adriamycin alternating with actinomycin D, IVA ;VAC, but with ifosfamide replacing cyclophosphamide and VAIA: IVA with adriamycin alternating with actinomycin D.

Radiotherapy

Radiation doses for the primary tumour according to histology and IRS - group

for children age 3 years or older (RT: radiotherapy; F: fractions).

IRS Group	embryonal RMS	alveolar RMS
I	no RT	41.4 Gy; 23 F
IIa, b and c	41.4 Gy; 23 F	41.4 Gy; 23 F
III followed by:		
- secondary complete resection	36 Gy; 20 F (partial response) 41.4 Gy; 23 F (minor partial response, SD) Subgroup C: option A (no RT) or B (36 Gy)	41.4 Gy; 23 F
- second look surgery but incomplete secondary resection	50.4 Gy; 28 F	50.4 Gy; 28 F
- clinical complete remission, no second look surgery	41.4 Gy; 23 F	50.4 Gy; 28 F
- partial remission, minor PR, SD, progressive disease, no second surgery	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F) orbit and PR (>2/3) 45 Gy; 25 F	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F)

Radiation dose for regional lymph node areas (RT: radiotherapy; F:fractions)

Situation	embryonal/alveolar RMS
no clinical or pathological involvement of regional lymph nodes	no RT
clinically or pathologically positive lymph nodes; excised or in complete remission before RT	41.4 Gy; 23 F
positive lymph nodes, macroscopical residual disease before RT	41.4 Gy; 23 F + 9 Gy boost; 5 F

Follow up

	1st year	2nd year	3rd year	4th and 5th year
Clinical examination	Every 3 months	Every 4 months	Every 4 months	Every 12 months
Ultrasound ± CT scan or MRI of the primary tumour site				
Chest x-ray				

19 MALIGNANT BONE TUMORS IN CHILDREN

19.1 Osteosarcoma

Osteosarcoma and Ewing's sarcoma are the two commonest malignant bone tumors in children.

Clinical presentations

- Painful mass on the extremities,
- History of injury
- Pathological fractures
- Constitutional symptoms such as fever, weight loss and malaise are generally rare.

Work up

- Plain x-ray of the affected bone
- MRI
- Bone scan
- CXR/Chest CT-scan/MRI
- Tissue biopsy
- FBP, RFT.LFT. Serum electrolytes,Coagulation profile,Urinanalysis, LDH
- Echocardiogram
- Audiometry

NOTE: Sperm storage is recommended for male patients of reproductive age if available

Staging for Osteosarcoma

AJCC /TNM Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤8 cm in greatest dimension
T2	Tumor >8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed. Because of the rarity of lymph node involvement in bone sarcomas, the designation NX may not be appropriate, and cases should be considered N0 unless clinical node involvement clearly is evident.
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
cM1a	Lung
cM1b	Bone or other distant sites

Treatment

Sugical - Tumor resection with histological evaluation.

Chemotherapy – Methotrexate, Cisplatin(P), Adriamycin (Doxorubicin), Ifosfamide, Mesna +/- Etoposide.

Radiotherapy - median dose of 60 Gys (range, 40–68 Gys).

19.2 Ewing's Sarcoma

Introduction

Ewing's sarcoma is the second most common primary bone malignancy affecting children and adolescents, after osteosarcoma. The peak age for EWS is during second decade of life from 10 to 15 years.

Ewing sarcoma most often arise in the long bones of the extremities or soft tissue. Compared to undifferentiated ES of bone, patients with extraosseous ES (EES) are more frequently older, more likely to be female, and arise more often within the axial, rather than the appendicular, skeleton.

Clinical presentation

Localized pain or swelling

Trauma history which may be the initiating event that calls attention to the lesion.

Constitutional symptoms or signs, such as fever, fatigue, weight loss, or anemia.

Work-up

- FBP/RFT/LFT/ Serum electrolytes and Calcium, ESR, CRP, LDH, blood cultures
- Biopsy & Immunohistochemistry for CD99 positivity
- Plain CXR/ X-ray of affected bones as initial imaging shows poorly marginated destructive lesion with 'onion peel" pattern from reactive periosteum.
- CT scan and MRI
- Bone scan
- ECG and ECHO
- BMA
- Cytogenetics/Molecular testing

Treatment

Surgery - Tumor resection with histological evaluation.

Chemotherapy

Vincristine, Doxorubicin, Cyclophosphamide/ Ifosfamide, Etoposide (VAC/IE) – For localized disease

Vincristine, Doxorubicin, Cyclophosphamide (VAC) – For metastatic disease.

Radiotherapy

The dose ranges from 40 to 60 Gy.

Follow up

1st year 3 monthly clinic visits plus CXR and Echocardiography twice annually

2nd year 6 monthly clinic visits plus CXR and Echocardiography every year

3rd up to 5th year every year plus CXR and echocardiography

20 RETINOBLASTOMA

Introduction.

Retinoblastoma is the most common primary intraocular malignancy of childhood and accounts for 10 to 15 percent of cancers that occur within the first year of life. Majority of Retinoblastoma patients in Tanzania present with extraocular disease leading to vision loss after enucleation and mortality for metastatic disease.

Retinoblastoma occurs in heritable and nonheritable forms.

Heritable retinoblastoma – Is associated with germline mutations that occur in germline cells in the retinoblastoma gene (rb1 gene mutation).

Nonheritable retinoblastoma – Results from somatic mutations that occur in somatic cells.

Clinical presentation

- Leukocoria
- Strabismus, nystagmus.
- Poor vision,ocular inflammation, heterochromia.
- For metastatic disease may include anorexia or weight loss, vomiting, headache, neurologic impairment, orbital mass, or soft tissue mass and symptoms of bone marrow failure.

Work up

- Ophthalmologic examination under anesthesia with biopsy
- Ocular ultrasonography
- Magnetic resonance imaging (MRI) of the brain and orbits
- Bone marrow aspiration and biopsy
- Lumbar puncture for CSF cytology
- Radionuclide bone scan

Classification of retinoblastoma and recommended treatment options according to the International Retinoblastoma Staging system (IRSS)

Stage	Clinical description
0	Eye has not been enucleated and no dissemination of disease

I	Eye enucleated , completely resected histologically.
II	Eye enuacleated, microscopic residual tumor.
III	Regional extension [(a) overt orbital disease, (b) preauricular or cervical lymph node extension
IV	Central nervous system extension (with or without any other site of regional or metastatic disease) -Hematogenous metastasis: single lesion, multiple lesions; -CNS extension: prechiasmatic lesion, CNS mass, -Leptomeningeal disease and celebral spinal disease.

Treatment options for retinoblastoma as per classification.

Two systems of RB classification will be used concurrently to classify all the patients with retinoblastoma. One is the International classification of retinoblastoma (ICRB) which was devised by the International Society of retinoblastoma and eye disease. Another staging system is the International Retinoblastoma Staging system (IRSS).

Group	Clinical features	Recommended Treatment options
A	All small tumors (3mm across or less) that are only in the retina and are not near important structures such as the optic disc or the foveolar i.e. Not less than 3mm from the foveolar and 1.5mm from the optic disc.	Focal therapy (cryotherapy or Thermotherapy (TTT) alone for smaller tumors (< 3mm in diameter and height) located in visually non-crucial area. TTT uses diode laser (810nm). Tumour is heated until it turns a subtle gray. Complete tumor regression can be achieved by using 3-4 sessions. Observe 5 minutes limit in one session to avoid complication Cryotherapy done to small tumour at equatorial and peripheral retina. Under general anaesthesia place probe precisely on the sclera directly behind the intraocular focus of RB. Apply triple freeze/thaw at 3-week intervals until complete tumor regression Administer cryotherapy 3-6 hours prior to chemotherapy if systemic treatment is indicated. Focal therapy synergistically increases medicine penetration to the tumour

B	Tumour of more than 3mm and close to the optic disc or foveola No subretinal fluid	6 cycles of standard dose chemo-reduction are indicated to allow adequate tumour reduction. Note : standard dose =combination of Carboplatin, Vincristine and etoposide Do not perform focal therapy if tumors are located in the macular and juxtapapillary areas. If focal therapy is indicated chemotherapy should be given within 6hours of focal therapy.
C	Well-defined tumors with small amounts of subretinal or vitreous seeding	Standard dose Chemo-reduction is indicated. Chemotherapy should be given within 6hr of focal therapy (cryotherapy or TTT or subtenon carboplatin (2ml of 20mg) depending on site and response to treatment. Chemotherapy cycles are given at 3-week intervals
D	Large or poorly defined tumors with widespread vitreous or subretinal seeding. There is retinal detachment up to 50% of the globe	Enucleate all unilateral Retinoblastoma to prevent spread of the tumour. If bilateral Start 3 cycles of chemoreduction. Observe. If no response and no visual potential enucleate the eye If there is response complete 6 cycles of systemic chemotherapy. Chemotherapy cycles are given at 3 week intervals Chemotherapy should be given within 6hr of focal therapy because it acts synergistically to increase medicine penetration to the tumour (cryotherapy or TTT or subtenon carboplatin 2ml of 20mg) given under aseptic precaution Local radiation for persistent vitreous seeds may be indicated to use a plaque which is placed on the sclera over the tumour. It stays 36-72hrs.However, this requires licensing.
E	The tumor is very large with one or more of the following features:- No visual potential Tumor in the anterior segment Tumor in or on the ciliary body Neovascular glaucoma Vitreous hemorrhage obscuring the tumor or	Enucleation with minimal manipulation is indicated for All group E with no visual potential, Tumour invasion to anterior chamber, When direct visualization of an active tumor is obstructed by cataract or vitreous haemorrhage. If all known effective treatment has failed Glaucoma secondary to neovascularization of the iris NOTE: Optic nerve length should not be less than 17mm to minimize the chances of leaving tumour

	significant hyphema Phthisical or pre-phthisical eye Orbital cellulitis-like presentation Total RD more than 50%	at surgical site. Also when performing enucleation: - Take care not to perforate the globe Use primary orbital implant to achieve excellent cosmetic appearance If histopathology results are positive for high risk factors Chemo-reduction is indicated. High risk factors include: Extra scleral extension Post-laminar optic nerve invasion with Disease at the cut margin of optic nerve Massive choroidal invasion of more than 3mm Anterior chamber extension If no HRF no need of chemotherapy. Protective glasses are indicated for all children who have been enucleated
EOE	Orbital RB	3–6 cycles of high dose chemo-reduction followed by enucleation /exenteration if disease shown to be responsive. External Beam Radiotherapy and adjuvant chemotherapy for a total of up to 8/12 cycles
	CNS involvement RB	Palliative care according to the National palliative care guideline
	Metastatic RB	Palliative care according to the National palliative care guideline

Chemotherapy: Carboplatin, Vincristine and Etoposide

Radiotherapy

The dose ranges from 40- 45 Gy

NOTE: For more references refer to National Retinoblastoma Management Guideline

21 GERM CELL TUMOUR

Introduction

Germ cell tumors (GCT) arise from primordial pluripotent germ cells, which migrate during embryogenesis from the yolk sac through the mesentery to the gonads. Childhood GCTs can be divided into the following two types:

Gonadal	Extragonadal
Ovary	Brain, neck
Testis	Mediastinum
	Retroperitoneum
	Sarcococcygeal region

Most childhood extragonadal GCTs arise in midline sites which may represent aberrant embryonic migration of the primordial germ cells.
Childhood extracranial GCTs are broadly classified as the following:

- Teratomas.
- Mature teratoma.
- Immature teratoma.
- Malignant GCTs.
- Seminomatous GCT.
- Seminoma (testis).
- Dysgerminoma (ovary).
- Germinoma (brain).
- Non-seminomatous GCT.
- Yolk sac tumor (endodermal sinus tumor).
- Choriocarcinoma.
- Embryonal carcinoma.
- Gonadoblastoma.
- Teratoma and yolk sac tumor.
- Mixed GCT (contains at least two of the malignant histologies listed above).

GCT may produce tumor markers and based on this are divided into secretoric or non-secretoric GCT.

Work up

- FBP, RFT, LFT, Serum electrolytes, LDH, AFP , CA-125 and β-HCG
- Biopsy for histopathology
- USS ,CXR, CT scan/MRI
- Bone scan
- Audiometry
- Lung function test

Staging

TNM Classification

T:TUMOR	Clinical/Radiological Staging (use in patients with no initial surgery)	Post Surgical Staging (use in patients with biopsy/initial surgery)
	T0 No primary tumour	pT0 No tumour on histology
	T1 Localised T<5cm	pT1 Complete resection of localised tumour
	T2 Localised T>5cm and <10cm	pT2 Complete resection of a T4 tumour
	T3 Localised T>10cm	pT3 Residual tumour
	T4 T of any size with locoregional extension.	pT3a microscopic (+ascites for ovarian tumors) pT3b macroscopic
	T5 Bilateral	pT3c biopsy alone
	Tx Unknown	pTx Unknown

N:Nodes	N0-No lymph node involved	pN0 No regional nodes
	N1 Clinical or imaging node involvement	pN1 Involvement of regional nodes
	Nx Unknown	pN1a completely removed
		pN1b incompletely removed
		pNx Unknown

M:Metastasis	M0 No metastasis	pM0 No metastasis
	Including distant nodes (lumbar-aortic are loco-regional for testicular tumours)	M1 Metastases present including distant nodes
	Mx Unknown	Mx Unknown

Stages:		Clinical				Postsurgical		
Stage 1	CSI	T1	N0Nx	M0	pSI	pT1	pN0pNx	pM0
Stage2	CSII	T2T3	N0Nx	M0	pSII	pT1	pN1a	pM0
						pT2	pN0pNxpN1a	pM0
Stage 3	CSIII	T1,2,3	N1	M0	pSIII	pT3b+c	all pN	pM0
		T4	any N	M0		pT2	pN1b	pM0
						pT3a	pN0pNxpN1a	pM0
Stage 4	CSIV	all T	any N	M1	PSIV	all pT	all pN	pM1

Risk groups for extracranial Malignant Germ Cell Tumours (MGCTs)

Low Risk

Gonadal Stage 1 tumours (regardless of AFP level if secreting).
Boys who have inadvertently had an initial trans-scrotal biopsy but are otherwise Stage 1 can be included in this group with very close follow-up.

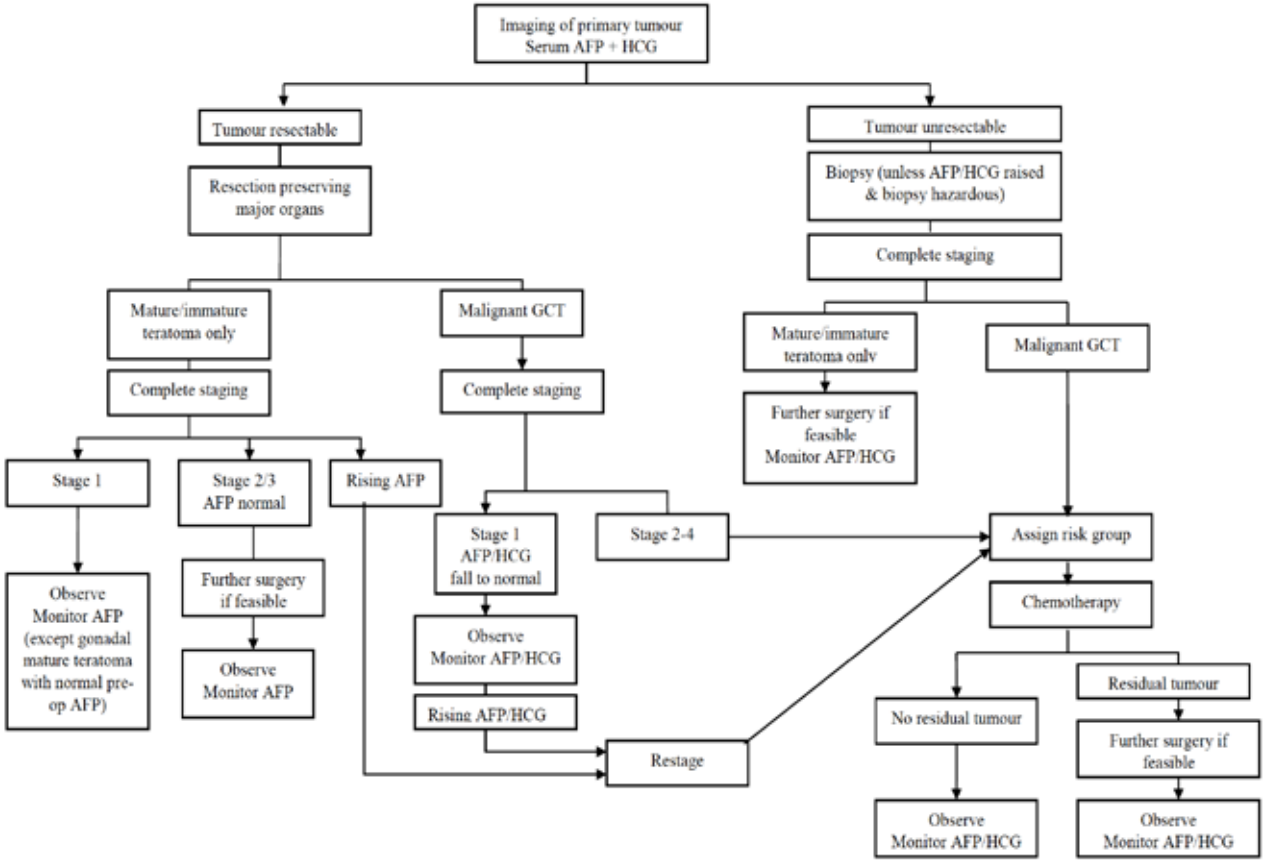
Intermediate Risk

Testis <5yrs, any AFP, Stage 2, 3 + 4
Testis ≥ 5yrs, AFP < 10,000 kU/L, Stage 2 + 3
All other sites, AFP < 10,000 kU/L, Stage 2+3 except thoracic tumours.
Pure germinoma/seminoma, any site, Stage 2, 3 + 4
Pure HCG secreting tumours, any HCG, Stage 2 + 3

High Risk

All Stage 4 tumours except testis < 5yrs and germinoma/seminoma
AFP ≥ 10,000 kU/L except all Stage 1 tumours and testis < 5yrs Stage 2,3+ 4.
All thoracic tumours, Stage 2,3 + 4

OVERVIEW OF MANAGEMENT OF GERM CELL TUMOURS



Treatment

Surgery

Gross total resection of the tumor is the goal.

If a residual mass is present at the end of chemotherapy, second look surgery should be considered if non-mutilating resection is thought to be possible.

Chemotherapy.

Bleomycin, Etoposide and Cisplatin/Carboplatib (BEP)

NOTE: For children <6 months of age 50% of calculated dose by body surface area

For children 6 months - 1 year of age 75% of calculated dose by body surface area

Radiotherapy

Radiotherapy is not an integral part of the management of extracranial germ cell tumours of childhood. It may however be useful for the occasional patient with relapsed tumour. Dysgerminoma of the ovary and seminoma of the testis are exquisitely radio-sensitive and large tumours would be expected to regress with only modest doses of radiation (20 - 40 Gy). Those tumours with secreting or teratomatous elements are moreradio-resistant(40-45Gy)

Follow-up

- Monitor Alfa Fetoprotein and Human chorionic gonadotropin levels monthly for 6 months (period of the highest risk) and then every 3 months, for a total of 2 years (3 years for sacrococcygeal teratoma). The exception to this is completely resected gonadal mature teratomas where AFP/HCG were known to be normal prior to or immediately following surgery. In this case early postoperative follow-up only is appropriate.
- MRI/CT, CXR
- Guided imaging of the primary site may be performed every 3 months for the first year and every six months for the second year.

NOTE: Seminomas and dysgerminomas may recur later, so the imaging schedule may need to be extend

22 HEPATOBLASTOMA

Introduction

Hepatoblastoma is the commonest primary hepatic malignancy in early childhood. The majority of hepatoblastomas occur in the first two years of life and rarely in children older than five years.

The incidence of hepatoblastoma in boys is twice that in girls there is a roughly 20-fold increased risk of hepatoblastoma among children with very low birth weight (<1,500 g) and a double risk among those with moderately low birth weight (1,500-2,500 g).

Clinical presentation

- Abdominal distension/discomfort or abdominal mass in the right upper quadrant.
- Generalized fatigue, and loss of appetite
- Children with a ruptured tumor usually present with vomiting, symptoms of peritonism and severe anemia.
- Rare cases manifest precocious puberty/virilization due to β-human chorionic gonadotropin (hCG) secretion by the tumor.
- Hemihypertrophy, Macroglossia in children with Beckwithwiedeman syndrome

Work-up

Laboratory tests: FBP, LFT,RFT,AFP.

Imaging: CXR,CTscan/MRI, PET scan

Tissue Biopsy

STAGING.

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion

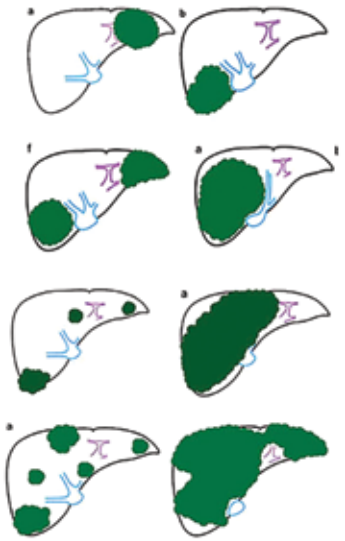
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein,or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral Peritoneum

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIB
Any T	Any N	M1	IV

PRETEXT STAGING



PRETEXT = pretreatment extension:

PRETEXT number	Definition
I	One section is involved and three adjoining sections are free
II	One or two sections are involved, but two adjoining sections are free
III	Two or three sections are involved, and no two adjoining sections are free
IV	All four sections are involved

+

V hepatic veins involvement
P vena portae involvement
E extraliver disease
R rupture of the tumor
F multifocal disease

TREATMENT

Surgery
Complete resection of tumour for stage I and II .

Chemotherapy
Single agent : Cisplatin
Combination: Doxorubicin, Vincristine, Cyclophopshamide, 5-FU OR
Cisplatin, Vincristine, 5-FU .OR Gemcitabine and Bevacizumab.

Radiotherapy
Dose : 12-20 Gray (Gy).

Table for follow up

Time of diagnosis Relevant Examinations	1st & 2nd year	3rd year	4th & 5th years	Subsequent years
Physical examination	Every 2-3 months	Every 6 months	Every 6 months	As clinically Indicated.
Alpha-fetoprotein	1st year every month 2nd year every 3 months	Every 6 months	Every 6 months	
Chest X-Ray	Every 3 months	Every 6 months	Yearly	
Abdominal USS	Every 2-3 months	Every 6 months	Yearly	
Serum magnesium	Yearly	Yearly	Yearly	
GFR: 51Cr EDTA-clearance	1 year off treatment – to be repeated yearly if <80ml/min/1.73m	Yearly if < 80ml/min/1.73m	Yearly if < 80ml/min/1.73m	
Audiometry	Yearly until reliable result obtained with pure tone audiometry (age ≥3.5 years)	Yearly until reliable result obtained with pure tone audiometry (age ≥3.5 years)	Yearly if no reliable result obtained previously or if clinically indicated.	

23 NASOPHARYNGEAL CARCINOMA

Introduction

Nasopharyngeal carcinoma is the predominant tumor type arising in the nasopharynx, the narrow tubular passage behind the nasal cavity.

Risk factors

Epstein-Barr virus (EBV) infection
Environmental factors, such as the high intake of preserved foods and smoking
Genetic predisposition

Clinical presentation

- Nasal symptoms(bleeding , obstruction and discharge)
- Ear symptoms (infection, deafness and tinnitus)
- Headache
- Mass in the neck
- Cranial nerve palsy

Work up

- FBP, RFT, LFT, EBV titres (IgG, IgA Antibodies)
- Biopsy
- CT scan/MRI/ PET
- Audiogram
- Bone scan

Subtypes of NPC

Pathology

Three subtypes of NPC are recognised in the World Health Organisation (WHO) classification:
Type 1 - Squamous cell carcinoma, typically found in the older adult population,
Type 2 - non-Keratinizing carcinoma
Type 3 is undifferentiated carcinoma.
Most cases in childhood and adolescence are type 3, with a few type 2 cases. Type 2 and 3 are associated with elevated EBV titres, but type 1 is not.

STAGING

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No tumor identified, but EBV-positive cervical node(s) involvement
Tis	Tumor 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

N Category	N Criteria
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

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T1, T0	N1	M0	II
T2	N0	M0	II
T2	N1	M0	II
T1, T0	N2	M0	III
T2	N2	M0	III
T3	N0	M0	III
T3	N1	M0	III
T3	N2	M0	III
T4	N0	M0	IVA
T4	N1	M0	IVA
T4	N2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Treatment

Radiation therapy is the mainstay , with chemotherapy used in advanced cases.
Doses : 45-50.4 Gy /1.8-2Gy per fraction for bigger field.
Boost: 15-25Gy to a total dose of 65-70 Gy .

Chemotherapy

Cisplatin/Carboplatin , 5-Fluorouracil concurrent with radiotherapy.
OR Sequential chemoradiation with Gemcitabine and Cisplatin.

PART IV

SUPPORTIVE CARE FOR CANCER PATIENTS

24 NUTRITION IN CANCER

Nutrition management in Cancer

Goals of Nutrition Management in Cancer

Conduct early nutritional assessment in order to prevent or minimize weight loss from increased basal metabolic rate. Some patients are hypo-metabolic; others hyper-metabolic by 10-30% above normal rates. Greatest losses occur from protein stores and body fat.

- Overcome side effects/diminishing toxicity of treatment.
- To correct cachexia from anorexia, redistribution of host nutrients and nutritional depletion.
- To control cancer and complications such as anemia or multiple organ dysfunction.
- To prevent further depletion of humoral and cellular immunity from malnutrition.
- Prevent infection or sepsis and prevent starvation
- To control gastrointestinal (GI) symptoms which are more common with weight loss greater than 10%.

Nutritional Assessment in Cancer Patients

All patients should be assessed for nutritional risks as soon as the patient reach at the hospital

Patients' anthropometrical measurements such as weight, height, BMI, Weight for Height, MUAC and other nutritional methods should be assessed according to patients condition and status.

Patients biochemical analysis should be evaluated, components such as triglycerides, cholesterol, BUN, creatinine, alkaline phosphate, magnesium, white blood cell count, calcium, hemoglobin and hematocrit, sodium, glucose, albumin, uric acid and other necessary investigations

Patient's dietary intake and pattern should be evaluated accordingly

Dietary and nutritional recommendations for management of cancer

In general, intake of energy and protein should be high; for (1-1.5g/kg) body weight to maintain weight and 1.5-2g/kg to replace losses.

It is recommended to give 25-35 Kcal/kg body weight to maintain weight or 35-50Kcal/kg body weight to replete stores. If the patient is febrile or septic more calories should be added. Take on average 30-50% of healthy fats.

- Give patient small but frequent meals daily, five to six meals a day. If patient is on tube feeding, feed small liquid or semi liquid feeds 3-4 hourly.
- Use total parenteral nutrition if enteral feeds are contraindicated.
- Provide adequate but not excessive micronutrients supplements such as vitamin B6, pantothethenic acid, folic acid, vitamin A, E and C. Use more foods high in B-carotene; include lots of fruits and vegetables in appropriate forms.
- Review each patient individually and manage accordingly.

Other Healthy Eating Recommendations

If the client feels too weak, high energy foods may assist to boost the levels such as 1 tea spoon of plumpy nut/ground nut paste once a day in severe weight loss may help.

Take a lot of fruits and vegetables

Vegetables of all types including dark green leafy e.g.: spinach, pumpkin leaves, cassava leaves, mgagani, mchunga, sukuma wiki, broccoli, light green vegetables(Chinese, lettuce, cabbage, cauliflower etc)

Fruits such as citrus and yellow coloured ones e.g.: mango, oranges, tamarind, passion, pawpaw etc: These fruits and vegetables produce ant-oxidants which may help to reduce free radicals that are generated from different foods and chemical reactions in the body by eliminating them out of the body as waste products.

Reduce the consumption of total saturated fats

From poultry skin, red meat e.g. fatty beef, lamb, goat, pork, beef offals, intestines etc. Meat may affect cancer risk because of chemicals formed during digestion that have been found to damage the cells that line the bowel. Other likely factors include the fat content, and the way it is processed or cooked; or because big meat eaters miss out on other protective foods such as fruit and vegetables or wholegrain cereals. It is advised to take meatless foods in some days of the weak.

Increase fiber intake per day

May come from whole grain foods like maize, local rice, millet, sorghum, brown bread and also fruits and vegetables and some legumes

Minimize the consumption of salt cured, salt-pickled, and smoked foods

Diets containing high amounts of food preserved by salting and pickling are associated with an increased risk of cancers of the stomach, nose and throat. As salt strongly enhances and promotes chemical gastric carcinogenesis and H. pylori infection , there is an association between work, salt intake, and development of stomach cancer. Reducing salt intake, especially during pregnancy, also reduces the risk of developing breast cancer and many other diseases, as well as obesity.

Reduce alcoholic beverages

Evidence suggests all types of alcoholic drinks may increase your risk of a number of cancers, including mouth, throat (pharynx), voice box (larynx), esophagus, liver, breast, colon and rectum. It is considered more harmful when combined with smoking. If you drink at all, limit alcoholic drinks to no more than one drink daily for women and two for men.

Take a lot of water per day; it helps to remove waste products (2-3liters/day)

Water flushes toxins out of the body and therefore prevents many diseases of the colon or rectum, like colorectal cancer. Drinking water and eating more water-heavy foods can also help promote the healthy growth, survival, and reproduction of your body's cells. Also drinking a lot of water during chemotherapy treatment is important since treatment and some medications have side effects that could cause severe dehydration. Drink plenty of water during treatment can help recovery a smoother process

Control weight and obesity (avoid becoming overweight or obese)

Maintaining a healthy weight is key to reducing your risk of cancer and other diseases. Being overweight or obese is likely to raise your risk for developing more than 13 types of cancer. Obesity can negatively affect inflammation in the body, the immune system, the way in which body cells grow and levels of certain hormones.

Vary food choices.
Foods contain combinations of nutrients and other healthful substances. No single food can supply all nutrients in the amounts you need. For example, oranges provide vitamin C but no vitamin B12; cheese provides vitamin B12 but no vitamin C. To make sure you get all of the nutrients and other substances needed for health, choose the recommended number of daily servings from each of the five major food groups.

Common Side Effects of Cancer Treatment that can affect eating and what to do;

Loss of appetite
In case of loss of appetite try to use spices such as ginger, cinnamon, cardamom which will help to increase appetite when they are used in food preparations.
Eat small meals frequently.
Try to eat favourite foods and drinks which are healthy
Try to eat variety of food.
Try to exercise.
Eat with family members or friends.

Sore mouth or throat
Try eat soft diets such as blended bananas, avocado, pawpaw etc
Avoid hot foods and with lots of spices.
Rinse your mouth using warm water mixed with blended garlic.
Drink yoghurt which will slow down the growth fungus within the mouth.
Drink with straw if possible.

Dry mouth
Drink plenty of fluids that provide calories, such as juices, smoothies, milk, and shakes. These fluids can help you get good nutrition without having to chew and swallow food. (Refrain from drinking caffeinated beverages, which can contribute to dehydration.)
If solid food is something you can tolerate, take small bites, and chew slowly and completely.
Think soft and moist food such as soft fruit, yogurt or pudding.
Add broth or sauces to foods such as bananas, potatoes, and rice to soften

them.
Try sucking on frozen fruit, such as frozen grapes, peach slices, and watermelon. The chill will be soothing, and you'll get loads of nutrients.

Changes in taste or smell
If your favourite foods taste different, avoid them so you don't develop a distaste for them
If foods taste metallic, try eating with plastic utensils.
Use your favourite spices to help bring flavour to your main dish.

Nausea and Vomiting
Avoid high spiced foods, high sugary food and high fatty foods.
Try to eat sour foods dry and with low salt such as slice of bread.
Eat small meals frequently.
Eat while seated in upright position.
Don't skip meals; nausea is worse when you're hungry.

Diarrhoea
Drink clean and safe water to avoid dehydration. (at least 1.5L/day)
Use ORS, rice water or coconut water
Eat warm food, neither too cold nor too hot.
Eat ripe fruits eg. Bananas which may help to decelerate the situation.
Avoid oily foods as they may accelerate diarrhoea.
Avoid caffeinated drinks which may cause dehydration.

Constipation
Drink a lot of water (at least 1.5L/day)
Eat high fiber foods such as whole grain cereals
Eat fruits like pawpaw and mangoes.

Feeling very tired all the time (fatigue)
Try to take on a lighter workload, maintain a proper nutritious diet, exercise daily and rest if they feel tired.

Depression
Try to eat with your family members or friends.

25 ONCOLOGICAL EMERGENCIES

Introduction

An oncologic emergency may be defined as any acute potentially morbid or life threatening event directly or indirectly related to patient's tumour or its treatment.

For prevention and early detection of oncologic emergencies physicians must maintain a high degree of suspicion and must adequately educate patients about preventive measures and reporting of symptoms.

25.1 Neurologic emergencies

25.1.1 Spinal cord compression.

Introduction.

Delay of treatment can lead to permanent damage of the spinal cord leading to sensory loss, loss of sphincter control and paralysis. Approximately about 15 – 20% of cases of spinal cord compression in adults start from metastatic breast, lung, or prostate cancer. Some cancers are frequently source of spinal cord metastases and can lead to compression such as lymphoma, melanoma, renal cancer, sarcoma, and myeloma.

Spinal cord compression can happen as a result of the following;

- Haematogenous spread of metastatic tumour into the Epidural space
- Presence of paravertebral tumours which can spread to spinal cord canal through intervertebral foramen and hence causing direct compression
- Vertebral body bone destruction by the tumour or metastatic lesion can lead to collapse with bone fragments displacement into epidural space
- Rarely can be due to direct metastasis to the spinal cord and meninges

The majority of patients with SCC more than 90% frequently present with the progressive back pain. The pain due to compression is habitually provoked by movement, Valsalva's maneuver, straight leg raise, and neck flexion on clinical examination.

Thoracic Spine is more affected by approximately (60%) since it is the narrowest

part of the cord, followed by lumbosacral (30%) and cervical spine (10%).

Work up
X- ray of the spinal cord/Magnetic resonance imaging (MRI)/CT scan of the spine

NOTE: Myelography: Reserved for patients (with cardiac pacemakers) contraindicated to undergo MRI.

Management
The key objective of therapy is to preserve and recover neurological functions and survival. The mainly significant factor for determining prognosis is the level of neurologic function at the start of therapy.

Steroids: Dexamethasone/Prednisolone

Radiotherapy:It has been used as an ultimate treatment for majority of the patients.
Dose is 8gy single fraction/20Gy in 5 fractions/30GY in 10 fractions.

Surgery: Is indicated for solitary metastatic focus/lesion or if histopathology is unknown

Chemotherapy: In some chemosensitive cancers chemotherapy has been used as primary therapy, although not used alone as a single modality of treatment.

25.1.2 Increased intracranial pressure
Introduction
Tumours involving the brain parenchyma or lesions that obstruct the flow of the cerebrospinal fluid (CSF) can lead to an increased intracranial pressure. Severe intracranial pressure can lead to herniation of the brain and death. When ICP raises to a greater than 20mmHg (normal <10mmHg) results in brain autoregulation, development of ischemia and the injury leads to symptoms development.

Clinical presentation

Common presentation of patients with increased ICP includes headache, cranial nerve symptoms, nausea and vomiting and sometimes seizures.

Three herniation syndromes include;

- Central herniation: Patient may present with slow deterioration in the level of consciousness, coupled with headache and focal neurologic deficits.
- Uncal herniation: Patient present with rapid loss of consciousness, lateral papillary dilatation, and ipsilateral hemiparesis. Mostly common with tumours of the temporal lobe or the lateral fossa of the frontal lobe.
- Tonsillar herniation: patients presents with symptoms including occipital headache, vomiting, and hiccups accompanied by reducing level of consciousness and respiratory compromise; commonly due to a posterior fossa mass.

Work up

CT scan or MRI

Treatment

Patients with signs of imminent herniation either clinically diagnosed or following imaging, should be urgently treated with Hyperventilation to keep up an arterial PCO2 at 25 -30 mmHg, Mannitol IV and Dexamethasone IV.
Once herniation has been prevented or controlled then a definitive management should follow such as a surgical intervention or radiotherapy.

NOTE:Mannitol may be given every 4 to 6 hours in doses adjusted to avoid unnecessary volume contraction and hypernatremia.
Serum osmolality of higher than 320 mOsm/L have to be avoided.
Avoid lumber puncture in patients with increased ICP, do CT scan first.

25.1.3 Seizures

Introduction

Patients with brain metastasis can have seizures as their presenting symptom in approximately 15% to 30% of patients.Seizures can be as a consequence of complications of cancer therapy, such as infections, metabolic abnormalities,

or medications.

Work Up
MRI/CT Scan,cultures, medicine levels and monitor serum chemistries (Sodium, Potasium and calcium) daily.

Treatment
Acutely: Diazepam/Lorazepam/Dexamethasone first followed by a definitive therapy.
Anticonvulsant therapy phenytoin with a loading dose of 15 mg/kg then a maintenance dose of 300 mg/day.

25.1.4 Leptomeningeal disease

Introduction
Leptomeningeal carcinomatosis defined as diffuse seeding of leptomeninges by tumour metastases, presents commonly in patients with advanced adenocarcinomas. Solid tumors (breast carcinoma, lung carcinoma, and melanoma), some hematolymphoid cancers such as Lymphomas and leukemias metastatize to the leptomeninges, as well as primary brain tumors.

Clinical presentation
Clinical presentation depends on the area of the brain that is affected; common areas of metastases are in the cerebral hemispheres, the cranial nerves, spinal cord and roots.

- Headache.
- Altered mental status.
- Nausea or vomiting.
- Focal weakness of upper or lower limbs.
- Seizures.
- Pain in an axial or radicular distribution.
- Peripheral sensory loss.
- Bladder and/or bowel dysfunction.
- Involvement of the cranial nerves may result in to diplopia, hearing loss, facial numbness, loss of visual acuity, and ophthalmoplegia.

Wok up
Lumbar puncture
MRI and CT scan

Treatment
Radiation therapy – Dose is 8gy single fraction/20Gy in 5 fractions/30Gy in 10 fractions
Intrathecal chemotherapy treatment with thiotepa (Thioplex), cytarabine, or methotrexate can be administered with or without radiotherapy.

25.2 Cardiovascular diseases

25.2.1 Cardiac tamponade.

Introduction
Cardiac tamponade occurs when there is fluid accumulation in the Pericardial cavity, leading to an increase in intra pericardial pressure later affects diastolic filling of the heart, ending in decrease in cardiac output. Cancers that have been identified to have tendency of spreading to the pericardium includes advanced Lung cancer, Breast cancer, melanoma, Leukemia and lymphomas.
Other causes of cardiac Tamponade may includes Uraemia, Medicines such as chemotherapy in 1%-2% of patients exposed to agents like Busulphan, Cytarabine, Cyclophosphamide or Tretinoin in high doses or in combination during the treatment of haematological malignancies.

Clinical presentation
- Dyspnea.
- Cough (dry).
- Chest pain and tightedness.
- Fever with palpitations.
- Peripheral edema and orthopnea.
- Hoarseness.
- Hiccups, or nausea.
- Fatigue, anxiety and confusion.

Work up

Two –dimensional echocardiography (2D ECHO) and Electrocardiography (ECG)
Chest X-ray: provide proof of an enlarged cardiac silhouette
Pericardiocentesis: for cytological studies of the pericardial fluid aspirated.

Management

- Radiation: dose of 1 - 2 Grays/d over 3 to 4 weeks, with a total dose of less than 35 to 40 Grays should avoid radiation pericarditis.
- Chemotherapy: Cisplatin, Mechlorethamine, Teniposide, Fluorouracil, Thiotepa, Quinacrine hydrochloride, and Radioisotopes for the induction of sclerosis.
- Percutaneous balloon pericardiotomy and pericardial window can be considered.NSAID's are also recommended for patients with cardiac temponade.

NOTE: In cases where systemic therapy has failed to control pericardial effusion then other Local procedures are advised where resources are available, such as Subxiphoid pericardiostomy plus or minus intrapericardial instillation of sclerosing or cytotoxic agents such as Bleomycin.

25.2.2 Superior vena cava obstruction (SVCO)

Introduction

Superior vena cava syndrome includes a set of signs and symptoms as a result of incomplete or complete hindrance of blood flow from external compression or intrinsic obstruction of the superior vena cava (SVC) or related greater veins.

- Malignant diseases causing SVCO are Lung cancer (>SCLC and SCC histology cases) which accounts for nearly 85% of all cases followed by Lymphomas mainly NHL 10-15%, with less than 2% occurs in patients with Thymomas and mediastinal Germ cell tumours.
- Non malignancy causes of SVCO includes retrosternal goitre, sarcoidosis, tuberculosis, mediastinal post Irradiation, Idiopathic fibrosis. There is also an increase of SVCO in cancer patients with long term central venous catheters.

Clinical presentation

- Dyspnea.
- Facial swelling.
- Cough.
- Orthopnea.
- Head fullness and pressure sensation.
- Venous distension in the neck and thoracic wall, and plethora, proptosis, stidor.
- Arm swelling/edema.
- Horseness of voice.
- Dysphagia,
- Headache, dizziness, syncope.
- Chest pain.
- Alteration in mental status.
- Increased intracranial pressure, intracerebral bleeding.

Work up

Chest X-ray.
CT and MRI
Invasive contrast venography.
Sputum cytology.
Thoracentesis.
Bronchoscopy.
Needle aspiration of a peripheral lymph node, or mediastinoscopy.

Treatment

Head elevation (cardiac bed) and supplemental oxygen,
Steroids can be started (Dexamethasone)
Diuretics
NOTE: Role of thrombolytic (Streptokinase or Urokinase)/ anticoagulant (Heparin or Warfarin) therapy incases of venous thrombosis

Chemotherapy: For chemo sensitive tumors.

Radiation therapy: Dose - 20Gy/ 5 #s or 30Gys/10#s or 37.5Gys/15#s

Surgical care: Bypass.
Stenting, per cutaneous transluminal angioplasty (PTA), thrombolysis or combination there of.

25.3 Respiratory emergencies

Introduction
Respiratory complications are frequently encountered in cancer patients, can be directly due to tumor growth and invasion such as; obstruction, hemoptysis, lymphangitic spread, and leukostasis or indirectly following cancer therapy for example; infections, pulmonary edema, hypersensitivity reactions, and toxic injury from chemotherapy or radiation.

25.3.1 Airway Obstruction
Airway obstruction may arise from endobronchial lesions or extrinsic compression of the bronchial tree from adjacent structures. Depending on the type of lesion, patient may present as acute or subacute.
Known common cancers that can lead to obstruction include bronchogenic cancer, head and neck cancers, lymphoma, thymoma, or thyroid malignancies.

Clinical Presentation
Cough and dyspnoea
Hemoptysis
Stridor.
Pneumonia

Treatment
Supportive
Oxygen and corticosteroids.

Surgery
Intubated or tracheostomy.
Bronchoscopy with stent placement.

Radiotherapy

Dose – 10Gys single or 8.5Gys x 2(1 week apart) or 20Gys/5#s or 30Gys/10#s or 37.5Gys/15#s

25.3.2 Massive haemoptysis

Introduction

Massive hemoptysis, defined as expectoration of 400 to 600 mls of blood within 24 hours. Patients with non-life-threatening hemoptysis should be evaluated and managed carefully as the episodes may herald to a more serious event.
Conditions that can lead to hemoptysis are - malignant diseases (bronchogenic carcinoma), infection (PTB, lung abscess, aspergillosis, bronchiectasis) and chemotherapy induced clotting factors depletion.

Treatment

Supportive

Bed rest in a semi-erect position, sedation with anti anxiolytics, humidified oxygen, blood products (RBCs, Platelets) and fluid replacement.
Correction of abnormal clotting parameters by administration of VIT K.

Surgery

Surgical resection, laser ablation, and bronchial artery catheterization and embolization.

25.4 Gastrointestinal emergencies

25.4.1 Neutropenic Enterocolitis

Introduction

Neutropenic enterocolitis (typhlitis) is an acute life threating condition characterized by transneuro inflammation of the caecum, abdominal distension, tenderness on the right side of the abdomen, watery/bloody diarrhea, nausea, vomiting and fever.

Risk factors

NEC was initially reported in children managed with intensive chemotherapy, such as those with leukemia. The syndrome is commonly associated with

hematologic malignancies, aplastic anemia, myelodysplastic syndromes, and seldom solid tumors.

Work up

FBP,Serum electrolytes, PH value, stool analysis, stool and blood culture
Abd USS or CT Scan.
Endoscopy and biopsy.

Treatment

Supportive
GCSF, bowel rest and nasogastric suction, IV fluids, Blood and platelets transfusion, IV antibiotics(broad spectrum), parenteral nutrition.

Surgery

Cecostomy and drainage
2-stage right hemicolectomy with or without primary anastomosis
Defunctioning of the colon with a loop ileostomy.

25.5 Metabolic emergencies

25.5.1 Tumor lysis syndrome

Introduction

Tumour lysis syndrome is a complication caused by tumours or their treatment (especially chemotherapy) or rapid kill of cancer cells that can lead to release of intracellular ions and metabolic by products into the circulation resulting into potentially deadly metabolic derangements.
The syndrome is mostly observed in cancers with a rapid proliferation index such as Burkitt's lymphoma, acute lymphocytic leukemia, acute non-lymphocytic leukemia, and less frequently, solid tumors of small-cell type, breast cancer, and medulloblastoma.

Clinical Presentation

Majority of the patients are clinically asymptomatic at the initial stages of the syndrome. Clinically, the syndrome is characterized metabolically by the

presence of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and acute renal failure. Severe electrolyte imbalances can result in cardiac arrythmias, seizures, carpopedal spasm, and neuromuscular disturbances with deranged level of consciousness.

Prevention

- Hydration for high risk patients 12 to 48 hours prior to chemotherapy.
- Prophylactic measures including alkalinization of the urine with sodium bircabornate.
- Rigorous hydration.
- Prevention of hyperuricemia by administration of allopurinol or Rasburicase

Work Up

FBP, RFT, LFT, LDH, Serum electrolytes phosphates and calcium, Urine pH and output
ECG.
CXR/ CT-Scan.
Abd Pelvic USS

Treatment

- Frequent monitoring of electrolytes such as blood-urea-nitrogen (BUN), creatinine, uric acid, potassium, sodium, phosphate, calcium levels and Lactate dehydrogenase (LDH) at least three times per day
- Also Alkalization of urine by Sodium bicarbonate added to IV fluids at 100 mEq/L this should continue for 48-72 hours after start of chemotherapy.
- Hydration in high risk patients must start 12-48 hours prior the start of chemotherapy and continue 48- 72 hours post chemotherapy; continuous infusion should exceed 3 L/m^2 daily, resulting in urine volumes of at least 3L/Day.
- Use of diuretics such as Furosemide or mannitol has not been established to be valuable as a front-line therapy.
- Allopurinol
- Patients with high potassium levels must be evaluated and monitored constantly for cardiac rhythm disorders, do administer calcium and exchange resins, those with continuously low levels calcium a calcitriol

must be given.

- Empiric antibiotics can be administered for opportunistic infections, consider also perenteral nutrition (TPN) and GCF (neupogen) if indicated.

NOTE: Stop alkalinization of urine if the elevated levels of calcium and phosphate is >70% , hence continue with hydration and regular monitoring of serum electrolystes at least twice daily .

25.5.2 Hyponatremia and SIADH

Introduction

Hyponatraemia is defined as a serum sodium levels of less than 135mEq/l, and is severe once the serum sodium level is below 125mEq/l.

Clinical presentation

Presentation depends on the level of hyponatremia and the rapidity of its occurrence. Slow onset with mild hyponatremia presents with slight changes in mental status and cognitive changes including memory loss, apathy, impaired abstract thinking, fatigue, anorexia, myalgias, and headache. Severe hyponatremia with rapid onset (serum sodium less than 115 mEq/L) may present as asterixis, distorted mental status, confusion, lethargy, seizures, and coma. On physical examination may reveal papilledema, pathologic reflexes, and focal findings.

Work up

Urine osmolality
Serum osmolality
Urinary sodium concentration
CXR, CTscan

Treatment

Restriction of fluid intake .
Patients with severe hyponatremia and presents with coma or seizures could be managed with 3% hypertonic saline by slow infusion at a rate adequate to increase the serum sodium level by 0.5 to 1.0 mEq/L/h.
Management of the tumour producing antidiuretic hormone or atrial natriuretic

factor along with fluid therapy is important.

25.6 Febrile Neutropenia

Appllied only to the management of patients with:

- Fever and neutropenia as a result of a known or suspected malignancy or the use of chemotherapy
- Fever and neutropenia as a result of a bone marrow failure syndrome.
- Fever (or evidence of infection) who are receiving chemotherapy or who have completed cancer therapy within 6 months even though they are not neutropenic.

NOTE: The need for initiating empiric antibiotic therapy in such cases is assessed by the severity of the presenting signs and symptoms, the results of initial investigations and the presence/absence of a peripherally inserted central catheter (PICC lines). PICC cultures must be drawn as part of this assessment. Aerobic Blood cultures must be taken every 48 hours while patient remains febrile, and/or prior to the addition of a new antibiotic.

Work up

FBP,LFT,RFT
Malaria screen
Urine analysis
Urine / blood / stool culture
Serum electrolytes
Throat Swab

Treatment

Antibiotic administration
Anti pyretics and analgesics

Initial (first-line) and subsequent (second-line – deteriorating patients) empiric antibiotic selection.

Patient Condition	Antibiotics & Doses	Comments
PATIENTS with no significant beta-lactam reactions:	Piperacillin-tazobactam (Tazocin) 4 g piperacillin / 0.5 g tazobactam given every IV 6 hourly AND Gentamicin 3-6mg/kg once daily	Adjust Tazocin doses for renal impairment. Tazocin usually provides adequate coverage for G positive organisms including viridans streptococci. However, if additional coverage against resistant G positive organisms (e.g. coagulase negative staph, MRSA) is desired, the addition of Vancomycin is recommended. Consider discontinuation of Vancomycin once culture and susceptibility results are available. Maximum dose of GENTAMICIN is 400mg daily.
DETERIORATING PATIENTS on first line treatment with no history of anaphylaxis to Beta Lactams (i.e. if history of rash only, can still use Meropenem)	Meropenem 500mg dose IV 8 hourly AND Amikacin 15mg/kg/dose in 2-3 devided dose (or Ciprofloxacin 200 – 400 mg IV 12 hourly) AND Vancomycin 15 - 20mg/kg/dose 8 - 12 hourly	Meropenem: Max single dose: 2g Ciprofloxacin: dose reduce if creatinine clearance <20ml/min/1.73m^2, use half normal dose. Max single dose: 400mg
PATIENTS with history of definite anaphylaxis to Beta Lactams	Ciprofloxacin as above AND Metronidazole 500mg – 750mg dose IV 8 hourly AND Amikacin dose as above AND Vancomycin dose as above	Adjust ciprofloxacin doses for renal impairment. Max single dose: 400mg Metronidazole max single dose: 4g.

NOTE: In an effort to avoid or minimize aminoglycoside-induced hearing loss, patients with known, significant, pre-existing hearing loss or renal impairment or Hepatoblastoma should receive single agent Ceftazidime (with the addition of oral Metronidazole if anaerobic infection suspected) rather than gentamicin. Similar patients with significant beta lactam allergy may receive one dose of aminoglycoside.

Continued Management

Continue with antibiotic management as outlined above, relative to the patient's culture report, temperature, ANC and clinical condition.

Culture Negative Patients

First 48 hours.

- Patient had a single spike of fever (i.e.patient's temperature returns to normal within 4 hours of the initial fever),antibiotics may be discontinued.
- Patient had more than a single spike of fever, antibiotics must be continued for a minimum of 7 afebrile days.

Also consider the following

- If patient develops oral herpes or severe mucositis, commence IV Aciclovir.
- Obvious fungal infection – suspect candida – add fluconazole IV; suspect other fungal infection – add Amphoteracin B IV.
- Diarrhoea and vomiting – culture stool and commence ciprofloxacin and metronidazole
- Signs of skin infection – add vancomycin
- No clinical focus but deteriorating rapidly or extremely unwell – consider adding vancomycin

If by day 5-7 patient remains febrile, neutropenic, consider performing a fungal work-up, prior to commencing empiric appropriate antifungal treatment.

Fungal work-up:

CXR
CT chest
Abdominal U/S (or CT abdo)
CT sinuses (if patient is > 7 yrs of age)

By day 7+ if patient having responded to initial regimen becomes febrile again or has had persistent fever and fungal work-up not yet done, perform above fungal work-up and commence on empiric appropriate antifungal treatment.

If persistently neutropenic patient becomes febrile again after discontinuation of a 10 – 14 day course of antibiotics, reculture and restart broad-spectrum

antibiotics as per day 1 of F&N guidelines. If fever persists for a further 48hrs or more, add in empiric appropriate antifungal treatment.

Culture Positive Patients

If patient becomes afebrile and is clinically well, re-culture and await identification of organism and sensitivity data before modifying treatment. If patient remains neutropenic continue with broad-spectrum IV antibiotics for at least 7-10 days.

Antibiotics specifically directed toward the identified organism should ordinarily be ADDED to the broad spectrum therapy if the initial antibiotics do not provide adequate coverage.
I.E. Broad spectrum coverage must not be replaced by organism-specific antibiotic(s) alone in the neutropenic patient.

Deteriorating status

Patients who become haemodynamically unstable or appear to be progressively deteriorating should be brought to the immediate attention of the consultant Oncologist and the Infectious Disease service.

See Table One above for the empiric antibiotic guideline changes recommended for patients deteriorating on first-line treatment. If the patient has received 5 to 7 days of empiric antibiotic therapy, consider the addition of empiric antifungal coverage too.

Discontinuation of Antibiotic Treatment

Table:

PATIENT PARAMETERS	PLAN
Afebrile > 48hrs; ANC = 1 x 10^9/L, cultures negative. Febrile on only one occasion, any ANC, culture negative, patient is well.	DISCONTINUE antibiotics.
Afebrile >7 days, ANC < 0.5 x 10^9/L, no evidence of hematological recovery, no documented focal infection, IV antibiotic duration = 7-10 days	CONSIDER discontinuing antibiotics.
Afebrile > 48 hrs, ANC = 0.5 x 10^9/L, cultures positive or documented focus of infection	CONSIDER discontinuing broad spectrum coverage after 7 days, CONTINUE specific therapy, and tailor duration to diagnosis, e.g. Skin/soft tissue infection: 7 – 14 days Uncomplicated bacteremia: G –ve: 10 – 14 days G +ve: 7 – 10 days S. Aureus (no endocarditis): min 14 days Bacterial pneumonia: 10 – 21 days HSV/VZV: 7 – 10 days

26 PAIN AND PALLIATIVE CARE

Introduction to Palliative care

Palliative care is 'an approach which improves the quality of life of patients and families facing a life threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems – physical, psychosocial and spiritual.' Palliative care should begin from the time of diagnosis in conjunction with other therapies that are intended to prolong life such as radiation therapies, chemotherapies, antiretroviral and surgery **(WHO 2002).**

Essential components of palliative care are:

- Multi-disciplinary Teams (MDT)
- Effective symptom control
- Effective communication and support in decision-making
- Identification of surrogate decision maker
- Psychosocial support
- Spiritual support
- Sexuality concerns
- End of life care
- Support in bereavement
- Education and research
- Patient and family education and involvement in the care process
- Pain assessment and management
- Transitions of care between settings (inpatient, outpatient, home-based)

Many of our patients are incurable,hence pain management is a cornerstone to our patient care, and caregivers must take pain as symptoms that needs immediate attention.

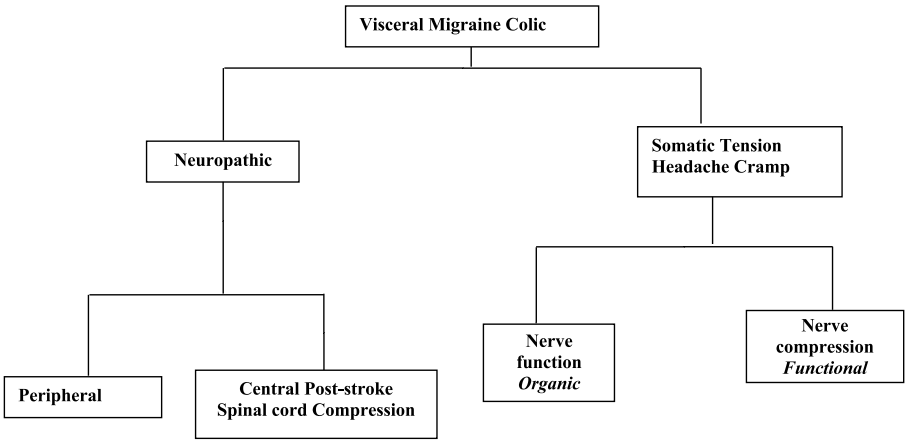
NOTE: Palliative care doses not involve management of pain only,it includes mangement of other symptoms such Nausea and vomiting, Anorexia and cachexia, Hiccup,Dry mouth/ ulceration,Sores/Ulcerated oral cavity, Oral candidiasis,Delirium, Breathlessness,Wounds and Pruritus of malignancy

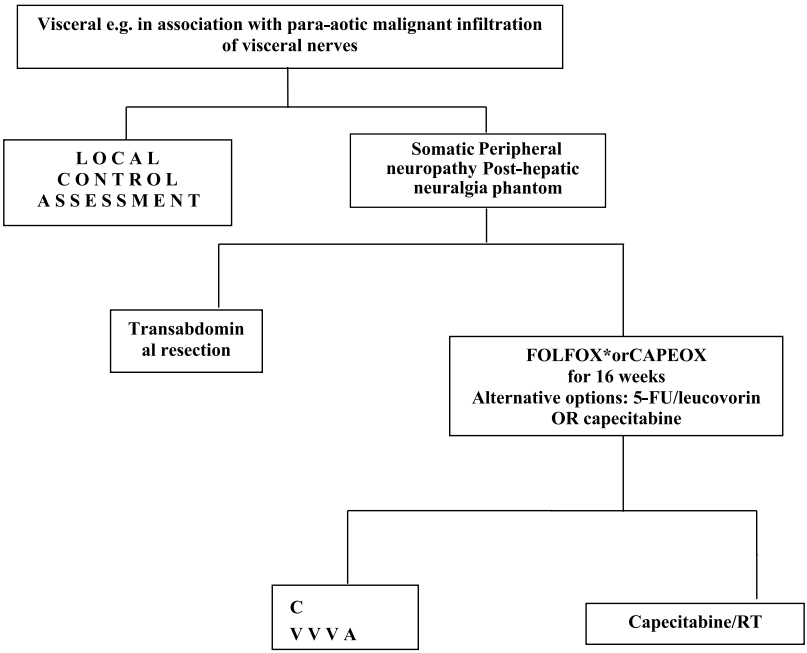
Common Causes of Pain

Clinical Setting Cause	Acute Procedural Pain	Iatrogenic Pain due to:	Comorbidity-related pain	Pain in cancer Survivors
Adjuvant Setting	Diagnostic intervention Lumbar puncture ± headache Transthoracic needle biopsy Endoscopy ± visceral dilatation Bone marrow aspiration/ biopsy, Blood sampling, Central ine position, Arterial line, Injections, Medication of skin ulcers Myelography and lumbar puncture, Thoracocentesis, etc.	Surgery, Chemotherapy, Hormonal therapy, Target therapy, Osteonecrosis of the jaw, Radiation therapy, Steroids can cause pain due to: skin lesions, peripheral neuropathy, mucositis, aseptic head of femoral necrosis, infections	Cardiovascular, Pulmonary Diabetic neuropathy, Vasomotor headache, Fibromyalgia, The comorbidity -related pain may be worsened by anticancer treatments and / or worse cancer-related pain, Postherpetic neuralgia, Acute thrombosis pain	Follow up procedures, Persisting postsurgical pain, Persisting anticancer medicine-related pain, Persisting radiation therapy related pain, Postherpetic neuralgia
Neoadjuvant setting	As adjuvant setting plus: Diagnostic and prognostic tissue Biopsy	As adjuvant setting without surgery-related pain	As adjuvant setting	As adjuvant setting
Locally advanced setting	As adjuvant setting plus: Pleurodesis, tumor embolization, Suprapubic catheterization, Nephrostomy insertion	As adjuvant setting, plus: Cryosurgery, Radiothermoablation-high intensity focused ultrasound; Transarterial chemoembolization Spinal/epidural injection; Opioid hyperalgesia	As adjuvant setting	As adjuvant setting

Metastatic setting	As locally advanced setting plus: Liver, lung, soft tissue diagnostic biopsies, Wound care, Movement procedural pain	As neoadjuvant setting	As adjuvant setting	As adjuvant setting plus: Synergistic pain effects between iatrogenic and disease related causes in long survivors

Classification of pain





Pain Assessment tools

There are at least 10 pain scales in common use.

The are broadly categorized in two major groups:

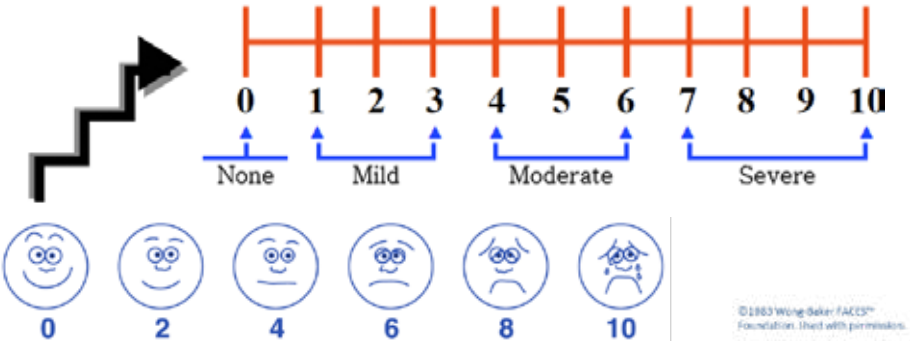
- **Qualitative scales**(especially useful in assessing your response to treatment because they can clearly define whether your pain has improved or worsened)
- **Quantitative scales**

Most pain scales have both quantitative features and qualitative features.

They can be further categorized to:

- Numerical rating scales (NRS) use numbers to rate pain. (above 9 years)
- Visual analog scales (VAS) typically ask a patient to mark a place on a scale that aligns with their level of pain.
- Categorical scales use words as the primary communication tool and may also incorporate numbers, colors, or relative location to communicate pain.

1.Numerical Rating Pain Scale



2. Wong-Baker FACES scale

Used in children who can talk (usually 3 years and older) Explain to the child that each face is for a person who feels happy because he has no pain, or a little sad because he has a little pain, or very sad because he has a lot of pain. Ask the child to pick one face that best describes his or her current pain intensity. Record the number of the pain level that the child reports to make treatment decisions, follow-up, and compare between examinations

3. FLACC scale:. stands for face, legs, activity, crying, and consolability. This scale was developed to help medical observers assess the level of pain in children who are too young to cooperate verbally. It can also be used in adults who are unable to communicate.

FLACC scale is based on observations, with zero to two points assigned for each of the five areas.As seen below.

DATE/TIME						
Face 0 - No particular expression or smile 1 - Occasional grimace or frown, withdrawn, disinterested 2 - Frequent to constant quivering chin, clenched jaw						
Legs 0 – Normal position or relaxed 1 – Uneasy, restless, tense 2 – Kicking, or legs drawn up						
Activity 0 – Lying quietly, normal position, moves easily 1 – Squirming, shifting back and forth, tense 2 – Arched, rigid or jerking						
Cry 0 – No cry (awake or asleep) 1 – Moans or whimpers; occasional complaint 2 - Crying steadily, screams or sobs, frequent complaints						
Consolability 0 – Content, relaxed 1 – Reassured by occasional touching, hugging or being talked to, distractible 2 – Difficult to console or comfort						
TOTAL SCORE						

The overall score is recorded as follows:
0 = Relaxed and comfortable
1 to 3 = Mild discomfort
4 to 6 = Moderate pain
7 to 10 = Severe discomfort/pain

By recording the FLACC score periodically, healthcare providers can gain some sense of whether someone's pain is increasing, decreasing, or stable.

Color Analog Scale: uses colors, with red representing severe pain, yellow representing moderate pain, and green representing comfort. The colors are usually positioned in a linear format with corresponding numbers or words

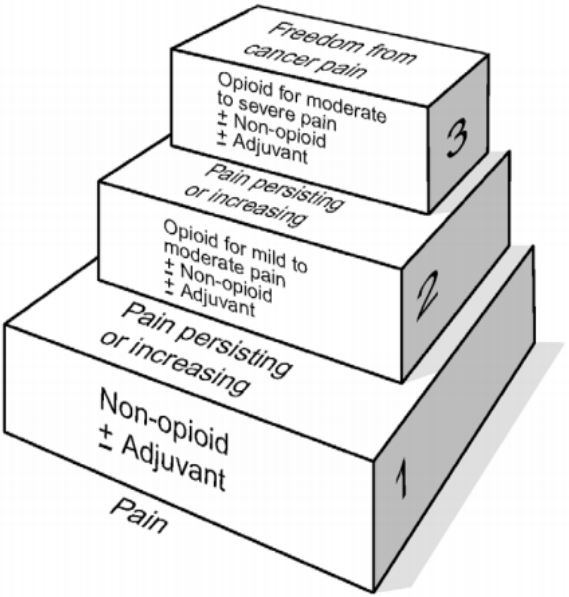
that describe your pain. The color analog scale is often used for children and is considered reliable.

Others include: CRIES Scale,COMFORT Scale, McGill Pain Scale, Mankoski Pain Scale
Brief Pain Inventory and Descriptor Differential Scale of Pain Intensity

Pain management
According to WHO guidelines. Pain management should be by the:

- Mouth: use the oral route where possible
- Clock: analgesia should be given at fixed time intervals. Give the next dose before pain recurs.
- Individual: involve adults and children fully in their care. Link doses to their daily routine.
- Ladder: choose analgesics according to the WHO analgesic ladder (see below), covering mild, moderate and severe pain.

WHO 3 STEP ANALGESIC LADDER (1986/1996)



Mild pain

Use,non opioid analgesics such as acetaminophen/paracetamol or an NSAID. Paracetamol and NSAIDS combination can be part of the treatment of cancer pain at any stage.

NOTE:long-term use of NSAIDs may lead to gastrointestinal bleeding, platelet dysfunction and renal failure. COX-2 selective inhibitors may increase the risk of thrombotic cardiovascular adverse reactions and do not offer protection from renal failure.

Moderate pain

Combination of Acetaminophen, aspirin or NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol or propoxyphene is the mainstay treatment of mild to moderate pain treatment which cannot be controlled by single therapy.

NOTE:The use of Tramadol produces significant side effects.
In the presence of renal impairment, all opioids should be used with caution and at reduced doses

Severe pain

Strong opioids such as Liquid Morphine are the mainstay. If a patient cannot tolerate oral morphine then parenteral route such as subcutaneous or intravenous analgesics should be used as alternative fentanyl transdermal patch can be used. If given via the subcutaneous route or transdermal route , the equivalent dose is 1: 2 or 1:3 of the oral medication.

Opioid Converting Chart

It is recommended that the new dose should be reduced by 30% to 50% to allow for incomplete cross tolerance. The patient should be monitored until stable when switching opioid medication, *** 24hrs** dose 2:1 of oral morphine may be used

Neuropathic pain

Neuropathic pain occurs as a result of damage to nerve tissue. There are two

clinical kinds of neuropathic pain, both elements may be combined:
Stabbing-type: pain in a nerve distribution with minimal pain in between (e.g. trigeminal neuralgia) but can occur with any nerve. Responds to Phenytoin
Paraesthesia dysaesthesiae, or burning-type pain: (e.g. post-herpetic neuralgia). Responds well to small doses of Amitriptyline

Treatment
Trigeminal neuralgia or stabbing-type pain Acute phase Carbamazepine initially 100 mg every 12 hours – Increase gradually by 200 mg every 2-3 days according to response, max 1200 mg – Causes white cell depression
Burning type pain (post-herpetic neuralgia, diabetic neuropathy) Amitriptyline 12.5-25 mg at night or every 12 hours depending on response, max 50-75 mg

Adjuvant Medicines for Pain Management

Adjuvant pain management should be considered in skeletal and smooth muscle spasms, inflammatory pain, bone pain, visceral pain including liver capsule stretch. Options include Corticosteroids, Antidepressants, Anti-epileptic, Biphosphates, Muscle relaxants and anti-spasmodic medications.

Non- Pharmacological Pain Management

These are supportive methods used to complement the mainstream treatments for cancer pain. Which include **physical**: e.g. massage, exercise, physiotherapy, surgery, hypnotics, acupuncture; and **psychological** i.e. strengthen the patient's coping mechanisms through counseling, relaxation therapies, social and spiritual.

Opioids side effects: include constipation, nausea/vomiting, urinary retention, pruritus and central nervous system (CNS) toxicity (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and—rarely—opioid-induced hyperalgesia/ allodynia and Respiratory depression.

Management of Opioids side effects

Generally reducing the opioid dose may reduce the incidence and/or severity of adverse events.
If this is not effective, and an alternative opiate is available, transition to an

alternative opiate using a conversion chart, and appropriate 25-50% dose-reduction for cross-tolerance of opiates.(Refer conversion chart)
Naloxone is a short-acting opioid antagonist for i.v. use able to reverse symptoms of accidental
severe opioid overdose with initial dose of 400 micrograms to 2mg administered intravenously. If the desired degree of counteraction and improvement in respiratory function is not obtained it may be repeated at two to three minute intervals.

NOTE:If no response is observed after 10mg of naloxone being administered the diagnosis of opioid-induced or partial opioid induced toxicity should be questioned.
Intramuscular or subcutaneous administration may be necessary if dosing by the intravenous route is not feasible.

Constipation
90% of patients taking opioids need laxatives and so it is important to start prophylactic laxatives when starting opioid medicines and enquire about bowel function regularly.

Management of constipation
Use oral laxative in preference to rectal measures
Traditionally laxatives are divided into:

- Stimulants, e.g. senna, dantron, bisacodyl
- Osmotic agents, e.g. lactulose, magnesium salts, macrogols (polyethylene glycol)
- Faecal softeners, e.g. docusate
- Bulk-forming agents, e.g. methylcellulose, (celevac), ispaghula husk (fybogel)

Use a combination of stimulant laxative with a softener/osmotic laxative if necessary.
Titrate components to achieve optimum stool frequency and consistency

Non pharmacological
Increase fluid intake

Increase fruit/fibre in the diet
Encourage mobility
Get the patient to the toilet, if possible avoiding bed pans

Nausea and vomiting

Assess and consider all possible causes, including those which may require specific treatments rather than an antiemetic alone (e.g. hypercalcaemia, gastritis, oral candidiasis).

Pharmacological management

Domperidone or metoclopramide +/- proton pump inhibitor/ H2 receptor antagonist	**CAUSE FIRST-LINE MEDICINE STAT DOSE (PO or SC)**	**24 HR RANGE**	**Gastric stasis and irritation**
Metoclopramide 10mg SC (Only use SC)	10mg PO 10mg PO or SC	30 to 60mg PO or SC	Bowel obstruction WITHOUT colic
	30 to 60mg SC (Only use SC)	Bowel obstruction WITH colic	Cyclizine +/ haloperidol +/- hyoscine butylbromide (Buscopan®)
150mg SC 1 to 5mg SC 60 to 120mg SC	NB: cyclizine and buscopan can be incompatible	50mg SC 1mg SC 20mg SC	(Only use SC)
1 to 5mg PO or SC	(Only use SC)	Chemical e.g. • medicines • hypercalcaemia • uraemia	Haloperidol 500 micrograms PO or SC
8 to 16mg 100 to 150mg PO/SC	Raised intracranial pressure	Dexamethasone +/-cyclizine	8 to16mg 50mg PO or SC
300 micrograms sublingual 400 micrograms SC 50mg	Motion Hyoscine hydrobromide	OR	Cyclizine
Levomepromazine 6.25mg 6.25 to 12.5mg PO or SC	300 micrograms SL q.d.s. 800 to 1200 micrograms SC	150mg PO or SC	2nd line or Multifactorial

26.2 Anorexia and cachexia

Anorexia is loss of desire to eat and Cachexia is a complex metabolic syndrome, characterized by profound loss of lean body mass, in terminal illnesses.

Causes;

- Nausea and vomiting.
- Constipation.
- Gastrointestinal obstruction.
- Mouth sore, mouth tumours, malodour.
- Hypercalcaemia, hyponatraemia, uraemia.
- Liver failure.
- Medications and Depression.

Pharmacological management

Corticosteroids: Prednisolone 15-40 mg once a day for 7 days – Or dexamethasone 2-6 mg in the morning for 7 days

Non pharmacological management

Small amounts of food frequently.
Give energy-dense food, and limit fat intake.
Avoid foods with extreme taste and spices.
Pleasant environment and nice presentation of food.
Eating is a social habit and people eat better with others.
Nutritional counseling.
If prognosis <2 months, counsel patient and family to understand and adjust to reduced appetite as a normal disease process.

Hiccup

Repeated involuntary spasmodic diaphragmatic and inspiratory intercostal muscle contractions. Hiccups up to 48 hours are acute, those lasting more than 48 hours are persistent and more than 2 months are intractable.

Causes

- Gastric distension.
- GERD/gastritis.

- Diaphragmatic irritation by supraphrenic metastasis.
- Phrenic nerve irritation.
- Metabolic: uraemia, hypokalaemia, hypocalcaemia, hyperglycaemia, hypocapnia.
- Infection: oesophageal candidiasis.
- Brain tumour, stroke, stress.

Non-pharmacological management

- Direct stimulation of the pharynx by swallowing dry bread or other dry food.
- Stimulation of vagus nerve by ingesting crushed ice or valsalva manouvre.
- Rapidly ingest 2 heaped teaspoons of sugar.
- Indirect stimulation of the pharynx – C3-5 dermatome stimulation by tapping or rubbing the back of the neck

Pharmacological management

For persistent or intractable hiccups use:

- Metoclopramide 10 mg 8 hourly (if the cause is gastric distension) Or Haloperidol 2–5 mg once a day Or chlorpromazine 25 mg 6 hourly

26.3 Dry mouth/ ulceration

Continue essential mouth care and look for reversible causes. Review medications; patients are often on multiple medicines which can cause dry mouth.

Non-pharmacological management.

Frequent sips of cold unsweetened drink
Sugar-free chewing gum/low sugar pastilles/boiled sweets
Topical artificial saliva substitutes: Biotene Oralbalance/AS Saliva Orthana
If the above measures are not effective, salivary stimulants may be an option; seek specialist advice.

Coated Tongue

This indicates poor salivary gland function. Continue essential mouth care management and address dry mouth.

Non pharmacological

Brush tongue gently with a soft small tooth brush.

Pineapple is sometimes suggested, but caution is suggested with the use of acidic substances, as they can increase risk of dental caries/infections. The importance of this depends on the person's prognosis and whether they still have teeth.

Sore or Ulcerated Mouth

Continue essential mouth care management and address dry mouth. Identify the cause and treat where possible. Sore mouth can be caused by infection, mucositis post-chemo or radiotherapy, by tumour, by aphthous ulcers or by vitamin deficiency.

Pharmacological and non pharmacological management

- If conscious and able to spit out, consider use normal saline.
- Topical analgesia options: paracetamol mouth rinse, benzydamine hydrochloride
- If not responsive to the above measures, consider use of topical anaesthetics and apply directly to painful area, e.g. lidocaine (Xylocaine) 10% spray applied using cotton bud. Avoid anaesthesia to pharynx before meals/drinks.
- For severe oral pain, consider the combined use of topical and systemic preparations.

26.4 Oral Candidiasis

Presents with dry mouth, loss of taste, reddened tongue, soreness, dysphagia, angular cheilitis and asymptomatic.

Causes:

Immunosuppression.

Steroid use (oral/inhaled).

Dry mouth, dehydration, poor oral hygiene, mucosal damage.

Pharmacological and non pharmacological management

Nystatin oral suspension 100,000 units/ml, 5mL q.d.s. for 7 days

Taste disturbance can improve with essential mouth care management,

addressing dry mouth and infection. Maintain nutrition where possible and refer to a dietician.

26.5. Delirium

Delirium is extremely common in patients with advanced disease. It is a source of increased morbidity and distress and interferes with the ability to communicate effectively at the end of life.

Clinical features

- Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
- A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

Assessment:

- Obtain a thorough history to determine the patient's pre-morbid level of functioning, their use of alcohol and illicit substances and the chronology of the onset of the changes in their mental state.
- Cognitive assessment tools such as the abbreviated mental test score should be used to gauge the patient's cognitive state but will not differentiate delirium from other causes of cognitive impairment.
- Identify any reversible causes: medication (e.g. medicines with anticholinergic side effects such as cyclizine, corticosteroids); infection; biochemical abnormalities.

Pharmacological and Non- pharmacological Management

Maintaining adequate fluid balance and nutrition

Managing the patient's environment to reduce confusion and distress e.g.

- Visible clock to aid orientation
- Encourage family to visit and provide them with a full explanation
- Consistent nursing
- Good lighting during daytime
- Consider using haloperidol Oral between 500micrograms and 1.5mg

b.d. with additional doses every four hours as needed or SC between 500micrograms and 1mg, observe for 30-60 minutes and repeat if necessary.

26.6 Breathlessness

Is an uncomfortable awareness of breathing. Breathlessness occurs very commonly in advanced cancer, and in cardiorespiratory and neurological diseases. Reversible causes listed in the table below.

Sudden onset breathlessness	
Possible cause	**Treatment option**
Asthma;	Bronchodilators, corticosteroids, physiotherapy
Pulmonary oedema	Diuretics, morphine
Pulmonary embolism	Anticoagulants, morphine
Pneumothorax	Chest drainage
Breathlessness arising over several days	
Exacerbation of COPD	Antibiotics, bronchodilators, corticosteroids
Pneumonia	Antibiotics, physiotherapy
Bronchial obstruction by tumour	Dexamethasone16mg o.d. early radiotherapy (RT), laser or stents
Superior vena caval obstruction	Dexamethasone16mg o.d. Urgent stenting
Breathlessness of more gradual onset	
Congestive cardiac failure	Diuretics, digoxin, ACE inhibitors
Anaemia	If chronic, this is unlikely to be the major cause of breathlessness. Transfusion may help. Oral iron is ineffective in chronic normochromic normocytic anaemia
Pleural effusion	Pleural aspiration and follow with pleurodesis if appropriate. These procedures may be distressing for frail patients
Pulmonary fibrosis	Possible if history of cytotoxics (esp.bleomycin), or lung radiotherapy
Ascites	Paracentesis if appropriate.
Primary/secondary carcinoma lung	Resection, RT or chemotherapy as appropriate

Palliative management for irreversible causes

- Modification of lifestyle, breathing retraining, relaxation and tailored exercise may be beneficial if instituted early enough and should be provided for all breathless patients as tolerated.
- A portable/table fan directed onto the face.
- Humidified oxygen may help acute breathlessness only in the presence of significant hypoxaemia. An exception to this rule is people with COPD where they may get benefit for breathlessness even with mild hypoxaemia. Use a trial of oxygen alongside other measures.
- Long term oxygen therapy for chronic respiratory illness should only be instigated by respiratory physicians.
- Most patients requiring palliation for breathlessness will not benefit from oxygen therapy (unless they are significantly hypoxaemic).

Pharmacological and Non-pharmacological management

- Position patient in most comfortable position in bed
- Reassure patient; explore patient's fears and anxieties (anxiety worsens condition)
- Breathing exercises and relaxation techniques; teach patient how to slow down breathing by pursing their lips and breathe with diaphragm rather than chest.
- Pulmonary rehabilitation
- Ensure good ventilation (e.g. open windows, use fans, loosen tight clothing)
- Conserve energy (e.g. encourage exertion to breathlessness)
- Opioids: Oral morphine sulphate modified release 5 to 10mg twice daily (with concurrent prescription of a laxative). Titrate by 5 to 10mg b.d. every 7 days until side-effects or a dose of 30mg b.d. is reached.

Alternatively, if there is concern about fluctuating renal function, oral morphine (immediate release) may be given as 2.5mg up to 4 hourly and converted to modified release if tolerated.

- Benzodiazepines: Lorazepam 500 micrograms to 1mg SL may give rapid relief during panic attacks.
- If anxiety appears to be a significant driver for the breathlessness, then try an anxiolytic anti-depressant, e.g. mirtazapine 15 to 30mg nocte, or

citalopram 10 to 20mg nocte.

- Midazolam 2.5mg SC may benefit patients who cannot tolerate the oral/ sublingual route. These medicines can be continued in the terminal phase

26.7 Wound care

Wound is the loss of continuity of epithelium, with or without loss of underlying connective tissue (i.e. muscle, bone, nerves) following injury to the skin or underlying tissues/ organs caused by surgery, a cut, chemicals, heat/ cold, friction/ shear force, pressure or as a result of disease, such as leg ulcers or carcinomas.

Types of wound

Acute Wound: An Acute wound is a wound that occurs suddenly and has a short duration. Example include surgical wounds and burns that heal easily with few complications.

Chronic wound: Is a wound that remains unhealed for longer than 6 weeks, influenced by complex and multiple factors that impede healing.
Wound chronicity is attributed to the presence of intrinsic and extrinsic factors including medications, poor nutrition, co-morbidities or inappropriate dressing selection. Examples; Malignant wounds, pressure ulcers.

Pressure ulcers

Is an area of local necrosis developing when soft tissue is compressed between a bony prominence and a rigid external surface.
Any severely ill patient may develop pressure ulcers. Immobility and prolonged pressure on a body part is the major risk factor.

Malignant or Fungating Wound.

Occurs when tumor invades the epithelium and breaks through the skin surface. The wound may either be ulcerative or proliferative, meaning that the wound forms ulcerating craters or raised, cauliflower-like nodules.

Wound management

Use Aseptic technique procedure

Cleansing should be performed in a way that minimizes trauma to the wound
Wounds are best cleansed with sterile isotonic saline or water
The less we disturb a wound during dressing changes the lower the interference to healing
Skin and wound cleansers should have a neutral pH and be non-toxic
Avoid alkaline soap on intact skin as the skin pH is altered, resistance to bacteria decreases

Antiseptics are not routinely recommended for cleansing and should only be used for infected wounds.

26.8 Pruritus of malignancy

Itching associated with malignancy presents special challenges and dilemmas. It can be among the most severe and uncooperative forms of secondary pruritus. Patients with malignancy-associated pruritus represent a significant percentage of those requiring palliation, and many may manifest this symptom at some time during their illness.

Symptomatic skin care

- Patients with itching of malignancy may manifest different types of pruritic skin lesions that warrant individualized therapies.
- As a routine, close trimming and filing of sharp edges of fingernails as well as wearing cotton gloves, if necessary, are initial steps to minimize further skin injury.
- Tepid (not too warm or too hot) baths are usually soothing and temporarily relieve the itch.
- Patients often relate that a hot bath or shower feels more relaxing and offers symptom relief, but the itch is worse afterwards due in part to vasodilation and the accentuated neural response of cutaneous heating.
- Immediately following the bath and a light towelling, the patient or caregiver should lubricate the skin with a fragrance-free cream-base emollient containing phenol or menthol. Applying a cream results in better maintenance of skin hydration and lessens the chance of further aggravation of pruritus from xerosis.
- Wearing clothing that is loose fitting, less irritating (e.g. avoid wools), and

minimizes heat retention and sweating (e.g. avoid synthetics) can also be helpful in lessening the frequency and intensity of itch. Cotton fabric clothing usually meets these requirements.

Pharmacological management of pruritis

Pruritus therapies
Anti-inflammatory agents
Corticosteroids
H_1, H_2, H_3 blocking agents
Salicylates
Vasoactive medicines
Î±-Blockers
Î²-Blockers (e.g. propranolol)
Central and peripheral nervous system agents
Anaesthetic agents
Lignocaine etc.
Antidepressant agents (tricyclic, SSRI)
Neuroleptic agents
Tranquillizing agents
Sedatives;
Opioid antagonists (naloxone, naltrexone, nalmephene)
Serotonin antagonists (ondestranon)

Specific management
Cholestasis: if stenting, if not possible consider:
Uraemia: Gabapentine 100-400mg
Hodgkin`s lymphoma
Radiotheraphy/ chemotherapy or
Prednisolone 30-60mg once daily
Cimetidine 800mg/24Hrs
Carbamazepine 200mg b.d

Paraneoplastic/idiopathic itch: Antidepressant –SSRI

26.9 Palliative care emergencies

26.9.1 Chocking

Is the sudden failure to breathe due to an acute obstruction of the pharynx, larynx or trachea. It usually occurs when food is not chewed well and passes through the upper airway.

Clinical features

Typically occurs while eating and this may includes; Coughing or gagging, Panic, Sudden inability to talk.
Hand signals e.g. clutching or pointing to the throat, Wheezing, Cyanosis, Loss of consciousness leading to death

Management

Partial

Patient is capable of speaking, breathing, cough forcefully and not cyanosed
-encourage coughing to clear obstruction but do nothing else.

Complete

Not able to speak, breathe or cough, cyanosed
Give up to 5 back blows;

- stand to side and slightly behind to the person
- support chest with one hand and lean the person well forward to aid in clearance of the obstructing object out of the mouth
- with the heel of your other hand, give a sharp blow between the shoulder blades
- check after each blow for success; if 5 blows fails, proceed to abdominal thrusts

Give up to 5 abdominal thrusts (Heimlich manoeuvre)

- stand behind the person and lean them forward
- make a fist with one hand; put your arms around the person, and grasp your fist with your other hanf in the midline, halfway between the lower sternum and the umbilicus
- make a quick, hard movement inward and upward
- check after each thrust for success; if 5 thrusts fails, return to back blows

- continue alternating back blows and abdominal thrusts until the obstruction is cleared
- the person can breath and cough forcefully
- if the person loses consciousness and if appropriate e.g. the person was not already close to death before chocking;

Call for cardiac arrest team and begin CPR

A severe episode of aspiration can be a terminal event, for example in patients with neurological impairment are at high- risk of aspiration, it is advised to have emergency medicines accessible at home for use to lessen the expected distress,Morphine 5-10mg SC/IV OR Midazolam 5-10mg SC/IV OR Hyoscine butylbromide 20mg or glycopyrroniun 200microgram SC/IV

26.9.2 Hypoglycaemia

Hypoglycemia is a blood glucose concentration lower than < 4mmol/L. It can present as 'mild' if self treated and 'severe' if support is required to be provided by a different person. Diabetic patients they may present without adrenergic warning symptoms because of autonomic neuropathy.

Features of Hypoglycemia

ADRENERGIC	NEUROGLYCOPENIC	
Hunger Tremor Sweating Tachycardia	Pallor Mental detachment Clumsiness Mannerisms Personality change confusion	Mutism Drowsiness Seizures Transient hemiplegia Coma

Causes

MEDICINES	ENDOCRINE	ORGAN DAMAGE	CANCER
Medicines for Diabetes -insulin -sulphonylureas -alcohol -quinine	Addison's Pituitary insufficiency	Hepatic failure Pancreatitis	Auto immune (e.g. insulin receptor antibodies in Hodgkins disease) -Ectopic production of insulin like hormone -insulin production(islet cell tumour)

Management

- Oral glucose
- IV dextrose: 5-20% solutions, 50% ampules
- IM glucagon
- Monitor glucose q 2-4 hours

NOTE: If adrenal insufficiency, administer 100 mg hydrocortisone & 1 mg glucagon.
If resistant hypoglycemia secondary to sulfonylureas, administer diazoxide 300 mg over 30 minutes IV q 4 hours PRN

26.9.3 Overwhelming distress

Occasionally, a patient who is imminently dying becomes severely distressed, most commonly because of an agitated delirium but sometimes because of pain or breathlessness.
When specific measures fail to relieve, it may be important to deliberately reduce the patient's wakefulness by prescribing sedatives. This is a treatment when everything else has failed. The intention is to reduce suffering and not to kill the patient.
Sedation should all the time be proper, and progressive.

Step wise management of Distress

STEP 1	Refractory distress: Prescribe anxiolytics-sedative
STEP2	Distress persist: Increase sedation to drowsness
STEP3	Distress persist: Increase sedation to stupor
STEP4	Distress persist: Deep sedation to coma

NOTE: Add antipsychotic for actual or potential delirium

Medicines for sedation in the imminently dying patient.
First line medicines
Midazolam
Start with 2.5-5mg stat and qlh p.r.n
If necessary increase progressively to 10mg SC/IV stat
Maintain with CSCI/CIVI 10-60mg/24h

Consider adding in an antipsychotic if midazolam 30mg/24h is inadequate to settle the patient

Haloperidol
Start with 2.5-5mg SC Stat and qlh p.r.n. (1-5mgSC qlh in the elderly)
Maintain with CSCI 10-15 mg/24h.

Second-line medicines
Levomepromazine
Generally given orally if intended to reduce a patients level of consciousness
Start with 25mg SC Stat and qhl p.r.n. (12.5mg in the elderly)
If necessary, titrate dose according to response
Maintain with 50-300mg/24h CSCI.
Although high dose (> 100 mg/24h) is best given by CSCI, smaller doses can be given as an SC Bolus at bedtime-bd, and p.r.n

Third line medicines
Phenobarbitol and Propofol: specialist use only for failing to respond to the above.
A small number of dying patients experience persistent overwhelming existential distress despite optimal psychosocial and spiritual support. Management of this must be supervised by professionals skilled in psychological evaluation.
Psychososial and spiritual support much continue to be offered and, if used, sedation should be undertaken in proportionate and progressive manner. Respite sedation for a few hours each day or for 2-3 days are normally the first steps, and often are sufficient. A decision about a CDS should be made only by a specialist palliative care team, and after discussion with both the patient and their family.

26.10 Psychosocial/Spiritual issues

Psychosocial assessment leads to a good psychosocial intervention that aims to reduce complaints and improve functioning related to mental disorders and/or social problems (e.g., problems with personal relationships, work, or school) by addressing the different psychological and social factors influencing.
A principal goal of psychosocial care is to recognize and address the effects that

cancer and its treatment have on the mental status and emotional well-being of patients, their family members, and their professional caregivers. Caregivers should be assessed for caregiver burnout issues.

Psychosocial issues and assessment
4 main areas to consider:

1. Family:
Has 3 main areas:-

- Immediate family; wife and children
- Support
- Extended family and close friends

Patient's understanding of the disease
Patient's fears and worries about the disease
Number of children and their ages
Number of wives
Family's understanding of the disease
Family's fears or worries about the disease
Support from the family and extended family members
Has the disease affected his sexuality

2. Roles and status:
Has 3 main areas:

- In the family
- In the community
- At work

Roles and status:
-Has the disease affected any of his roles and status, in the house as a husband or wife? Father or mother?
-Has the disease affected any of his roles and status, in the community as a leader? Church elder?
- Has the disease affected any of his roles and status at work?
What is his perception of his role/status, poor?
-how is he managing (coping up with) current roles and status?

3. Financial:

Has 5 main areas:

- Income / employment
- Medical bills
- School bills
- Food (home) expenses
- Travel

What is his current employment or source of income?

- How is he sustaining his income?
- Does he have any financial support?
- Has he got any fears or worries about his income or his employment or finances?
- How is he managing (coping up with) his financial issues?
- How is he paying for his medical bills? School fees? Food?
- Do guardians travel a long distance in order to visit him?
- How is he finding travel expenses, affordable? Expensive?

4.Community:

Has 2 main areas:

- Perception (cultural)
- Support

what is the community's perception of the disease, is it a taboo? Witch craft?
-how is the relationship with the community, any stigma? Any discrimination?
-how has the community been supportive?

Social stages

Social class assessment chart guide

Income per month (TZSH)

1	2	3	4	5
> 800,000	**500,000-799,999**	**200,000-499,999**	**100,000-199,999**	**<100,000**

Housing & transport

1	2	3	4	5
> House, has vehicle	1 house +/- vehicle	Renting house >3rooms,+/- vehicle	Renting house <3 rooms, no vehicle	No house, no vehicle

Occupation

1	2	3	4	5
Professionals with 1st class jobs, prominent businessmen, senior government officials, etc	Professionals with middle –class jobs, senior religious leaders, ordinary businessmen etc.	Small business owners, junior religious leaders etc.	Peasant farmers, petty traders, etc	Survival by chance

Education Level

1	2	3	4	5
Univ /Tert. Inn	A level	O level	Up to Primary 7	No education

Family Level

1	2	3	4	5
Total support ie. Financial, moral, social , spiritual	3 support	2 Support	1 Support	No Support at all

Assessment and Management

ASSESSMENT

Parameters	**Score**	**Remarks**
Income		
Housing/ Transport		
Occupation		
Education Level		
Family support		
Total		
Average		

NOTE: **Derived Social class of patient is** **1** **2** **3** **4** **5**
(Please circle)

26.11 Spiritual issues

Spirituality

Spirituality defines a relationship given throughout life and often comes to a greater meaning during times of crisis especially when coming towards old age or deaths.

Spirituality involves:- Search for meaning and purpose in life

Identity thoughts and feelings and the ability to accept and be comfortable with who you are.

Relationship with others, friends and families as well as connection with the community and the world. Spiritual needs may range from religious rituals such as prayers or holy communion, to secular observances like music/poetry.

Elements of Spirituality

- Values & beliefs
- Experiences
- Assumptions
- Motivations
- Dreams
- Relationships
- Thoughts
- Emotions

Religion:-

- The means by which we organise our spiritual yearnings.
- Religion is the mode of transport while spirituality is a journey.
- Usual path to introduce God
- Offers formal structures to reach spirituality
- Ideally includes love for all if based on holy books.
- Gives basics to spirituality.
- Has often been abused by people seeking power
- All formal religion try to help people in their search for inspiration and insight when they are
- forced to grapple with great existential questions provoked by suffering.
- The sense of purpose and meaning that religion provides is a comfort in the face of crisis.

Spiritual needs in general

- We all have spiritual needs. What are they?
- Need for meaning to life
- Need to receive love
- Need to give love
- Need to have a sense of forgiveness
- Need for hope and creativity

SPIRITUAL ASSESSMENT - Spiritual stages, score and grades
What is your relationship with God? (not religion but belief, spiritual communication with God or nature)
What religion were you raised in? What is your religion now? Why did you change? Are you at peace with the present religion?
Has your illness in any way affected your relationship with God? In what way?
Do you pray with others? Does it help you?
Are you at peace with your God?
Are you at peace with your family?
Can we help in any way?
Stage of spirituality (1-4) (see explanations in spiritual assessment below) (circle) **1 2 3 4**

Spiritual stages

Stages	**Compared to development stages (Ages)**	**Assessment /Criteria (can occur at any age)**
1	> 5	Not differentiating between good /evil
2	6-12	Comfortable in structures: cannot move out
3	13+	Searching (Agnostic)
4	Old Age	Peace with God

Management of Spiritual Needs

- Caring with compassion
- Understanding
- Empathy

- Being present and listening is often answering the need of the patient
- Don't give false promise
- God loves you, Jesus said so
- We need to reflect back what they are trying to say, let them know that you understand. Also to comfort them. involve the family.
- They may ask you to pray. Be prepared to do so. Don't suggest prayer to an obviously angry patient or whom has demonstrated negative feeling to God.
- Refer to appropriate services according to the wishes of the patient

27. End of Life

Although most health professional have seen dying patients, the general public rarely witnesses the process of dying. Those who provide care to the actively dying have the opportunity to help patients and their families prepare for the final hours of life.

If managed poorly the family may experience unnecessary suffering, and family distress may continue long after patient's death. When managed well family and friends will experience a positive first step-in their bereavement.

- Preparation for the dying experience often should occur from the beginning of palliative care involvement.

Families may need to have the following medication at home;

- For pain and dyspnea; morphine
- For anxiety and agitation: benzodiazepam
- For nausea or restlessness: haloperidol or lorazepam
- For secretion: anticholinegic, Hyoscyamine or atropine

In preparing families and professional care givers for the visible changes that will occur as death approaches, it is helpful to discuss physiological changes that commonly occur in the last hours to days of life;

- Weakness and fatigue-patient will gradually lose mobility, therefore minimize the risk of pressure sore
- Decrease food intake-although decreased oral intake of food and fluids can occur early in terminal illness and the result in progressive weight loss, patient and family need to be educated that loss of appetite and development of dehydration are nearly universal prior to death.
- Decreased ability to swallow and cough-the process of dying impairs the cough/gag reflex and the ability to clear secretion and protect the airway from aspiration. The pooling of saliva in the posterior oropharynx and the retention of secretion in the tracheobronchial tree can lead to noisy respiration. Simple measures such as repositioning the patient can result in postural drainage and effectively relieve some symptoms.
- Reduced circulation and renal function-dehydration and reduced cardiac output result in reduced peripheral perfusion, causing extremities to appear

cyanotic and feel cool to the touch. Patient may develop tachycardia and hypotension. Decreased renal perfusion eventually causes renal failure. The administration of parenteral fluids will not reverse the circulation shut down at this stage of illness and can potentially worsen cases of fluid overload as renal function decreases.

- Decrease level of consciousness-as patients approach death, most will have increased periods of drowsiness or lethargy, sometimes leading to coma. They may spend a large portion of the day asleep and will only interact with family and friends briefly before drifting back to sleep. It is advisable to suggest to family members that a patient can still hear and feel the presence, even after he/she stop talking encourage them to talk softly to the patient.
- Incontinence-as patient becomes bedbound and sphincters control is gradually lost, demonstrate on how to help patient at this stage
- Changes in breathing-for all patients, the dying process eventually involves noticeable changes in respiratory pattern. Breathing becomes shallow and mixed with increasing periods of apnea which sometimes can appear as" breath holds" Often families worry that a patient may be uncomfortable or suffocating and they need early education regarding these expected changes in breath pattern.
- Loss of ability to close eyes-changes in the orbit surrounding the loss of fat and fluid, cause the eye to fall Posteriorly into the orbital sockets and leave the eye lead partially open. It is important to explain to the family that the changes are common and to attempt to maintain moisture on the conjunctiva by applying ophthalmologic lubricants or artificial tears several times a day.
- When death occurs, preparation of family caregiver also should include a discussion about the steps to take after death. Family members should be allowed to spend time with deceased. Allow time and space for immediate grief reaction
- Advance care plan

Surrogate Decision Maker

Patients should be asked which person in their lives they would want to make medical decisions for them, if they were unable to make decisions for

themselves. Patients should be guided that this individual should be chosen to make the medical decisions that they would want for themselves, and not necessarily be the individual who is supporting their care financially. Providers should respect this decision, understanding that this person may be a family member or friend and may not necessarily be their financial provider or partner. This should be formally documented as early as possible after conversations with patient/next of kin.

Goals of Care and Decision-Making

Patients should be assessed for their current understanding of their disease

- What they wish to know about their disease?
- What their hopes and worries about their disease are?
- How they would want to be cared for?

In particular, they should be educated about the potential benefits and risks of all possible and available interventions, and guided in making educated decisions based on this information and an understanding of what is important to them as an individual. These decisions may include whether or not to pursue chemotherapy, radiotherapy, surgery, hospital transfer, ICU admission or resuscitation, among others.

Grief and Bereavement

Grief is a process that occurs in response to a loss. In palliative care, the losses tend to occur in association with debilitating illness and include the loss of life, function, purpose, independence, home, dignity and loved ones.Grief surrounding the dying process;

- Anticipatory grief; is expected both by patients and loved ones before death occurs, for family and friends, anticipatory grief involves preparing for future without the patient.
- Normal grief; encompasses a wide range of experiences. Although there can be common element to the grieving process (disbelief, yearning, anger, acceptance),these do not occur in any specific order and some may not occur at all.

Common grief reaction includes;

- Somatic symptoms
- Sleep and appetite disturbance

- Memory loss and impaired concentration.
- Social withdraw
- Visual hallucination
- Questioning of spiritual /religious belief
- Emotional reaction

Complicated grief which occurs about 10% to 20% is prolonged and pathological grieving process that includes experiences listed above. Specific markers for complicated grief include;

- Yearning for the deceased to a distressing or disruptive degree
- Trouble accepting death
- Inability to trust others
- A high degree of bitterness or anger
- Difficult forming new relationship
- Feeling detached or emotionally numb.
- Feeling the life is empty or meaningless.

Bereavement refers to the period after a loss during which grief is experienced and mourning occurs. The amount time spent in bereavement will depend on of a wide range of factors including:

- How attached the individual was to the deceased
- The circumstances of the death
- The individual's other coping mechanism and support.

Mourning is the process by which people adapt to loss. It can be influenced by cultural customs, rituals and social rules about coping with loss.

Although there is no simple formula for responding to grief and bereavement the EASE tool provides some guidance for an initial approach;

Educate survivors about the wide variety of experiences in normal grief; validate their emotions and reactions while reminding them everyone have different reactions.

Assess for common grief reactions

Support by listening actively

Explore which support method work best for bereaved individual.

All hospice programmers and many palliative care programs have formal support programs for bereaved family members.

Death and dying

Death is part of life; palliative care neither hastens nor postpones death. People deserve to die with peace and dignity.

A holistic approach should be taken towards end-of-life care and beyond. Services should be available to help patients and their families with the medical, psychological, and spiritual issues. Having loved ones present during the dying process, holding hands, touching, praying etc. can bring comfort to the patient. The importance of having friends and family present needs to be recognized and respected.

27.1 Ethic and Legal Issues

Ethics refers to collective belief and value system of any moral community, social or Professional group.

Medical ethics is the study of rules, principles and values applied to the fields of medicine and health care. Ethics describe what is good for the individual and society and what rules we need to prevent people from being harmed.

Importance of Ethics

Views about right and wrong vary

Many ethical issues arise in palliative care—truth-telling, confidentiality, when to stop treatment etc

Terminally ill patients are often vulnerable and require extensive care advancing medical technology means new ethical issues constantly arise.

Principles of Medical Ethics

Much discussion about medical ethics is based on the four principles of Medical Ethics:

- Respect for Autonomy
- Beneficence
- Non-Malificence
- Justice
- Fidelity
- Human rights & Palliative care

Human rights
Universal legal guarantees for all human beings, set out in international standards, protecting human dignity and fundamental freedoms and privileges. Human rights cannot be waived or taken away.

Human rights covenants/conventions
Treaties which are legally binding on states which ratify them.

Human rights declarations
Statements of non-binding human rights norms and principles (though they may reflect binding customary international law).
De facto (in fact, in reality) - Existing in fact.
De jure (by right, lawful) - A situation or conclusion based on law.

Human rights issues

Dignity
The quality of being worthy, honored, or esteemed. Human rights are based on inherent human dignity and aim to protect and promote it.

Discrimination
Distinction between persons in similar cases on the basis of race, sex, relation, political opinions, national or social origins, association with a national minority, or personal antipathy (WHO).

Domestication
Process by which an international treaty is incorporated into domestic legislation

Ratification
Follows **signature** and indicates a state's acceptance of a treaty and agreement to be bound by it.

Reservation: A unilateral statement by a state when signing, ratifying, or acceding to a treaty which purports to exclude or modify the effect of certain treaty provisions. Under the Vienna Convention on the Law of Treaties, a state

cannot enter a reservation that is "incompatible with the object and purpose of the treaty."

Respect, protect, and fulfill
Governments'obligations with respect to rights.

Respect: government must not act directly counter to the human rights standard**.**

Protect: government must act to stop others from violating the human rights standard.

Fulfill: government has an affirmative duty to take appropriate measures to ensure that the human rights standard is attained.

Right to health
Right to the enjoyment of a variety of facilities, goods, services, and conditions necessary for the realization of the highest attainable standard of health

Ethical issues and Ethical dilemmas
Certain Ethical Conflicts may arise in Palliative care:

Patients refusal of treatment:
"a patient who is conscious and refuses further treatment must have his wishes respected whatever his condition, provided he is mature and lucid enough to make such a decision"

Withholding or withdrawing Active Treatment
We are morally and legally responsible for both our acts (withdrawing) and our omissions (withholding) Considerations:
Patient's wishes
Patient's physical condition
Financial issues
Health- worker's autonomy

High tech medicine and resuscitation

When a patient is near death- a doctor is not obliged to embark upon or continue heroic treatment which has no prospect of benefiting the patient." This concept is known as 'medical futility'.

Too painful

Too difficult

Too dangerous

Pain Killing or Patient Killing?

"A doctor's obligation, when he can no longer hold back death, is to make the patient comfortable including easing his pain. If to make the patient comfortable the doctor must take measures which may hasten death, this is permissible providing the doctor's aim is only the relief of pain

Decisions: by patient or relatives?

"The relative of patients have no right to make decisions unless the patient is incompetent" Old age -Does not mean Incompetence

Lack of education - Does not mean Incompetence

27.2 Euthanasia

Means the deliberate killing of a human being to relieve their suffering. Or to relieve them of life in a body judged to be unable to function normally by others.

Types euthanasia

1**."Voluntary" Euthanasia**

Means that the person asks themselves to be put to death either at the time of the illness or have left a written request, while in a state of health, indicating that if they are terminally ill or suffer from an incurable illness, that they want to be helped to die.

2:"Passive" Euthanasia

Means totally withdrawing food or curative treatments with the intention of letting the patient die. Withdrawing treatments which will make the patient uncomfortable, or are questionable in the dying patient is NOT passive

euthanasia!
Euthanasia and assisted suicide: "The doctor may not embark on any conduct with the primary intention of causing the patients death" "If a terminally ill patient expresses a desire to commit suicide a doctor may not in law facilitate suicide."

The Hippocratic Oath
"I will maintain the utmost respect for human life from the time of conception; even under threat, I will not use my medical knowledge contrary to the laws of humanity"
Declaration of Geneva (amended Sydney 1967)
"When someone asks for euthanasia - defined not as desisting from active treatment but as a killing act we find that someone, or society as a whole, has failed that person".
Dame Cecily Saunders, founder of the modern hospice movement
Doctors need to be able to elicit the fears of the dying and to discuss and answer those fears, so that patients can see that they will not be -abandoned or left helpless. Only when this becomes the norm can society expect to dissipate pressure to force doctors to do things that the medical profession should not accept. Conclusions of the British Medical Association working party on Euthanasia 1988 (Sir Henry Yellowlees)

27.3 Children Palliative care

Introduction
Palliative care in children is the total holistic approach to care given to the children and family members including physical, social, psychological, and spiritual support**.** The aim of palliative care in children is to reduce distress, suffering and to provide optimum care.Therefore,comprehensive palliative care needs a multidisciplinary approach including child health care providers, family members and should be provided from the time of diagnosis throughout the course of illness and bereavement. Children have right to receive palliative care and all information must be protected.
Children Special need

Dependency to adult

The families of dying children have a different role than the families of dying adults, and therefore their experiences of bereavement differ.These require well- structured support and development systems. Children tend to have a broader range of people involved in their care, and so team-working and an understanding of team dynamics is especially important.

Developmental stages and physiological changes

In that sense, children's palliative care cannot claim to protect the quantity of a child's life. But children's palliative care can claim to protect the quality of a child's life, and of course to relieve suffering. There can be few things more important or more valuable in life than to relieve the suffering of a child and to help the child live the life they have as fully as possible.

Pediatrics pain control

Assessment and treatment of pain is different with adult consider two issues
Pain Assessment tool and model is by using FACES
Dosage of medication is calibrated
Bad news is relied to next of keen or careers – dependent

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PART V

Appendices

APPENDIX 1: Palliative care essential medicines.

Name of Medicine	Properties	Clinical Uses
Paracetamol	Non opioid Analgesic Antipyretic	Fever Pain
Aspirin	Non opioid Analgesic Antipyretic Anti-inflammatory	Pain Fever Sore Mouth
Ibuprofen	NSAID	Pain (esp. bone pain) Fever Anti inflammatory
Tramadol	Weak opioid Analgesic	Pain
Morphine liquid	Strong opioid Analgesic	Pain Introduction Breakthrough pain Difficulty swallowing **children** Breathlessness Severe Diarrhoea
Morphine (slow release tablets)	Strong opioid	Pain Severe diarrhoea
Dexamethasone	Corticosteroid Antinflamatory	Painful swelling and inflammation Poor appetite
Amitriptyline	Tricyclic Antidepressant	Neuropathic pain (nerve pain)
Hyoscine Butyl bromide (Buscopan)	Antimuscarinic Antispasmodic	Abdominal pain (Colic)
Diazepam	Benzodiazepine Anticonvulsant	Muscle spasm Seizure Anxiety, sedation
Phenobarbitone	Anticonvulsant	Seizure
Metoclopramide	Antiemetic	Vomiting
metoclopramide	Pro-kinetic	Abdominal Fullness
Chlorpromazine	Antipsychotic	Hiccups
Magnesium Trislicate	Antacid	Indigestion Gastrooesophageal reflux Gastritis

Loperamide	Antidiarrhoeal	Chronic diarrhea
Bisacodyl	Stimulant laxative	Constipation
ORS	Rehydration Salt	Diarrhoea
Chlorpheniramine	Antihistamine	Medicine reactions
Flucloxacillin	Antibiotic	Chest infection Skin infection
Cotrimoxazole	Broad Spectrum Antibiotic	PCP treatment and prophylaxis Infective diarrhea in HIV/AIDS Urinary Tract Infection
Metronidazole	Antibacterial for anaerobic infections	Foul smelling wounds gingivitis dysentery Vaginal discharge
Acyclovir	Antiviral	Herpes zoster
Chloramphenicol eye ointment/drops	Antibacterial	Eye infections
Fluconazole	Antifungal	Oral and Oesophageal candidiasis Cryptococcal Meningitis
Clotrimazole 1% Cream	Topical antifungal Fungal	Skin Infection
Nystatin Suspension and pessaries	Antifungal	Oral and vaginal candidiasis Prophylaxis for patients on steroids
Petroleum jelly .	Skin moisturizer and Protection	Dry skin Pressure area care.
Potassium permanganate	Drying agent antiseptic	Oozing lesions wet skin
Gentian Violet Paint	Antimicrobial Astrigent	Bacterial & fungal skin infection
Chlorinated Lime	Disinfectant	Infection Prevention
Calamine Lotion	Itch	Rash

Consumables

Gauze
Bandages
Cotton wool
Crepe bandage
Foley Catheters
Surgical and clean Gloves
Incontinence pads
Colostomy bags and Plaste

APPENDIX 2

List of Chemotherapeutic medicines recommended in the National cancer treatment guideline

LIST OF CHEMOTHERAPEUTIC MEDICINES - Level of Medicine use

A.Medicine used at Dispensary level
B.Medicines used at Health Centres level
C.Medicines used at Council Hospital level
D.Medicines used at Regional Referral Level
S. Medicines used at Zonal Referral, National and Special Hospitals

No:	Name of medicine	Dosage forms and Strength	Level of Medicine use
1.	Abiraterone	Tablet 250mg, 500mg	S
2.	Actinomycin D	injection 0.5 mg	S
3.	Adriamycin	injection 10mg ,50mg	S
4.	Afatinib	Tablet 20mg,30mg ,40mg	S
5.	Anastrozole	Tablet 1mg	S
6.	Arac C		S
7.			S
8.	Aromasin	Tablets 25mg	S
9.	Asparaginase	Powder for injection 10,000IU	S
10.	Bendamustine	Injection 45mg,180mg	S
11.	Bevacizumab	Injection 100mg ,400mg	S
12.	Bleomycin	Injection 15IU,30IU	S
13.	Bortezomib	Bortezomib 2mg,3.5mg	S
14.			S
15.	Cabazitaxel	Injection 60mg/1.5ml	S
16.	Capecitabine	Tablets 150mg,500mg	S
17.	Carboplatin	Injection 150mg,450mg	S
18.	Carmustine (BCNU)	Powder for injection100mg	S

19.	Casodex	Tablets 50mg,150mg	S
20.	Cetuximab	Injection 100mg,200mg	S
21.	Chlorambucil	Tablets 2mg	S
22.	Cisplatin	Injection 50mg,100mg	S
23.	Crizotinib	Capsule 200mg,250mg	S
24.	Cyclophosphamide	Tablets 500mg, Injection 500mg, 1000mg	S
25.	Cytarabine	Injection 10mg,20mg,100mg	S
26.	Cytosine arabinose		S
27.	Dacarbazine (DTIC)	Injection 200mg,500mg	S
28.	Daunorubicin	Injection 5mg,Powder for injection 20mg	S
29.	Denosumab	Injection 60mg	S
30.	Dexamethasone	Tablets 0.5mg,1mg,4mg,Injection 4mg,10mg	B
31.	Docetaxel	Injection 30mg,120mg	S
32.	Enzalutamide	Capsules 40mg	S
33.	Epirubicin	Injection 10mg,50mg	S
34.			S
35.	Etoposide	Injection 100mg,50mg Capsule 100mg	S
36.	Everolimus	Tablets 2.5mg,5mg	S
37.	Exemestane	Tablets 25mg	S
38.	Fludarabine	Tablets 10mg, Injection 25mg,50mg	S
39.	5 Fluorouracil	Injection 250mg 500mg,1000mg	S
40.	Folinic acid	Tablets 50mg, Injection 6mg	S
41.	Gefitinib	Tablets 250mg	S
42.	Gemcitabine	Injection 200mg,1000mg	S
43.	Goserelin	Implant 3.6mg, 10.8mg	S
44.	Granulocyte Colony		S
	Stimulating factor (G-	Injection 300mcg	S
	CSF)-Filgrastin		S
45.	Trastuzumab	Powder for injection 150mg,440mg	S
46.	Hydroxyurea	Tablets 500mg	S

47.	Ifosfamide with Mesna	Injection 1mg,2mg with 200mg	S
48.	Imatinib	Capsules 100mg,400mg	S
49.			S
50.	Irinotecan	Injection 40mg,100mg	S
51.	Lenalidomide	Tablets 10mg,25mg	S
52.	Letrozole	Tablets 2.5mg	S
53.	Liposomal doxorubicin	Injecton10mg,50mg	S
54.	Lomustine (CCNU)	Capsule 5mg, 40mg	S
55.	Megestrol acetate	Tablets 20mg, 40mg	S
56.	Melphalan	Powder for injection 50mg,tablets 2mg	S
57.	Methotrexate	Tablets 2.5mg; Injection 200 mg/ml	S
58.	Mitomycin C	Powder for Injection 5mg,20mg,40mg	S
59.	Paclitaxel	Injection 6mg/mL in 5-mL ampoule	S
	Leucovorin	Injection 50mg,200mg	S
	Mesna	Injection: 200 mg	
60.	Navelbine	Injection 10mg	S
61.	Ibandronate	Tablet 20mg, 50mg	S
62.	Onvovin (Vincristine)	Injection 1mg	S
63.	Oxaliplatin	Injection 50mg,100mg	S
64.	Paclitaxel	Injection 260mg,100mg	S
65.	Pamidronate	Tablets 150mg	S
66.	Pemetrexed	Injection 500mg	S
67.	Pertuzumab	Injection 30mg,420mg	S
68.			S
69.	Prednisolone	Tabletes 5mg	C
70.	Procarbazine	Capsule: 50 mg (as hydrochloride).	S
71.	Regorafenib		S
72.	Rituximab	Injection 100mg, 500mg	S
73.	Sorafenib	Capsules 200mg, 100mg	S

74.	Sunitinib	Capsules 12.5mg, 25mg,50mg	S
75.	Tamoxifen	Tablets 10mg, 20mg	S
76.	Temozolomide	Tablets 100mg,200mg	S
77.	Temsirolimus	Injection 25mg	S
78.	Thalidomide	Capsules 50mg, 100mg	S
79.	Trabectedin	Powder for injection 1mg	S
80.	Vemurafenib	Tablets 250mg	S
81.	Vinblastine	Injection 1mg, 10mg	S
82.	Vinorelbine	Injection 10mg	S
83.	Zoledronic acid	Injection 4mg	S
84.	Pegfilgrastin	Prefilled syringe 6mg	S

APPENDIX 3

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Dr. Revelian Iramu	Specialist Radiologist	ORCI
Dr. Japhet Ngerageza	Specialist Neurosurgeon	MOI
Ms. Jennifer Mlingi	Nurse	ORCI
Dr. Merida Makia	Specialist Thoracic Surgeon.	MNH
Mr. Juma Simba	Nurse	ORCI
Dr. Latifa Rajabu	Specialist Radiologist	ORCI
Dr. Leah Mnango	Specialist Pathologist	MNH
Dr. Living Mumburi	Specialist Paediatrician	MNH
Dr. Lulu Sakafu	Specialist Radiologist	MUHAS
Dr. Magreth Moshi	Specialist Clinical Oncologist	ORCI

Dr. Maguha Steven	Public Health Specialist	ORCI
Dr. Mamsau Ngoma	Specialist Clinical Oncologist	ORCI
Ms. Mary Haule	Palliative Care Nurse	ORCI
Ms. Mary Matepo	Palliative Care Nurse/Social worker	ORCI
Mr. Mpanda Mgoya	Radiotherapist	ORCI
Ms. Mwamvita Said	Nurse	ORCI
Dr. Nuru Mlagalila	Specialist Clinical Oncologist	ORCI
Mr. Nyakaji Mashauri	Palliative Care Nurse	AKH
Dr. Patrick Amsi	Specialist Pathologist	KCMC
Dr. Peter Muhoka	Specialist Clinical Oncologist	MNH
Mr. Rashid Mruma	Radiotherapist	ORCI
Dr. Rehema Laiti	Specialist Paediatric Oncologist	MNH
Ms. Rose Ngowi	Nurse	ORCI
Dr. Sadiq Siu	Specialist Clinical Oncologist	ORCI
Dr. Salama Iddy	Specialist Clinical Oncologist	ORCI
Dr. Sarah Nyagabona	Specialist Clinical Oncologist	ORCI
Mr. Shaid Yusuf	Medical Physicist	ORCI
Dr. Shakiru Jumanne	Specialist Paediatric Oncologist	BMH
Dr. Sikudhani Muya	Specialist Clinical and Radiation Oncologist	ORCI
Mr. Mnaro Msuya	Radiotherapist	ORCI
Dr. Sintayenu Temesgen	Specialist Clinical Oncologist	ORCI
Ms. Stella Kendi	Nurse	ORCI
Dr. Tausi Maftah	Specialist Nuclear Physician	ORCI
Mr. Tegemea Kalolo	Medical Physicist	ORCI
Dr. Trish Scalan	Specialist Paediatric Oncologist	MNH
Dr. Victor Sensa	Specialist Urologist	MNH
Dr. Yemela Ndibalema	Specialist Clinical Oncologist	ORCI
Dr. Mbonea Yonaz	Specialist Haematologist	MNH
Dr. Zaituni Sanya	Specialist Paediatric Oncologist	MNH
Wema Mwilongo	Nurse	ORCI

Dr. Hadija Mwamtemi	Specialist Paediatric Oncologist	MNH
Dr. Frank Chacha	Specialist Urologist	BMC
Ms. Abella Kakuru	Nurse	ORCI
Dr. Frank Manase	Palliative Care Physician	CCP Medicine Medical Centre
Selis Tarimo	Palliative care Physician	CCP Medicine Medical Centre
Mr. Humphrey Nyimbo	Radiotheerapist	ORCI
Dr. Dalliah Black	Oncologist	MDACC
Dr. Debu Tripathy	Oncologist	MDACC
Dr. Mariana Chavez-MacGregor	Oncologist	MDACC
Dr. Mary Edgerton	Oncologist	MDACC
Dr. Michael Stauder	Oncologist	MDACC
Scholastica Mlinda	Nutritionist	MNH
Mariam Nyamwaira	Nutritionist	MNH
Elizabeth Lyimo	Nutritionist	MNH
Brenda Maro	Nutritionist	MNH
Denis Mbinga	Nutritionist	MNH
Maduhu Mashini	Nutritionist	MNH
Dr Sarah Maongezi	Clinician and Public Health Specialist	MoHCDGEC
Dr Safina Yuma	Clinician and Public Health Specialist	MoHCDGEC
Dr. Owino Mac'Osano	Palliative Care Physician	PTR-NET

APPENDIX 4

List of Reviewers

Dr. Katherine Van Loon	Associate Professor, Medicine, Hematology/Oncology Director, Global Cancer Program	UCSF
Dr. Rebecca DeBoer	Assistant Professor, Medicine, Hematology/Oncology	UCSF
Dr. Geoffrey Buckle	Clinical Fellow, Medicine, Hematology/Oncology	UCSF
Dr. Hope Rugo	Professor, Medicine, Hematology/Oncology, Breast Oncology	UCSF
Dr. Tracy Sherertz	Assistant Professor, Department of Radiation Oncology, GYN	UCSF
Dr. Ronald Balassanian	Professor, Pathology, Anatomic Pathology	UCSF
Dr. Amie Lee	Assistant Professor, Clinical Radiology	UCSF
Dr. Michael Alvarado	Professor, Surgery, Breast Cancer and Melanoma Specialist	UCSF
Italia Paola Diaz	Fellowship Coordinator	UCSF
Dr. Jean Nakamura	Professor, Radiation Oncology	UCSF
Dr. Michael Prados	Professor, Neurological Surgery	UCSF
Dr. Steve Braunstein	Assistant Professor, Radiation Oncology	UCSF
Dr. Kate Matthay	Professor, Pediatric Hematology/Oncology	UCSF
Dr. Mary Feng	Professor, Radiation Oncology	UCSF
Dr. Melody Xu	Resident, Radiation Oncology	UCSF
Dr. Andrew Ko	Professor, Interim Division Chief, Hematology/Oncology	UCSF
Dr. Alan Venook	Professor, Medicine, Hematology/Oncology	UCSF
Dr. Terence Friedlander	Associate Clinical Professor, Medicine, Hematology/Oncology	UCSF
Dr. Mack Roach	Professor, Radiation Oncology & Urology	UCSF
Dr. Stefanie Ueda	Associate Professor, Gynecologic Cancer Surgeon, Ob/Gyn, Reproductive Sciences	UCSF
Dr. Ben Davoren	Professor, Hematology/Oncology Associate Chief of Staff for Clinical Informatics	UCSF
Dr. Sue Yom	Professor, Radiation Oncology & Otolaryngology-Head and Neck Surgery	UCSF

Dr. Chia-Ching Wang	Clinical Instructor, Medicine, Hematology/Oncology	UCSF
Dr. Charalambos Andreadis	Associate Professor, Medicine, Hematology/Oncology	UCSF
Dr. Katy Tsai	Associate Professor, Oncologist and Melanoma Specialist	UCSF
Dr. Michelle Hermiston	Associate Professor, Pediatric Hematology/Oncology	UCSF
Dr. Ross Okimoto	Assistant Professor, Medicine, Hematology/Oncology Clinical Instructor, Thoracic Oncology	UCSF
Dr. Rosanna Wustrack	Associate Professor, Orthopedic Surgery	UCSF
Dr. Matthew Gubens	Assistant Clinical Professor, Thoracic Oncologist, Hematology/Oncology	UCSF
Dr. Elizabeth Murphy	Professor, Chief of the Endocrinology and Metabolism Division	UCSF
Dr. Carolyn Seib	Assistant Professor of Surgery, Endocrine Surgery	UCSF
Dr. Jessica Humphreys	Assistant Professor, Palliative Care	UCSF
Dr. Carly Zapata	Assistant Professor, Palliative Care	UCSF
Dr. Stella Bialous	Professor, Social Behavioral Sciences	UCSF
Linda Abramovitz	Associate Clinical Professor Clinical Practical Nurse	UCSF
Stephanie Kennell-Heiling	Family Nurse Practitioner Oncology Nurse Educator	UCSF
Mairead Shaw	Nurse PD, Cancer Center Infusion	UCSF