Republic of Rwanda
Ministry of Health

Rwanda Biomedical Centre
Healthy People, Wealthy Nation

NATIONAL CANCER TREATMENT GUIDELINES

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FOREWORD

The burden of cancer continues to rise globally with an estimated 19.3 million new cases and 10 million deaths in 2020. According to IARC, in Rwanda there were an estimated 8,835 new cancer cases and 6, 044 deaths in 2020. Data from the National Cancer registry also show a continuous increase of cancers in Rwanda from 634 new cases in 2007 to 5,040 cases in 2019. The increasing cancer burden is due to several factors, including population growth and aging as well as the changing prevalence of certain causes and risk factors of cancer linked to social and economic development. Mortality from cancer in Rwanda, like in other developing countries, is high mainly because access to timely diagnosis and effective treatment services is not yet optimal. The Ministry of Health aims to address this challenge through development of these Cancer Treatment Guidelines, among other initiatives. These are the first National Cancer Treatment guidelines and they aim to harmonize the diagnosis and treatment of cancers across all cancer care and treatment centers in Rwanda.

The key areas covered are diagnosis, imaging, pathology, surgery, rehabilitation, palliative care and survivorship. It emphasizes a multi-disciplinary team approach which is paramount for quality cancer care. The specific cancers covered are breast, central nervous system, gastrointestinal, gynecological, head and neck, hematological, Kaposi's sarcoma, lung, prostate and pediatric cancers.

These guidelines have been developed through an extensive consultative process with various experts in the field of oncology. They are an important tool meant to be used by health workers in Rwanda working in facilities where cancer diagnosis and treatment services are offered. They are presented in a simplified manner using a public health approach to cancer treatment. The aim of this document is to ensure that patients with cancer seen in any health facility in Rwanda are given due services and that their evaluation, treatment, rehabilitation and continuum of care through to survivorship or palliation is done in a well-coordinated manner. It also seeks to ensure best practice in service delivery within the facilities providing any cancer care and treatment services.

We call upon all hospital leaders, partners and clinicians to adopt and support the implementation of these guidelines to help achieve its goal of reducing mortality in Rwanda through access to quality diagnostic, treatment and palliative care services. I trust that this guiding document will provide the much-needed framework and impetus to move towards universal access for cancer care services.

Dr. Sabin Nsanzimana
Minister of Health

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The Rwanda Biomedical Centre (RBC) within the Ministry of Health appreciates all who contributed to the successful development of these National Cancer Treatment Guidelines. The development of these National Cancer Treatment Guidelines was led by the Non-Communicable Disease Division in close collaboration with the National Cancer Technical Working Group.

Our gratitude is extended to the National Comprehensive Cancer Network (NCCN) and the American Cancer Society (ACS) that coordinated the development of NCCN Harmonized Guidelines for Sub-Saharan Africa that served as reference while developing the Rwanda National Guidelines.

We also acknowledge the continued support from Partners in Health in the provision of cancer care and treatment services and financial support from Clinton Health Access Initiative during the development of these guidelines.

Finally, though certainly not least, I would like to also acknowledge the health care professionals throughout our country working within cancer prevention and control services. Without these care providers, their dedication to patients with cancers and to enhancing the quality of cancer care services delivery, we would not be able to sustain and develop services to save as many lives as possible.

The development of these National Cancer Treatment Guidelines has been a lengthy journey with many challenges, but we finally have this document that provides a big milestone in the country's response to cancer.

Prof. Claude Mambo Muvunyi
Director General
Rwanda Biomedical Centre

RATIONALE

The cancer care continuum involves a series of interventions aimed at curing the disease or prolonging the patient's life considerably while improving the quality of life.

The landscape of cancer care and treatment in Rwanda is changing rapidly with introduction of new diagnosis and treatment modalities as well as availability of qualified human resources to provide a quality treatment of patients with cancer diseases.

Currently, cancer diagnosis and treatment services are scattered at five hospitals including four University Teaching Hospitals (CHUK, RMH, CHUB and King Faisal Hospital) and Butaro Level II Teaching Hospital. There is no single hospital able to provide a comprehensive treatment to all patients with cancer; patients are obliged to navigate across different hospitals seeking for services that are not available at the initial facility to complete their treatment plan.

In light of the above, there is a need to establish harmonized national cancer treatment guidelines that should be used across all hospitals diagnosing and treating cancers.
The national guidelines will help to:

- Improving the quality of treatment by giving clinicians access to the most up-to-date clinical knowledge in cancer management adapted to local settings
- Improving the speed and ease with which new clinical recommendations can be communicated to practicing clinicians
- Making it possible to develop supporting resources that can also be used across the country, including training curricula, e-learning and job aids
- Enabling the quantification and forecasting of needed cancer treatment drugs and related consumables.

These national cancer treatment guidelines built on the work previously done to customize NCCN Harmonized Guidelines for Sub-Saharan Africa to Rwanda settings. In addition, other guidelines like ASCO and ESMO were consulted to make final national guidelines.

EXECUTIVE SUMMARY

These National Cancer Treatment Guidelines combine evidence-based and best-practice recommendations, with the aim of ensuring availability of equitable, high-quality services for cancer patients. They cover aspects of clinical evaluation, diagnosis, imaging, surgery, radiotherapy, chemotherapy, hormone therapy, psychosocial support, palliative care, rehabilitation, and survivorship.

The document contains the guidelines for the following cancer diseases

Breast Cancer
Cervical Cancer
Uterine Cancer
Vulvar Cancer
Ovarian Cancer
Gestational Trophoblastic Neoplasia (GTN)
Head and neck cancers
Thyroid cancer
Thymus cancer
Esophageal cancer
Gastric cancer
Colon cancer
Rectal cancer
Anal cancer
Hepatobiliary cancer
Pancreatic cancer
Small Cell Lung Cancer
Non-Small Cell lung cancer
Pediatric cancers.
Testicular cancer
Penile cancer
Prostate cancer
Kidney cancer
Bladder cancer
Soft tissue sarcoma
Bone Cancers
Neuro endocrine cancer
Kaposi sarcoma
Multiple Myeloma
Hodgkin lymphoma
Non-Hodgkin Lymphoma
B-cell lymphoma
Central Nervous System cancers
Chronic Myeloid Leukemia
Chronic Lymphocytic leukemia
Acute Myeloid Leukemia
Acute Lymphoblastic leukemia
Skin cancers

Structure of the guidelines

The National Cancer Treatment Guidelines are made of the following sections:

1. Introduction on the disease
2. Screening recommendations (where applicable)
3. Clinical presentation
4. Laboratory work up: (histopathology, IHC, ...), biochemistry, hematology,..
5. Medical imaging exams
6. Staging recommendations
7. Treatment per subtype of the diseases and Stage (Surgery, Drugs, Radiotherapy)
8. Drug regimens and dosage with 1st Option, 2nd Option, ...
9. Follow up information which can include some side effects, ...
10. References.

INTRODUCTION

General principles of cancer management

Patients with cancer require high levels of specialized complex multimodal care from a multidisciplinary team that includes oncologists, physicians, surgeons, pathologists, radiologists, pharmacists, oncology nurses, dietitians, dermatologists, plastic surgeons, dentists, psychologists and palliative care specialists from the pre-treatment assessment to the point where rehabilitation is complete and beyond. These guidelines have been developed with input from specialists within the major hospitals treating cancer patients in Rwanda. In addition, external oncologist experts have been consulted to capture inputs from a broad range of cancer specialists.

The guidelines will be reviewed regularly, in line with guidance from the Ministry of Health and other national and international guidance, as well as significant new evidence from researches.

Cancer services should be patient centered and should respond to patient and carer feedback. Excellent communication between professionals and patients is particularly important to improve patient satisfaction.

Early Diagnosis and Referral

There is evidence that patients with cancer attend health facilities a number of times with symptoms related to their cancer and are treated otherwise before onward referral. These guidelines recommend that cancer patients/cancer suspects be referred appropriately in a timely manner to the appropriate level of care where the specific service required in the care pathway is available. The patients should be triaged before referral based on their signs and symptoms.

Designated clinicians should work together to ensure that an appropriate diagnostic work-up is provided for patients suspected to have cancer. The definitive diagnosis of cancer is confirmed by histopathological examination of the biopsy specimen. Patients confirmed with cancer should be referred without delay to the appropriate multidisciplinary team (MDT) in the nearest facility providing cancer care. There should be pre-booking systems for appointments at both referring and receiving clinics, where each patient with a new cancer diagnosis should be seen by an oncologist/cancer specialist. The referring clinician should also be informed of the diagnosis and decision made.

Inter-Professional and Patient Communication

Communication needs to be timely and concise. The main communication points along the patient journey must include:

- What the patient has been told about their condition
- What written/other information was offered
- Next steps – when the patient is being seen or treatment started
- Intent of treatment (curative/palliative)
- Summary of medication and alterations to medication
- Contact details for further information/discussion
- Specialist assessment and intervention summary
- Treatment plan summary – when created and when amended
- Written correspondence to be copied to all appropriate team members who have actions to undertake in patient's care.

Key points at which to communicate include: Diagnosis, multidisciplinary team discussions, assessment clinic, clinic appointment reviews, treatment reviews, decision points for changes in care planning and decision point for end-of-life care planning

Multidisciplinary Team Meeting

Multidisciplinary team (MDT) care is considered as best practice in the delivery of high quality cancer management globally. They have been shown to improve cancer care delivery to patients. Co-morbidities, performance status and staging are assessed and recorded, appropriate diagnostic tests generated and treatment plans developed, reviewed and implemented by MDT members.

It is advised that the MDTs at each cancer center develop terms of reference as a concise summary of their meeting standards and processes. The following should be included as a minimum:

- Statement of purpose/function of the MDT;
- List of health care professional membership including core members, disciplines and their roles and responsibilities, chair, vice-chair and secretary;
- Procedure to maintain attendance records; data management, auditing and reporting on MDT meeting activity.
- Meeting venue, format, frequency and duration
- Communication: referral to MDT process, discussion criteria and documentation;
- Patient confidentiality in selection and review of cases and who is responsible.
- Education and training.
- Video-conferencing is essential to allow regional sites or primary care providers the opportunity to participate in their patient's discussion at the MDT meeting.

Where appropriate, participation in clinical trials, including the process for identifying eligible patients, should also be addressed in the terms of reference.

Characteristics of an effective MDT meeting

- Treatment decisions and care is delivered by specialists with knowledge and skills in the relevant aspects of the particular cancer type;
- Patients are offered information and support to cope with their cancer;
- Good communications and continuity of care regardless of who or where care is provided;
- The MDT has collegial working relationships;
- The MDT has an educational component;
- Economic use of resources, such as the use of telehealth
- Alerts on significant changes to the recommended treatment plan to provide opportunity to review and record variances and learn from these cases;
- Auditing and monitoring of MDT processes to drive service improvement and assist service planning, including sustainability of the MDT.

Palliative care, supportive care and end of life care

Palliative, supportive and end of life care should be offered at any point in the patient journey at all levels of care.

Palliative Care

Palliative care is defined as an approach that improves the quality of life of patients and their families facing the problems associated with life- threatening illnesses, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual (WHO, 2002). Palliative and supportive care must be multi-disciplinary. Integrating palliative care from the time of diagnosis improves patient and family experience, which ultimately leads to better patient reported outcomes

Components of Palliative Care

They include:

- Treatment navigation – integrates palliative care with standard cancer care
- Assistance in communication to both the patient, family members and caregivers
- Pain and symptom management
- Psycho-social assessment and support e.g. patient's social support system, coping strategies, fears, self-care activities
- Spiritual assessment and support
- Chronic wound and stoma care
- Image and sexuality support
- Anticipatory approach to symptom management
- Ethical-legal support e.g. palliative care as a human right, writing a will

- Advanced directives – a legal document that expresses the desire of the patient in relation to different medical treatments when the patient is unable to make those decisions. It's in three formats: living will, appointment of a healthcare proxy and legal status of preferences.
- Rehabilitation e.g. physical therapy, occupational therapy, speech therapy prosthetics etc that improve mobility, function, pain relief and other aspects of the patient
- Support groups
- Transition/continuity of care – to improve care, enhance patient and family caregiver outcomes and manage the cost of care.
- Complementary and alternative therapies
- Home based care.

Supportive care

Supportive care is given to improve the quality of patients with life-threatening disease. The goal is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social and spiritual problems related to a disease or its treatment.
General supportive care includes:

- Management of central venous catheters including chemoports and peripheral venous access
- Hydration
- Blood and blood products transfusion
- Nutritional support
- Management of acute Radiation and chemotherapy side effects including;
  - Nausea & vomiting
  - Fever
  - Mucositis
  - Constipation
  - Anorexia & cachexia
  - Fatigue
  - Diarrhea
  - Dehydration
  - Premature menopause
  - Keratinization - Skin and hair changes.

End of life care

End of life care is care for those with a life-threatening condition that has become advanced, progressive and incurable. It requires a range of decisions, including patients' right to self-determination (of treatment, life etc), ethics and efficacy of extraordinary medical interventions, efficacy of routine medical interventions, rationing and allocation of resources. The components of end-of-life care include:

- Prognostication: giving information to the patient and their family about life expectancy to help plan realistically for their future.
- Pain and symptom management
- Spiritual assessment and support
- Anticipatory approach to symptom management
- Ethical-legal support
- Home based care
- Palliative care emergencies treatment
- Discussions around goals of care
- Family conferences
- Issues around nutrition and hydration
- Surrogate decision making determination when patients lack decision making capacity, a surrogate should be identified to make decisions.
- Do Not Resuscitate (DNR) orders
- Withdrawal/withholding treatment
- Futile care
- Last rites
- Bereavement and grief support.

Survivorship care

Survivorship focuses on the health and life of a person with cancer post treatment until the end of life. It covers the physical, psychosocial and economic issues of cancer, beyond the diagnosis and treatment phases. It includes issues related to the ability to get health care and follow-up treatment, rehabilitation, surveillance for late effects of treatment, screening for recurrence & secondary cancers and quality of life. Family members, friends and caregivers are also considered part of the survivorship experience.

Care of the cancer survivor should include:

1. Prevention of new and recurrent cancers and other late effects.
2. Surveillance for recurrence/spread of cancer and screening for subsequent primary cancers at least annually.
3. Assessment for late psychosocial and physical effects.
4. Interventions for consequences of cancer treatment such as pain and peripheral neuropathy management, lymphedema management, for those who received anthracyclines, assess for anthracycline-induced cardiotoxicity (evaluate for heart failure signs and symptoms, presence of risk factors), need for immunizations.
5. Care coordination between specialists and primary care givers with specific roles delineated to ensure the health needs of the cancer survivor are met.
6. Survivorship care planning: This plan will include a summary of treatment received, follow-up care, surveillance and screening recommended for the survivor, post-treatment needs of the survivor, healthy lifestyle behavior recommendations and information on treatment related side effects and anticipated health risks.

Evaluating success of survivorship care will include:

- Improved communication and care coordination: (perceived)
- Patient-physician communication, physician-physician communication.
- Improved understanding of needed follow-up tests, their purpose and timing, and who will conduct them, potential late effects of illness and what symptoms might be important to report.
- Better adherence to recommended follow-up activities; fewer requests for
- Unnecessary tests; reduced duplication of services.
- Improved ability to identify providers and resources to address persistent
- Effects of cancer and its treatment.
- Improved overall survival with decreased cancer-related morbidity.
- Improved healthy lifestyle choices with better quality of life and function.
- Improved knowledge about and ultimately standardization of follow-up care behaviors.
- Improved ability to monitor survivors' health and implement changes in care in response to new information about treatment exposures and follow-up needs.
- Improved access to information necessary to guide follow-up care; less time spent searching for this.
- Enhanced quality of care delivery (such as compliance with evolving quality standards)

BREAST CANCER

1. Introduction

Breast cancer is the second most common malignancy among women in Rwanda, 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.

Age, nulliparity, not breastfeeding, first pregnancy age 35years, previous radiation exposure, family history of breast cancer, smoking and alcohol consumption, are the common risks associated with breast cancer.

Majority (90%) of breast cancers occur sporadically and only about 10% of patients have a 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. JMRI 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.

2. Workup

a. Ductal Carcinoma in Situ (DCIS) – Tis, N0, M0

- History and Physical examination
- Diagnosis bilateral mammogram
- Pathology review
- Determination of tumor estrogen receptor (ER) status

b. Early breast cancer – T0-3, N1, M0 and T1-3, N0-1, M0

- History and Physical examination
- Diagnostic bilateral mammogram; ultrasound as necessary
- Axillary assessment with exam; ultrasound or other imaging as necessary, and percutaneous biopsy of suspicious nodes
- Pathology review
- Determination of tumor estrogen/progesterone receptor (ER/PR) and HER-2 status.

- Counseling for fertility concerns if pre-menopausal; pregnancy test in all women of childbearing potential
- If possible – breast MRI (optional) with special consideration for mammographically occult tumors
- CBC, metabolic panel, liver function tests, and alkaline phosphatase
- Abdominal +/- pelvic diagnostic CT with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis
- Chest diagnostic CT with contrast (if pulmonary symptoms present)
- Cardiac ultrasound – with baseline ejection fraction and follow-up

Note: Pathology

Core needle biopsy done manually, or preferably by ultrasound is recommended. FNA should only be done as a screening test where core biopsy is not possible/available. Any atypical/suspicious or malignant cytology on FNA must be confirmed on histopathological examination. 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 (HER-2 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+ is equivocal; perform FISH test to ascertain the diagnosis
- IHC 3+ is considered "positive"

3. Staging

Table: TNM Classification for breast cancers

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	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 >1mm but ≤ 5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm).
T1b	Tumor > 5mm but ≤ 10mm in greatest dimension in greatest dimension
T1c	Tumor > 10mm but ≤ 20mm in greatest dimension
T2	Tumor > 20mm but ≤ 50mm in greatest dimension
T3	Tumor > 50mm 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

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

Clinical N Staging

N Category	N Criteria
cNX	Regional lymph nodes cannot be assessed (e.g. previously removed)
cN0	No regional lymph node metastases (by imaging/examination)
cN1	Metastases to movable ipsilateral level I, II axillary node(s)
cN1mi	Micrometastases (approximately 200 cells, larger than 0.2mm but none larger than 2.0mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph nodes with or without level I, II axillary lymph node involvement; OR in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; OR metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Pathological N

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.

Distant Metastasis

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 non-regional 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 0.2mm

Note – imaging studies are not required to assign the cM0 category

4. Management

1.1. Ductal Carcinoma in Situ (DCIS)

Options include:

- Total mastectomy with or without sentinel node biopsy + reconstruction (optional) OR
- Excision to negative margins of 2mm without lymph node surgery + whole breast radiation therapy with or without boost to tumor bed –Category 1 OR
- Excision to negative margins of 2mm without lymph node surgery + accelerated partial breast irradiation with or without boost to tumor bed OR
- Excision to negative margins of 2mm without lymph node surgery without radiation therapy

- Consider endocrine therapy for 5 years (for ER+ DCIS or patients treated with excision alone); Tamoxifen for pre-menopausal patients or tamoxifen or aromatase inhibitor for patients <60 years or with concerns for thromboembolism
- Consider counseling regarding risk reduction therapy for contralateral breast

1.2. Treatment of Early stage or locally advanced breast cancer

1.2.1. Upfront surgery

The general management option is upfront excision to negative margins (lumpectomy with no ink on tumor) with surgical axillary staging.
Adjuvant options are:

- If ≥4 positive axillary nodes: Radiation therapy to the whole breast with or without boost to tumor bed, infraclavicular region, supra-clavicular area, internal mammary nodes, and any part of the axillary bed at risk –Category 1. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated;

- If 1-3 positive axillary nodes: Radiation therapy to the whole breast with or without boost to tumor bed –Category 1. Strongly consider radiation therapy to the infraclavicular region, supra-clavicular area, internal mammary nodes, and any part of the axillary bed at risk. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated ;

- If negative axillary nodes: Radiation therapy to whole breast with or without boost to tumor bed, and consider regional nodal irradiation with exclusion of the dissected portion of the axilla in patients with central/medial tumors or tumors >2cm with other high-risk features (young age or extensive lymphovascular invasion [LVI]). It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.

For patients whom are offered total mastectomy with surgical axillary staging – Category 1:

- If ≥4 positive axillary nodes: Radiation therapy to chest wall + infraclavicular region, supra-clavicular area, internal mammary nodes, and any part of the axillary bed at risk –**Category 1**. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated
- 1-3 positive axillary nodes: Strongly consider radiation therapy to chest wall + infraclavicular region, supra-clavicular area, internal mammary nodes, and any part of the axillary bed at risk. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated
- Negative axillary nodes and tumor > 5cm – Consider radiation therapy to chest wall +/- infra-clavicular region +/- supra-clavicular area, +/- internal mammary nodes, and any part of the axillary bed at risk. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated

- Negative axillary nodes and tumor ≤ 5cm and negative margins but <1mm - Consider radiation therapy to chest wall +/- regional nodal radiation in patients with central/ medial tumors or tumors > 2cm with other high risk features (young age or extensive LVI)
- Negative axillary nodes and tumor ≤ 5cm and margins ≥1mm – No radiation therapy

1.2.2. Neo-adjuvant systemic therapy

Usually considered in patients with clinically evident lymph nodes or tumors that may result in positive margins with upfront surgery. The goal of neo-adjuvant systemic therapy is to render inoperable tumors operable, minimize surgical morbidity and facilitate a breast conserving surgical strategy rather than a modified radical mastectomy, in appropriate cases.
Response is usually evaluated either clinically or if possible or applicable, with imaging with diagnostic modality noted to be abnormal at the time of diagnosis.
The following applies:

- In case of clinical response and when tumor is operable – Mastectomy and surgical axillary staging OR Excision to negative margins with surgical axillary staging;
- In case of no response – consider additional systemic chemotherapy and/or pre-operative radiation (where utilized)
  - In case of response to response to the additional pre-operative chemotherapy and tumor is operable – follow with surgery
  - In case of no response to additional chemotherapy – individualize treatment

1.2.3. Systemic Adjuvant Treatment

1.2.4. Chemotherapy

General principles of adjuvant treatment for early breast cancer are outlined below. Indications are:

- Patients who receive neo-adjuvant systemic therapy and undergo surgery should complete planned chemotherapy regimen course in the 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.

A. Hormone receptor positive (ER/PR+) and HER-2 Positive

- If tumor ≤ 0.5cm, no pathological evidence of nodal disease:
  - Consider adjuvant endocrine therapy +/- adjuvant chemotherapy + Trastuzumab
  - If presence of micro-invasive nodal disease (pN1mi) –Adjuvant endocrine or Adjuvant chemotherapy with Trastuzumab followed by endocrine therapy;
- If tumor has a size between 0.6-1 cm – adjuvant endocrine therapy or adjuvant chemotherapy with Trastuzumab and endocrine therapy
- If tumor has a size > 1cm – adjuvant chemotherapy with Trastuzumab and endocrine therapy –**Category 1**
- Any size with positive nodes (1 or more ipsilateral metastases > 2mm):
  - Adjuvant chemotherapy with Trastuzumab and endocrine therapy –**Category 1**

B. Hormone receptor positive (ER/PR+) and HER-2 Negative or unknown

- If tumor ≤ 0.5cm, and no pathological evidence of nodal disease – Consider adjuvant endocrine therapy
- If tumor ≤ 0.5cm and micro-invasive nodal disease (present, but ≤2 mm) – Adjuvant endocrine therapy or adjuvant chemotherapy followed by endocrine therapy
- If tumor > 0.5cm, and nodes are negative – endocrine therapy or adjuvant chemotherapy followed by endocrine therapy **–Category 1**
- If tumor > 0.5cm, and nodes are positive –adjuvant chemotherapy followed by endocrine therapy **–Category 1**

C. Hormone Receptor Negative (ER/PR-) and HER-2 Negative

- If tumor ≤ 0.5 cm& no pathological evidence of nodal disease:
  - Recommended: No adjuvant therapy
- If tumor ≤ 0.5 cm & micro-invasive nodal disease (present to ≤ 2mm)
  - Consider: Adjuvant chemotherapy
- If tumor between >0.6-1cm & micro-invasive or no nodal disease (none to ≤ 2mm):
  - Consider: Adjuvant chemotherapy
- If tumor > 1cm and/or any positive node (>2mm)
  - Recommended: Adjuvant chemotherapy **–Category 1**

D. Hormone Receptor Negative (ER/PR-) and HER-2 Positive

- If tumor ≤ 1cm & micro-invasive or no nodal disease (none to ≤2mm)
  - Consider: adjuvant chemotherapy with Trastuzumab
- If tumor > 1cm and /or any node positive disease (>2mm)
  - Recommended: Adjuvant chemotherapy with Trastuzumab **–Category 1**

E. Usual chemotherapy regimens (neo-adjuvant and adjuvant treatment)

1. HER-2 negative or unknown

- Doxorubicin + Adriamycin (AC) every 3 weeks, followed by Paclitaxel or Docetaxel every 3 weeks; can also be given as a dose dense regimen (AC- every 2 weeks and Paclitaxel weekly or 2-weekly); Doses are: IV Doxorubicin 60mg/m^2 + Cyclophosphamide 600mg/m^2 every 3 weeks for 4 cycles (every 2 weeks for dose dense regimen, coupled with Filgastrim). This is followed by IV Paclitaxel 175mg/m^2 every 3 weeks for 4 cycles (weekly in dose dense regimen, coupled with Filgastrim);
- Docetaxel and Cyclophosphamide (TC); Doses are: IV Docetaxel 75mg/m^2 + Cyclophosphamide 600 mg/m^2 every 3 weeks for a total of 4 cycles;

- Cyclophosphamide, Methotrexate, Fluoro-uracil (CMF); Doses are: IV Cyclophosphamide 600mg/m^2 + Methotrexate 40mg/m^2 + 5-Fluoro-uracil 600 mg/m^2 every 3 weeks for a total of 6-8 cycles;

- *Epirubicin**, Cyclophosphamide, Fluoro-Uracil (ECF); Doses are: IV *Epirubicin** 100mg/m^2 + Cyclophosphamide 500mg/m^2 + 5-Fluoro-Uracil 500 mg/m^2 every 3 weeks for a total of 6 cycles;

- Docetaxel, Doxorubicin, Cyclophosphamide (TAC); Doses are: IV Docetaxel 75mg/m^2 + Doxorubicin 60mg/m^2+ Cyclophosphamide 600 mg/m^2

- If triple negative breast cancer and residual disease after preoperative therapy with taxane, anthracycline and cyclophosphamide: Capecitabine; Doses are Oral Capecitabine 1000-1250 mg/m^2 twice daily for a total of 14 days (per cycle), with one week break. Repeat for a total of 3-6 cycles.

2. HER-2 positive disease (Hormone positive or negative)

- Mostly used regimen is Adriamycin, Cyclophosphamide, Paclitaxel and Trastuzumab. Doses are similar, but Trastuzumab is given with Docetaxel (after 4 cycles of Adriamycin and Cyclophosphamide), at a dose of 8mg/kg for the first dose, and 6mg/kg for the subsequent doses, every 3 weeks for a total of 18 cycles; Doses of Adriamycin, Cyclophosphamide and Paclitaxel are detailed above

- Taxane (Docetaxel), Carboplatin and Trastuzumab; Doses are: IV Docetaxel 75mg/m^2, Carboplatin AUC 5-6, given for 6 cycles, together with Trastuzumab (1st cycle at 8mg/kg and subsequent at 6mg/kg); continue Trastuzumab alone from cycle 7-18, every 3 weeks.
- Taxane (Paclitaxel) and Trastuzumab for select early disease patients; Doses are detailed above.

** Not on World Health Organization (WHO) Essential Medicine List (EML)*

3. Hormone Positive disease

- Same regimens as above. Additions are detailed below (point 4.2.3.3)

1.2.5. Radiation therapy

Planning: Supine, with breast board and arm-rest with an appropriate head rest;

Dose Delivery:

- **Whole Breast radiatio**n: Target = breast tissue in its entirety; dose to the breast – 50 Gy in 25 fractions (2Gy/fraction) or 40-42.5 Gy in 15-16 fractions (hypofractionation is preferred); Add boost to the tumor bed for patients with a high risk of recurrence, with doses of 10-16 Gy in 4-8 fractions; all dose schedules to be given 5 days per week;

- **Chest wall irradiation:** Target = ipsilateral chest wall, mastectomy scar + drain sites; dose = 50 Gy in 25 fractions (2Gy/fraction) +/- scar boost for a total dose of approximately 60 Gy. All dose schedules to be given 5 days per week;

- **Regional node irradiation:**

  - **Axillary nodes** – usually same dose as either chest wall or whole breast irradiation;
  - **Supra-clavicular nodes** – 46 Gy in 23 fractions, unless clinically positive (receives 50-55 Gy)
  - **Internal mammary nodes** – identifying done with reference to the internal mammary artery and vein; dose: similar to either chest wall or whole breast irradiation

In case preoperative chemotherapy was administered:
- Indications of radiation therapy and treatment fields are based on maximum stage from pre-therapy clinical stage, pathologic stage and tumor characteristics

1.2.6. Adjuvant Endocrine therapy

A. Pre-menopausal patients at diagnosis

- **Tamoxifen** for 5 years +/- ovarian suppression or ablation **–Category 1**; at the end of the first 5 years and if the patient is:
  - Pre-menopausal: Consider tamoxifen for an additional 5 years to complete 10 years. Doses are: Tamoxifen 20mg once daily
  - Post-menopausal: Aromatase Inhibitor for 5 years
- Consider Aromatase inhibitor for 5 years + ovarian suppression or ablation**–Category1**
- Aromatase Inhibitors options are: Letrozole* (Dose at 2.5mg once daily), Anastrozole (Dose at 1mg once daily)

B. Post-menopausal patients at diagnosis

- **Aromatase Inhibitor** for 5 years **–Category 1** or aromatase inhibitor for 2-3 years or Tamoxifen for 2-3 years ;
  - Consider Tamoxifen or aromatase inhibitor to complete 5 years (whether started on Aromatase inhibitor or Tamoxifen for 2-3 years) –Category 1
- If contra-indication to aromatase inhibitors is present, or declining aromatase inhibitors or who are intolerant of the aromatase inhibitors – Tamoxifen for 5-10 years;

** Not on WHO EML*

1.3. Recurrent Disease/ Treatment-naïve Stage IV

1. Work-up:

- History and physical examination
- Discuss goals of therapy, adopt shared decision-making, and document course of care
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Chest imaging (X-ray or CT scan)
- Abdominal +/- pelvic CT scan
- Brain or spine MRI if suspicious CNS symptoms
- Consider re-biopsy of the first recurrence
- Determination of ER/PR and HER-2 status if new disease

2. Management of local and regional recurrence

A. Local recurrence:

- If initial treatment was with excision to negative margins + radiation therapy – do total mastectomy + axillary lymph node staging if level I/II axillary dissection not previously done; consider systemic therapy afterwards (tailored on immuno-histochemistry profile);
- If initial treatment was with mastectomy + level I/II axillary dissection and prior radiation therapy – do surgical resection if possible; consider systemic therapy afterwards (tailored on immuno-histochemistry profile);
- If initial treatment was with mastectomy and NO radiation therapy was given – do surgical resection if possible and radiation therapy; consider systemic therapy afterwards (tailored on immuno-histochemistry profile)

B. Regional recurrence

- In case of axillary recurrence – surgical resection if possible +/- radiation therapy; consider systemic therapy afterwards (tailored on immuno-histochemistry profile)
- In case of supraclavicular recurrence – radiation therapy if possible (tailored on immuno-histochemistry profile)
- In case of internal mammary node recurrence – radiation therapy if possible (tailored on immuno-histochemistry profile)

C. Stage IV disease

1. Bone disease present

- Add Zoledronic acid or Pamidronate* (with calcium and vitamin D supplementation), with systemic treatment tailored based on immuno-histochemistry profile;

** Not on WHO EML*

2. Bone disease not present – ER/PR+ and HER-2 negative or unknown

2.1. Visceral Crisis present

- Consider initial chemotherapy, to be continued until progression or unacceptable toxicity;

2.2. No visceral crisis present and no prior endocrine therapy within 1 year

- Pre-menopausal: Ovarian ablation or suppression + endocrine therapy OR selective ER modulators **–Category 1**; if available, use ovarian ablation + Aromatase Inhibitor + CDK4/6 inhibitor* **–Category 1**, OR ovarian ablation+ Fulvestrant* + CDK4/6 inhibitor* **–Category 1**
- Post-menopausal: Aromatase Inhibitor OR selective ER modulators; if available, use Aromatase Inhibitor + CDK4/6 inhibitor* –Category 1, OR Fulvestrant* + CDK4/6 inhibitor* **–Category 1**

2.3. No visceral crisis present and prior endocrine therapy within 1 year

- Pre-menopausal: Ovarian ablation or suppression + a different endocrine therapy; if available, use CDK4/6* or mTOR inhibitor*;
- Post-menopausal: Consider a different endocrine therapy; if available, use Fulvestrant* + CDK4/6 inhibitor* **–Category 1**, OR mTOR inhibitor*

NOTE: Continue endocrine therapy until progression or unacceptable toxicity

- In case of progression or unacceptable toxicity on first line endocrine therapy – consider additional line of endocrine therapy if not endocrine refractory OR chemotherapy; IF no clinical benefit after up to 3 sequential endocrine therapy regimens or symptomatic visceral disease switch to chemotherapy;
- For patients with visceral crisis – progression or unacceptable toxicity on first-line chemotherapy – consider another line of chemotherapy; IF no clinical benefit – consider no further cytotoxic therapy and continue supportive care.

** Not on WHO EML*

2.4. Systemic treatment for recurrent or stage IV disease – ER+ and/or PR+, HER-2+

- Chemotherapy + HER-2 targeted therapy with:
  - Taxane + Trastuzumab OR
  - Taxane + Trastuzumab + Pertuzumab* - THP (if available) OR
  - Endocrine therapy +/- HER-2 targeted therapy (if premenopausal – consider ovarian ablation or suppression)

NOTE: Continue endocrine therapy until progression or unacceptable toxicity

- Progression on first line endocrine therapy – Consider additional line of endocrine therapy, if not endocrine refractory +/- HER-2 targeted therapy; if no clinical benefit after up to 3 sequential endocrine therapy regimens +/- HER-2 targeted therapy or symptomatic visceral disease; Consider no further HER-2 targeted therapy and continue supportive care;
- Progression on first line endocrine therapy + HER-2 targeted therapy – Consider another line of chemotherapy + HER-2 targeted therapy to be continued until progression; if no clinical benefit - Consider no further HER-2 targeted therapy and continue supportive care

2.5. Systemic treatment of recurrent or stage IV disease – ER/PR -, HER-2 +

- Chemotherapy + HER-2 targeted therapy with - Taxane + Trastuzumab OR Taxane + Trastuzumab + *Pertuzumab** - THP (if available);
- Continue therapy until disease progression; if no clinical benefit - Consider no further HER-2 targeted therapy and continue supportive care;

2.6. Systemic treatment of recurrent or stage IV disease – ER/PR -, HER-2 –

- Initial treatment will depend on presence or not of visceral disease; presence of visceral disease should prompt use of combination chemotherapy if response can outweigh toxicity
- Chemotherapy until progression or unacceptable toxicity – consider additional line of chemotherapy; and if no clinical benefit - Consider no further cytotoxic therapy and continue supportive care

3. Surveillance of metastatic disease

- Periodic assessment of varied combinations of symptoms, physical examination, routine laboratory tests, imaging studies. Results are classified as response/continued response to treatment, stable disease, uncertainty regarding disease status or disease progression.
  - Findings concerning for disease progression:
  - Worsening symptoms such as pain or dyspnea
  - Evidence of worsening or new disease on physical examination
  - Declining performance status
  - Unexplained weight loss

- Increasing alkaline phosphatase (ALT, AST, or bilirubin)
- Hypercalcemia
- New radiographic abnormality or increase in the size of pre-existing radiographic abnormality
- Increasing tumor markers (not specific) – CA-15-3

4. Follow-up

- **Exam:** History and physical examination every 3 months for the first 2 years, every 6 months for the 3rd to 5th years, then annually.
- If the patient is receiving adjuvant endocrine therapy, follow-up every 3 months. Consider recommending self breast exam and clinical breast exam if either breast conserving surgery was done (both breasts) or mastectomy was done (contralateral breast).
- Consider baseline bone density and periodic monitoring for patients on aromatase inhibitors or who undergo ovarian suppression.
- Post-surgical management: Educate, monitor and manage lymphedema;
- Imaging:

Mammography: If breast-conserving surgery was made – routine, every 12 month; If mastectomy was done, recommending mammography for contralateral breast, at same frequency.

Screening for metastasis – no indication for imaging (or laboratory) studies in the absence of clinical signs and symptoms suggestive of recurrent disease

- Assess and encourage adherence to adjuvant endocrine therapy; and if on Tamoxifen – annual gynecologic assessment if uterus is present.

5. Special Considerations

5.1. 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 tumors 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. Axillary dissection is also required.
- 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. In case of hormone positive disease, patients are to receive Aromatase Inhibitors (AI) in combination with a GnRH (Gonadotropin Releasing Hormone) agonist or orchiectomy to maximize the hormonal blockage effect.
- 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.

5.2. Phyllodes tumor

5.2.1. Workup and Investigations

- Clinical Suspicion of phyllodes tumor with:
  - Palpable mass
  - Rapid growth
  - Large size (>3 cm)
  - Imaging with ultrasound suggestive of fibroadenoma except for size and/or history of growth
  - Investigation:
  - History and Physical Examination
  - Ultrasound
  - Mammogram for women ≥ 40 years

5.2.2. Management

The management below details steps to be taken in case either core needle biopsy or upfront excisional biopsy is undertaken.

Core Needle Biopsy:

- Fibroadenoma - go on with excision biopsy and observe; if mass <3cm, observation; if mass >3cm and/or family history of breast cancer - excision biopsy
- Phyllodes tumor – wide excision WITHOUT axillary staging; malignant phyllodes – wide excision with 1cm margin
- Invasive or in situ cancer – treat as invasive disease

Excisional Biopsy:

- Fibroadenoma – Observe
- Phyllodes tumor (benign, borderline and malignant) – wide excision WITHOUT axillary staging
- Invasive or in situ cancer – treat as invasive disease

In case of recurrence:

- If no metastatic disease – re-excision with wide margins without axillary staging; consider post-operative radiation therapy;
- If metastatic disease present – metastatic disease management (following principles of soft tissue sarcoma)

5.3. Paget Disease

5.3.1. Workup and Investigation

- Clinical suspicion of Paget's disease:
  - Clinical breast exam
  - Diagnostic bilateral mammogram ultrasound as necessary
- Core biopsy of breast lesion and full-thickness skin biopsy of involved nipple-areolar complex (NAC) if imaging is positive for breast lesion
- Full-thickness skin biopsy of involved NAC – if imaging is negative for breast lesion.

5.3.2. Management

- If breast and NAC biopsies are negative – Clinical follow-up; re-biopsy if not healing;
- Breast DCIS and NAC Paget's – Treat as non-invasive breast cancer (DCIS above)
- Breast invasive and NAC Paget's – Treat as invasive breast cancer (see above)
- Breast negative and Positive NAC Paget's – Total mastectomy OR central lumpectomy +/- sentinel node biopsy without radiation therapy

5.4. Breast cancer during pregnancy

Note: Chemotherapy should not be administered during the first trimester of pregnancy, and RT should not be administered during any trimester of pregnancy.

5.4.1. First Trimester

- Discuss termination: non-therapeutic
  - If patient opts for continuing pregnancy: mastectomy + axillary staging; begin adjuvant chemotherapy in 2nd trimester +/- adjuvant radiation therapy (when possible) in post-partum +/- adjuvant endocrine therapy post-partum

5.4.2. Second trimester and late third trimester

- Mastectomy or excision to negative margins + axillary staging then – adjuvant chemotherapy +/- adjuvant radiation therapy (when possible) in post-partum +/- adjuvant endocrine therapy post-partum;
- Pre-operative chemotherapy – Mastectomy OR excision to negative margins + axillary staging +/- adjuvant radiation therapy (when possible) in post-partum +/- adjuvant endocrine therapy post-partum;

5.4.3. Late third trimester

- Mastectomy or excision to negative margins + axillary staging – adjuvant chemotherapy +/- adjuvant radiation therapy (when possible) in post-partum +/- adjuvant endocrine therapy post-partum.

CENTRAL NERVOUS SYSTEM CANCERS

1. Introduction

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.

1.1. Etiology

Most CNS tumors are sporadic and some are associatied with prior head trauma or radiation exposure, and immune deficiency syndrome (primary CNS lymphoma). Several familial syndromes are associated with primary brain tumors:

- Neurofibromatosis (NF) type 1 or Von Recklinghausen disease associated with optic nerve glioma;
- Malignant astrocytoma, Phaeochromocytoma, Carcinoid and
- Rhabdomyosarcoma;
- Neurofibromatosis (NF) type 2 associated with Vestibular schwanommas (frequently bilateral),OtherSchwannomas,Meningiomas,Gliomas-astrocytomasandependymomas;
- Tuberous sclerosis of Bourneville 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

2. Workup

a. **Clinical Presentation**

- Symptoms related to raised intracranial pressure (ICP) or local/general brain dysfunction;
- Raised ICP
- Headache (morning); bifrontal/occipital
- Nausea and vomiting
- Papilledema – leading 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

b. Imaging

- Brain MRI is the imaging of choice, and is superior to CT scan – due to better contrast resolution.

c. Histopathology

Final diagnosis is made by histopathology for examination after surgery. Immuno-histochemistry is recommended for confirmation of diagnosis.

Histologic grading provides uniformity of classification and categorization of CNS tumors.

G Category	G Criteria
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

A. Meningioma

1. Introduction

- 20% of all intracranial tumors, with 1-4% presenting as giant cell. 40% of patients have multiple lesions seen on CT scan. Commonest sites are cerebral convexity, para-sagittal and sphenoid ridge, making up 75% of cases.
- Female: Male ratio = 2:1
- Peak incidence in 7th decade
- Possible etiologies include ionizing radiation exposure, trauma, viral infections and sex hormone exposure (+/- 75% are PR positive). Associated with NF-2 and with breast cancer;

Common presenting symptoms include:

- Paresis
- Seizures, memory deficit, cranial nerve deficit (other than CN-2), visual field defect, paresthesia, aphasia, papilledema, and diminished visual acuity
- Spinal meningioma – pain in 72% of cases, progressing to sensory loss, weakness, bladder + bowel dysfunction.

2. Workup

- **Imaging:** Brain MRI is standard. Typically, lesions are well circumscribed, with smooth contours. Usually homogeneously increased density on unenhanced CT, and moderate to intense enhancement with contrast. 60% may have surrounding edema. Frequently, 15-20% of lesions are 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.

- **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.

3. Management

Surgery

- Both intracranial and spinal meningiomas are best managed with total excision if possibly achievable with acceptable morbidity;
- Recurrence Free Survival rates are 90%, 80% and 67% at 5, 10 and 15 years respectively.
- 1/3 of tumors are not fully resected because of location, size and proximity to critical structures (posterior fossa, sphenoid ridge and para-sellar)
- Sub-total resection is associated with inferior outcome: 60, 45, 10% at 5, 10 and 15 years;
- Post-operative MRI within 48 hours after surgery
- Post-operative RT improves these rates significantly and is standard of care.
- Post-operative RT depends on:
  - Patient features – age, performance score, comorbidities, treatment preferences
  - Tumor features – size, grade, growth rate, location, potential for causing neurologic consequences if untreated, presence and severity of symptoms
  - Potential for causing neurologic consequences if untreated

Post-operative RT:

- Grade I: observation or consider RT (for symptomatic patients)
- Grade II with complete resection – consider RT
- Grade II with incomplete resection – RT
- Grade III – RT.

Radiation Therapy

- GTV: Based on post-operative remnant for grade 1, and pre-operative scans for grade 2/3 lesions
- PTV = GTV + 1cm margin for benign lesions, and 2-3 cm margin for grade 2/3 lesions.
- Dose solutions – 1.8 Gy x 30 fractions – 54 Gy (5 times per week) for grade 1 lesions OR 1.8 Gy x 33 fractions – 59.4 Gy (5 times per week) for grade 2 and 3 lesions. Some patients may require steroids during RT if RT fields are large;
- RT can be used alone for unresectable tumors, with the same doses as above;
- Spinal meningioma is best treated with excision and this is achieved in all but about 7% of cases; Doses = 1.8 Gy x 25 fractions – 45 Gy (5 times per week)

4. Follow-up

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

B. Primary CNS Lymphoma

1. Introduction

Primary CNS lymphoma (PCNSL) rates are rare compared to other primary CNS tumors. It is related to immunosuppression, and 2-6% of patients with HIV are at risk of developing it over time and 1-5% for renal transplant patients. PCNSL may also present as a secondary malignancy.

- **Clinical presentation:**
  - Fever and general B symptoms
  - Headaches
  - Focal or generalized CNS symptoms

2. Workup

- Brain MRI or CT-scan
- Biopsy of brain lesions, when feasible
- CSF sampling (15-20mL, spinal fluid)
- If biopsy or CSF sampling is positive for primary CNS:
  - Full ophthalmologic exam, including slit lamp eye exam
  - Spinal MRI/CT
  - HIV status – with viral load and CD4 count
  - Contrast-enhanced chest/abdominal/pelvic CT scan
  - Bone Marrow Biopsy
  - Testicular ultrasound for men >60 years of age

3. Management

- Initiate steroids, as clinically indicated
- Whole brain MRI OR Focal spinal RT if CSF or Spinal MRI is positive
- If eye exam shows vitreous involvement and disease is not responding to systemic chemotherapy, consider orbital RT;
- In case of relapse:
  - Consider chemotherapy (systemic and/or intra-CSF) if prior WBRT was provided
  - Focal irradiation
  - Palliative/best supportive care

4. Follow-up

- Brain MRI: every 3 months until 2 years, every 6 months until 5 years, then annually, indefinitely
- For patients with previous spine disease, concurrent spine imaging and CSF sampling as clinically indicated
- For patients with prior ocular involvement, concurrent ophthalmologic follow-up as clinically indicated

C. Glioma

C.1. Low- Grade Glioma

1. Introduction

These are neuro-epithelial tumors, divided into: Astrocytoma, Oligodendroglioma, Ependymomas and mixed tumors.
Low-grade astrocytomas 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.

- **Clinical Presentation:**

2/3 of adult patients present with seizures, and the rest exhibit slowly progressive neurologic symptoms depending on site of tumor. These may evolve over months or even years. Seizures are usually associated with improved survival.

2. Workup

- **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.

- **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.

3. Management (Low grade glioma, Brainstem glioma, Oligodendroglioma)

Surgery:

- If maximal safe resection is feasible: Attempt gross total resection – if complete resection achieved – no further treatment indicated; if incomplete resection – observe and consider radiation therapy only if significant growth and neurologic symptom development;
- If maximal safe resection is not feasible: Subtotal resection or open biopsy – observe and consider radiation therapy only if significant growth and neurologic symptom development.

Radiation Therapy:

- PTV to encompass area of high signal on pre-operative FLAIR/T2 MRI or CT image + 1-2cm margin
- 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 (5 days a week, only when radiotherapy is given) and 150-200mg/m² day 1-5 days monthly for 6 months (28-day cycle).

Recurrent Disease

- If prior fractionated external beam RT:
  - For a resectable disease – surgery – brain MRI (follow-up)
  - Unresectable disease – consider biopsy. For both options, consider re-irradiation (if feasible) with focused RT, if new lesion is outside target of prior RT; consider observation for low-risk disease, chemotherapy (Temozolomide) or best supportive care.
- If no prior fractionated external beam RT:
  - Resectable disease – surgery – brain MRI (follow-up)
  - Unresectable disease – consider biopsy – then RT + Temozolomide (details above) or RT alone.

4. Follow-Up

Brain MRI every 3-6 months for 3-5 years then at least annually as clinically indicated.

C.2. High Grade Glioma: Anaplastic Gliomas and Glioblastoma

1. Introduction

High Grade Gliomas make 35-45% of all primary brain tumors, and of these, 85% are Glioblastoma Multiforme (GBM). The incidence of Anaplastic Astrocytoma (part of Gliomas) peaks in children <10 years of age, and remains constant in each subsequent decade. The 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 gliomas has increased at least 2-fold in the elderly over the past 2 decades.
They usually occur in cerebral hemispheres with frontal, parietal, temporal, occipital lobes most commonly involved (in that order), and present with features of mass effect, or focal signs depending on location. Multi-centric tumors occur in <5% of cases and CNS dissemination occurs in about 10% of end stage cases. Metastases outside of CNS are extremely rare.

2. Workup

- Imaging: MRI is the 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-tumoral edema is often extensive, and mass-effect is commonly seen in these patients.
- 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, micro-vascular proliferation.

3. Management

Surgery

- If maximal safe resection is feasible, with goal for image-verified complete resection – maximal resection then brain MRI (within 48 hours, preferably).
- If maximal safe resection is not feasible – open biopsy OR subtotal resection (with MRI after resection).

Adjuvant treatment (Anaplastic Astrocytoma/Oligoastrocytoma and Anaplastic Oligodendroglioma)

- Standard RT with concurrent and adjuvant Temozolomide OR standard RT and Adjuvant Temozolomide
- For Anaplastic Gliomas, with poor performance status (KPS <60) – RT (hypofractionated or standard) or Temozolomide.

Radiation Therapy

- PTV = to encompass enhancing lesion seen on pre-op T2/FLAIR scan, plus small (2cm) margin.
- Recommended dose – 60 Gy in 2 Gy per fraction or 59.4 Gy in 1.8 fractions; lower doses (54-55.8 Gy in 1.8 Gy) can be applied when the tumor volume is large or when there is brainstem/spinal cord involvement, or for grade III astrocytoma.
- If boost volume can be used – initial phase of the RT plan will receive 46Gy in 2 Gy per fraction or 45-50.4 Gy in 1.8 Gy per fractions. The boost plan will receive 14 Gy in 2 Gy per fraction or 9-14.4 Gy in 1.8 Gy per fraction.
- In poorly performing patients, or elderly – hypofractionated course is considered, with a goal to complete treatment in 2-4 weeks. Typical fractionations are 34Gy in 10 fractions or 40.05 Gy in 15 fractions. A shorter fractionation schedule of 25 Gy/5 fx may be considered for elderly and/or frail patients with smaller tumors for whom a longer course of treatment would not be tolerable.

Chemotherapy

- Concurrent (with RT) and Adjuvant Temozolomide at doses: 75 mg/m2 daily per oral during RT (5 days a week), then 150-200 mg/m2 given D1-D5 of a 28 day cycle for 12 cycles after RT; oral steroid/anti-emetics should be taken half an hour prior to chemotherapy tablet on each day; tablets must be taken in the morning on an empty stomach.
- Prophylaxis for PCP pneumonia with Co-trimoxazole (one tablet twice Daily) should be considered during daily Temozolomide treatment

Recurrent Disease

- Diffuse Or Multiple – consider surgery if symptomatic, large lesion, or Systemic chemotherapy (Temozolomide) or best supportive care if poor performance status
- If Local – resectable – resection, followed by brain MRI – systemic chemotherapy (Temozolomide) or best supportive care if poor performance status. If non resectable – Systemic chemotherapy (Temozolomide) or palliative best supportive care.

4. 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.

D. Adult Intra-cranial and Spinal Ependymoma

1. Introduction

Ependymomas are rare tumors, arising from ependymal cells of the ventricular lining of the brain and central canal of the spinal cord. In adults, ependymomas account for 2% of all CNS tumors. Adult ependymomas tend to occur mostly in the spine, differently from the pediatric form arising mostly from the posterior lobe.
Common signs are raised intra-cranial pressure, visual disturbance and headache, along with back pain, and progressive loss of lower functions for the spinal ependymomas.

2. Workup

- **Pathology:** Gold standard in diagnosis, when biopsy is feasible; consider CSF analysis when no gross spinal involvement is visible on imaging
- **Imaging** – MRI or contrast-enhanced CT scan, compatible with primary brain tumor or spinal cord tumor.

3. Management

Surgery (any location)
- Gross total resection, when feasible: adjuvant treatment
- Gross total resection, not feasible – open biopsy or subtotal resection – adjuvant treatment.

Adjuvant treatment
- Ependymoma, grade II – brain and spine MRI, and CSF analysis
  - If MRI spine and CSF analysis are negative – standard (localized) RT or observation if post gross total resection;
  - If evidence of metastasis – brain, spine, or CSF – Cranio-Spinal RT.
- Anaplastic ependymoma, grade III – same as above, whether MRI/CSF analysis are negative (standard RT) or if evidence of metastasis (Cranio-spinal RT).
- Spinal Ependymoma:
  - Myxopapillary ependymoma, grade I (brain and spine MRI; CSF analysis):
  - En-bloc resection without capsule violation and CSF cytology is negative – observe.
  - Gross total resection, but capsule violation occurred and CSF cytology negative or subtotal resection and CSF cytology negative – standard RT.
  - Gross total resection or subtotal resection and evidence of metastasis in brain or spine, or CSF cytology positive – cranio-spinal RT.
  - Ependymoma, status post resection, grade II (brain and spine MRI; CSF analysis):
  - Gross total resection, MRI brain and spine negative, CSF negative – observe;
  - Subtotal resection, MRI brain negative, CSF negative – standard RT or observe in select situations;

- Gross total or subtotal resection and evidence of metastasis (brain, spine or CSF) – Craniospinal RT
- Anaplastic ependymoma (grade III), status post-resection (brain and spine MRI; CSF analysis):
- Gross total or subtotal resection, MRI negative, CSF negative – Standard RT;
- Gross total or subtotal resection and evidence of metastasis (brain, spine or CSF) – Cranio-spinal RT.

Radiation Therapy Details

- Intra-cranial tumor – best defined using pre and post-operative MRI imaging, with enhanced T1 and/or FLAIR/T2. GTV is defined as anatomic areas touched by pre-operative tumor volume plus post-operative signal abnormality as seen on MRI. Dosing: 54-59.4 Gy in 1.8-2 Gy per fractions. PTV margin of 3-5mm is typically added to the CTV.
- Spinal tumors – CTV margins – 1-2mm added in the superior and inferior directions; PTV – 3-5mm typically added to CTV; RT dosing: 45-54 Gy in 1.8 Gy per fraction
- Cranio-spinal RT – Whole brain + spine to bottom of thecal sac, receives 36 Gy in 1.8 fractions, then followed by boosts – spine: to total of 45 Gy, or 54-59.4 Gy if primary tumor is intra-cranial.

Chemotherapy

- Mostly indicated for recurrent disease – platinum-based regimens: Single agent or combination – Temozolomide, Etoposide

Recurrence

- **Resectable disease:**
  - No prior RT – Gross total or subtotal resection and CSF cytology is negative – standard RT; if subtotal resection and evidence of metastasis – craniospinal RT:
  - If prior RT – gross total or subtotal resection and CSF cytology negative – re-irradiation or chemotherapy; if subtotal resection and evidence of metastasis – chemotherapy or best supportive care
- **Unresectable disease:**
  - No prior RT – Localized recurrence – standard RT; if evidence of metastasis – cranio-spinal RT;
  - Prior RT – Localized recurrence – re-irradiation or chemotherapy; if evidence of metastasis – chemotherapy or best supportive care

4. Follow-Up

Imaging – brain, spine MRI every 3-4 months for 1 year, then every 4-6 months for year 2, then every 6-12 months for 5-10 years, then as clinically indicated.

E. Adult Medulloblastoma

1. Introduction

In adults, medulloblastomas are rare, consisting of <1% of all adult CNS malignant tumors. The etiology of medulloblastoma is less known.
Clinical presentation varies from headache, visual disturbance and signs of raised intra-cranial pressure.

2. Workup

- **Pathology:** Gold standard in diagnosis; obtain CSF analysis to rule out microscopic spinal dissemination if no imaging evidence.
- **Imaging:** Brain and Spine MRI.
- **Staging** and risk stratification – same as pediatric medulloblastoma

3. Management

Surgery
- If gross total resection is possible – adjuvant treatment to depend on risk features (standard versus high risk)
- If gross total resection is not possible – open biopsy or partial resection and adjuvant treatment (treat as high risk if residual >1.5cm^2)

Adjuvant treatment
- If standard risk for recurrence – with no evidence of metastasis (brain, spine, CSF, extra-neural) OR small volume residual disease (<1.5 cm^2) OR classic/desmoplastic histology: Standard dose cranio-spinal radiation OR reduced dose cranio-spinal RT with chemotherapy, followed by post-radiation chemotherapy
- If High risk for recurrence – with unresectable tumor or residual tumor > 1.5 cm^2 OR disseminated disease within or outside of the neuroaxis OR large cell/anaplastic medulloblastoma: Cranio-spinal radiation with chemotherapy followed by post-radiation chemotherapy

Radiation Therapy
Details and dosing – similar to cranio-spinal RT in ependymoma

Chemotherapy
- Concurrent chemo-radiation: Weekly Vincristine – IV 1.5mg/m^2
- Maintenance chemotherapy after chemo-radiation: 1 month post-chemo-radiation - Cisplatin (IV 100 mg/m^2), Cyclophosphamide (IV 1000mg/m2) and Vincristine (IV 1.5mg/m^2), every 28 days for 6 cycles.

Recurrent Disease

- **Chemotherapy** – single agent Etoposide (palliative intent)
- Best supportive care

4. Follow-Up

- Brain and/or spinal MRI every 3 months for 3 years, then every 6-12 months for 5-10 years; then every 1-2 years or as clinically indicated.

F. Intra-Cranial Germ Cell Tumors

1. Introduction

Intra-cranial germ cell tumors are one of the variant of extra-gonadal germ cell tumors. 70% of patients are between the ages of 10-24 years, with a male to female ratio of 3:1, especially for pineal tumors.
Their common location is the pineal gland – 50-60%, followed by supra-sellar – 30-40%, and less commonly in the basal ganglia or thalamus (3-5%). 10% of the cases occur in multiple sites (multiple, midline tumors). Their natural spread is mostly laminar, along the sub-ependymal lining of walls V3 and V4.
Their clinical presentations depend on primary location – with pineal tumors presenting with hydrocephalus, with 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. Supra-sellar tumors present with Chiasmal compression causing bitemporal hemianopia and eventually diplopia and decreased VA, Panhypopituitarism and diabetes insipidus.

WHO Classification

- Germinoma (40%) – usually non-secreting but may be hCG positive, PLAP positive, but never AFP Positive
- Teratoma (19%)
- Choriocarcinoma (2%) – strongly hCG positive
- Yolk sac/endodermal sinus tumor (2%) – strongly AFP positive
- Embryonal carcinoma (3.3%) – may be weakly AFP or hCG positive
- Mixed tumors (32%) – Most common component: Germinoma

2. Workup

- 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.

3. Management

3.1. Management – Secreting GCTs

Surgery

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

Radiation Therapy

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 x 13 Fractions = 23.4 Gy

Boost= 1.80 Gy x 12 fractions = 21.6 Gy, Total Dose= 45 Gy

OR Chemotherapy + extended local RT Carboplatin 450 mg/m^2 D1

Etoposide 150 mg/m^2 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)

3.2. Management – Non-germinatous (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 Cranio-spinal 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.

Radiation Therapy

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

Chemotherapy

- Cisplatin containing regimens – PVB, carboplatin/etoposide/bleomycin/ carboplatin/ etoposide
- Ifosfamide-containing regimens- ICE, ifosfamide/etoposide

G. Primary Spinal Cord Tumors

1. Introduction

Primary spinal cord tumors are extremely uncommon and their etiology is generally unknown and they generally tend to occur in younger patients. Extradural lesions are usually metastatic, while intra-dural and extra-medullary tumors are evenly divided between metastatic and primary tumors. Intra-medullary tumors are usually primary gliomas.
Their clinical presentations generally depend on level of lesions – pain, segmental/nerve root weakness, sensory deficit (dermatomal). 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, while high-grade tumors may spread through CSF. Occasionally, hematogenous spread leads to lung involvement.

2. Workup

- **Pathology:** Histology correlates with location. Vertebral bone tumors are the most common – osteogenic sarcoma, chondrosarcoma, and chordoma (especially if sacral). Spinal canal tumors are usually – soft tissue sarcoma (esp. nerve sheath tumors), meningiomas. Cord tumors are – astrocytomas, ependymomas, hemangiomas.
- **Imaging:** MRI is the study of choice; the entire neuraxis should be visualized for ependymomas and high-grade tumors. CT chest may be appropriate for sarcomas.

3. Management

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

Radiation Therapy – indicated for:
- Incompletely resected low-grade lesions
- High grade astrocytic lesions
- Multi-focal/anaplastic ependymoma requires cranio-spinal RT
- Sub-totally resected meningioma
- Sarcomas – treated elsewhere in the body with chemotherapy and surgery.

For completely resected low-grade lesions, spinal meningioma (when completely resected, only 6% rate of recurrence) – RT is not indicated.
PTV – 3-5mm margin of normal cord (as seen on MRI, pre-operative T2 sagittal most useful) on both sides. Field width is usually about 7-8cm.

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 cranio-spinal 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

Recurrent Disease

- Re-resection OR
- RT or re-irradiation if surgery not possible OR
- Chemotherapy relative to cell type if further surgery or RT is not possible

4. Follow-Up

- Low-grade tumors (I-II): Spine MRI every 3-6 months until 5 years, then at least annually indefinitely
- High-grade tumors (III-IV): Spine MRI every 2-6 week after treatment, then every 2-4 months until 2-3 years, then every 3-6 months until 5 years, then every 6-12 months indefinitely.

H. Brain Metastases

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.
- The risk of developing brain metastasis varies with cancer type:
  - 50% associated with lung cancer
  - 15-20% with breast cancer
  - 10-15% with melanoma
  - Other sites: GI(colon, pancreatic), Genito-urinary(kidney, testes, cervix, ovary), head and neck
  - 10-15% with unknown primary
  - 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 metastases patients according to a recursive partitioning analysis. They identified 3 prognostic classes, which are summarized below:

Prognostic Class	Description	Median survival (months)
1	KPS >70 and Age <65 and Controlled primary and no extra-cranial metastasis	7.1
2	KPS > 70 + 1 or more of: Age >65 Uncontrolled primary Presence of extra-cranial metastasis	4.2
3	KPS <70	2.3

2. Management

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. Further 10-20% experiences seizures during the course of their illness. Prophylactic anticonvulsants are NOT generally indicated.
- **Phenytoin** is medicine of choice for generalized seizures. Take care to load patients or levels will be sub-therapeutic. Phenytoin also works well for partial/focal seizures, but Epilim may also be used.

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 Whole Brain Radiation Therapy provides benefit in certain well-selected patients with brain metastasis.

Radiation Therapy:
Dose – 4 Gy x 5 fractions =20 Gy, for clinical situations where survival over 1 year is unlikely; 3 Gy x 10 fractions = 30 Gy, where longer term survival is a possibility.

I. Spinal Metastasis

1. Introduction

Spinal metastases are commonly located on the vertebral bones. The primary malignancies are usually prostate, breast, lung and thyroid cancers. 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 are needed to reduce cord edema and symptoms, and urgent surgical decompression is 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 for patients not suitable for surgery, their outcomes are similar. For patients who present >36 hours after onset of total paralysis, elective treatment can be considered, as functional return is extremely unlikely. In patients without histological diagnosis or an obvious primary, every effort should be made to obtain this. Tuberculosis frequently mimics metastatic disease in the spine.

2. Management

When possible – surgical decompression is needed. Otherwise, radiation therapy is indicated in all cases.
Dose: 4 Gy x 5 fractions = 20 fractions, at cord depth can be used. Consider 30 Gy in 10 fractions in young patients with better prognosis, with breast cancer, prostate cancer with good performance status and multiple myeloma. Consider 8 Gy in 1 fraction for patients in very poor performance status.
Treatment fields – to extend 1-2 vertebrae beyond the tumor site, on both sides, if area is not too large.

J. Pituitary Neoplasms

1. Introduction

Represent 10% of intracranial malignancies. They rarely metastasize but frequently are 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.
Their etiology is unknown, but may be associated with MEN-1 syndrome, rarely. Pituitary tumors arise from the anterior lobe.
Their clinical presentations are mostly from local pressure effects – headache, visual disturbance, lateral extension causing interference with CN3, 4 and 6, epilepsy (from temporal lobe extension), hormonal changes (hyposecretion/hypersecretion).

2. Workup

- **Pathology:** Adenomas – functional or non-functional, carcinomas – functional or non-functional, sarcomas (rare), craniopharyngiomas (discussed under pediatric guidelines) and metastases. Pituitary adenoma – may be micro-adenomas (<10 mm) or macro-adenomas (>10 mm), when metastased, are called pituitary carcinoma. Classified on an immune-cytological basis:
  - Prolactin-secreting
  - GH secreting
  - ACTH-secreting
  - TSH-secreting
  - Gonadotrophin secreting (FSH, LH)
  - Non-secreting
  - Mixed.
- **Imaging:** Tumors should be assessed with Sella MRI and complete hormonal panel.

3. Management

Supportive – steroids, anti-emetics, anti-convulsants, physiotherapy

Medical Management:
All patients should be assessed for hypopituiarism at initial work-up, and started on hormone replacement if indicated. Please refer the patient to Internists or Endocrinologists for replacement therapy, and for treatment of hormonally active adenoma.

Surgical Management:
This is the primary treatment for most pituitary tumors, except for prolactinomas, which may be managed medically. The trans-sphenoidal approach is preferred in almost all situations as it is safer and better tolerated than the frontal craniotomy approach. Mortality is <1%, with rare complications. Hypo-pituitarism occurs in the post-operative setting in about 12% of patients.

Radiation Therapy:
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 disease. 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.
PTV = GTV + 1cm margin. Doses – 1.8 Gy x 28 fractions = 50.4 Gy and 1.8 Gy x 25 fractions = 45 Gy for small tumors (<4 cm). ACTH and TSH – secreting tumors or very large tumors may be treated to a higher dose: 1.8 Gy x 30 fractions = 54 Gy

4. 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.

GASTROINTESTINAL MALIGNANCIES

A. Esophageal Cancer

1. Introduction

Incidence: adenocarcinoma (AdenoCA) is increasing dramatically (due to obesity), squamous cell carcinoma (SCC) decreasing over time.

Risk factors

- Age
- Lifestyle
- SCC: smoking, alcohol, betel nut chewing, N-nitroso containing foods
- AdenoCA: obesity, smoking, N-nitroso foods

Other

- SCC: Achalasia, caustic stricture, HPV, prior head and neck SCC
- AdenoCA: H. pylori infection, Barrett's (Gastro-Esophageal Reflux Disease), obesity, Zollinger Ellison, Prior cholecystectomy, drugs that relax esophageal sphincter (nitrates, BDZ)

2. Workup

- CT chest/abdomen/pelvis
- Endoscopy/EUS: biopsy, location, T staging
- Differences between squamous and adenocarcinoma in staging
- In SCC, stages can change depending on grade and location
  - E.g. Poor grade, upper/middle location upgraded from 1A 1B, 1B 2A etc.
- In adenocarcinoma, only TNM stages affect the final stage.
- Upper (cervical) cancer, T4 generally difficult to resect and typically treated with chemoradiation.
- Multidisciplinary approach important
- Consider HER-2 and mismatch repair deficiency testing in patients with adenocarcinoma and advanced disease.

3. Staging

Primary tumor (T), squamous cell carcinoma and adenocarcinoma	
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
Regional lymph nodes (N), squamous cell carcinoma and adenocarcinoma	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1 or 2 regional lymph nodes
N2	Metastases in 3 to 6 regional lymph nodes
N3	Metastases in 7 or more regional lymph nodes
Distant metastasis (M), squamous cell carcinoma and adenocarcinoma	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

Squamous Cell Carcinoma (M0 disease)

- cT1b-cT2, N0 (low risk lesions: <3cm, Well differentiated) : Esophagectomy (for non-cervical esophagus)
- Recommendations after surgery
  - R0: Surveillance or consider chemoRT
  - R1: ChemoRT or chemotherapy
  - R2: ChemoRT or palliative management
- cT2,N0 (high risk lesions : LVI,>3cm , poorly differentiated), cT1b-cT2,N+, or cT3-T4a , any N
  - Preoperative chemoRT (for non cervical) OR
  - Definitive chemoRT (for cervical)
- cT4B (any N)
  - Definitive chemoRT (RT +Concurrent chemotherapy)
  - Consider chemotherapy alone in the setting of invasion of trachea, great vessels or heart.

Adenocarcinoma (M0 disease)

- cT1b-cT2, N0 (low risk lesions: <3cm, Well differentiated) : Esophagectomy (for non-cervical esophagus)
- Recommendations after surgery
  - R0: Surveillance or consider chemoRT
  - R1: Adjuvant ChemoRT or chemotherapy
  - R2: Adjuvant ChemoRT or palliative management
- cT2,N0 (high risk lesions : LVI,>3cm , poorly differentiated), cT1b-cT2,N+, or cT3-T4a , any N
  - Preoperative chemoRT (for non cervical) OR
  - Definitive chemoRT (for cervical)
- cT4B (any N)
  - Definitive chemoRT (RT +Concurrent chemotherapy)
  - Consider chemotherapy alone in the setting of invasion of trachea, great vessels or heart.

Radiation

RT Dosing

- Preoperative RT: 41.4–50.4 Gy (1.8–2.0 Gy/day) (total 23–28 fractions)
- Postoperative RT: 45–50.4 Gy (1.8–2.0 Gy/day) (total 25–28 fractions)
- Definitive RT: 50–50.4 Gy (1.8–2.0 Gy/day)6 (total 25–28 fractions)

Supportive Care

- Treatment interruptions or dose reductions for manageable acute toxicities should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment interruptions.
- During the radiation treatment course, patients should be seen for status check at least once a week with notation of vital signs, weight, and blood counts.
- Anti-emetics should be given on a prophylactic basis when appropriate. Antacid, proton pump inhibitors, and anti-diarrheal medications may be prescribed when needed.
- If estimated caloric intake is <1500 kcal/day, oral and/or enteral nutrition should be considered. When indicated, feeding jejunostomy tubes (J-tubes) or nasogastric feeding tubes may be placed to ensure adequate caloric intake. During surgery, a J-tube may be placed for postoperative nutritional support.
- Adequate enteral and/or IV hydration is necessary throughout chemoradiation and recovery

Chemotherapy Regimen

- Chemotherapy regimen for **preoperative** ChemoRT
  - Carboplatin/Paclitaxel weekly (Category 1)
  - Flurouracil and oxaliplatin (Category 1)
  - Flurouracil and Cisplatin (Category 1)

- Chemotherapy regimen for **definitive** ChemoRT
  - Carboplatin/Paclitaxel weekly
  - Flurouracil and oxaliplatin (Category 1)
  - Flurouracil and Cisplatin (Category 1)

- Chemotherapy regimen for **adjuvant** ChemoRT
  - Fluoropyrimidine (5FU or Capecitabine) before or after Fluoropyrimidine based radiation

RECURRENT / METASTATIC

- **Chemotherapy Regimen**
  - First-line therapy including Oxaliplatin is generally preferred over Cisplatin

  - Regimens for HER-negative or unknown
    - FOLFOX/CAPEOX
    - 5FU+Cisplatin or Capecitabine+Cisplatin

  - Regimens for HER-positive
    - FOLFOX/CAPEOX plus trastuzumab (Category 1)
    - 5FU+Cisplatin or Capecitabine+Cisplatin plus trastuzumab (Category 1)

  - Second Line or Other regimens
    - Carboplatin and Taxol
    - 5FU and Irinotecan*
    - Immunotherapy agents may be included in patients with MSI instability

B. Gastric Cancer

1. Introduction

Screening programs in Japan, Venezuela, Chile where high incidence
Surgery only curative treatment for early gastric cancer (5Y-OS=70%)
Most patients present with locally advanced disease (5Y-OS=30%)
2 histologic types of gastric adenocarcinoma: intestinal and diffuse (germline mutation in cell adhesion protein E-cadherin)

Risk factors
Environmental Factors
- Diet: nitroso compounds, high salt diet with low vegetables
- Smoking (risk 1.5x higher)
- Alcohol consumption
- Pylori infection: esp vacAs1-, vacAm1- and cagA-positive
- Specific types of cytokine polymorphisms (IL-1B-511*T/*T or IL-1B-511*T/*C)
- Obesity (OR = 1.5)
- Previous gastric surgery, especially Billroth II procedure
- EBV

Host-Related Factors
- Gastric ulcers, adenomatous polyps, intestinal metaplasia
- Blood Type A: 20% excess gastric cancer
- Familial predisposition: genetic predisposition to atrophic gastritis, HNPCC, FAP, Peutz Jeghers, Li-Fraumeni, juvenile polyposis, PTEN mutation
- Hereditary diffuse gastric cancer due to germline mutation in CDH1, loss of expression of E-cadherin; autosomal dominant, lifetime risk of gastric cancer = 70%
- Pernicious anemia: 3x risk

Signs & Symptoms
- Epigastric pain, dysphagia, weight loss, nausea, early satiety, bleeding
- Weight loss usually results from insufficient caloric intake rather than increased catabolism and may be attributable to anorexia
- Paraneoplastic: diffuse sebhorreic keratosis (sign of Leser-Trelat), acanthosis nigricans, microangiopathic hemolytic anemia, membranous nephropathy, hypercoaguable state, polyarteritis nodosa.

2. Workup

- EGD and biopsy
- Endoscopic ultrasound (good for T staging in depth of invasion and also LN assessment)
- CT chest/abdomen/pelvis
- PET scan (confirm malignant involvement of CT-detected adenopathy)

- Tumor markers (CEA, CA125, CA19-9)
- Staging laparoscopy (liver surface, peritoneum, local lymph nodes) – not commonly done now

GE Junction Cancers:

- Tumors arising at the GEJ or in the cardia of the stomach within 5 cm of the GEJ are staged using the TNM system for esophageal cancer
- Consider HER-2 and mismatch repair deficiency testing in patients with adenocarcinoma and advanced disease.

3. Staging

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 Δ
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures Δ
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. Δ 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.	
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1 or 2 regional lymph nodes
N2	Metastases in 3 to 6 regional lymph nodes
N3	Metastases in 7 or more regional lymph nodes
N3a	Metastases in 7 to 15 regional lymph nodes
N3b	Metastases in 16 or more regional lymph nodes
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

- Surgery is the mainstay of therapy with either partial or total gastrectomy. Survival is similar between the two provided that margins are negative with partial gastrectomy associated with improved nutritional status and quality of life.
- Extent of lymph node dissection is recommended to be at least 15 LNs for adequate staging.
- For clinical unresectable locally advanced disease, perioperative systemic therapy or preoperative chemoradiation followed by surgery is the best approach. If unresectable after neoadjuvant treatment or metastatic then consider palliative management.

Adjuvant treatment of gastric cancer after surgery

R0 Resection

- pTis or pT1, N0: Surveillance
- pT2N0: Surveillance OR Fluoropyrimidine (5FU or capecitabine) then fluoropyrimidine based chemoRT then fluoropyrimidine for selected patients.
- pT3, pT4, any N or Nx, Any pT, N+ : Fluoropyrimidine (5FU or capecitabine) then fluoropyrimidine based chemoRT then fluoropyrimidine for selected patients if less than a D2 dissection (Category 1). Or Chemotherapy for patient who have undergone primary D2 LN dissection (Category 1).

R1 resection

- Chemoradiation (fluoropyrimidine based), if not received preoperatively, or consider re-resection.

R2 resection

- Chemoradiation (fluoropyrimidine based), if not received preoperatively, or palliative management

Chemotherapy: There is a demonstrated OS benefit of about 6% with the use of 5 FU based chemotherapy in adjuvant settings compared to surgery alone. The following are options:

- Perioperative:
  - FLOT (Category 1)
  - Fluoropyrimidine and Oxaliplatin
  - 5FU + Cisplatin (Category 1)

- Preoperative chemoRT:
  - 5FU + Oxaliplatin (infusional 5 FU can be replaced by Capecitabine)
  - Paclitaxel and Carboplatin
  - 5FU or Capecitabine alone

- Postoperative chemoRT
  - Fluoropyrimidine (5FU or capecitabine) before and after fluoropyrimidine based chemoRT.

- Postoperative chemotherapy
  - °Capecitabine + Oxaliplatin (Category 1)
  - °5FU + Oxaliplatin
- ChemoRT for unresectable disease
  - °5FU+Oxaliplatin
  - °5FU+Cisplatin

- Unresectable locally advanced/recurrent or metastatic disease where local therapy is not indicated
  - °FOLFOX
  - °Fluoropyrimidine + Cisplatin
  - °Fluoropyrimidine+Irinotecan*

Radiation:

- **The indication for adjuvant RT include:** T2-4, node positive disease or positive margins. **Dose:** 45Gy/25 fractions. Consider 5.4Gy to 5.9Gy boost for positive margins or gross residual disease. Tumor bed is covered and coverage of gastric remnant is dependent on risk and organs at risk. LNs coverage in adjuvant settings is dependent on anatomic site of the primary. Consider omission of nodal coverage in patients with T2-3N0 and >15 LNs removed.
- **Paragastric LNs:** Always covered except for proximal T1-2aN0 patients with negative margins >5cm and 10 to 15 LNs removed.
- **Celiac and suprapancreatic LNs:** Cover for T4,N+ or T3N0 <15LNs removed
- **Portal-hepatic LNs:** Cover all T4, N+ except for proximal lesions with only one to two involved LNs and >15LNs resected.
- **Splenic LN:** Cover for all T4, N+ except distal lesions with only one to two involved LNs and >15 LNs resected
- **Distal paraesophageal LNs:** Lesions with esophageal extension

Recurrent/ Metastatic Disease

Locoregional recurrence

- Resectable and medically operable: Consider surgery or palliative management
- Unresectable or medically inoperable: Palliative management

Metastatic disease

- Palliative management

5. Follow-up

- H & P every 3-6months for 1-2 years, every 6-12 months for 3-5 years and annually thereafter
- FBC and chemistry profile as clinically indicated
- EGD as clinically indicated
- CT chest/abdomen/pelvis with oral and iV contrast as clinically indicated
- Monitor for nutritional deficiency in surgically resected patients and treat as indicated.

C. Pancreas Cancer

1. Introduction

Risk Factors:

- **Environmental/Chemical/Infections:**
  - Smoking increases the risk 1.53 fold and is responsible for 1525% of case
  - Chronic pancreatitis
  - Diabetes
  - Obesity
  - Heavy alcohol consumption
  - Others: Hx of Gallstones, H pylori, diet with high animal proteins also reported.

- **Genetic:**
  - 510% have a family Hx, several genetic syndromes has been described.
  - BRCA2: 3.510 fold
  - PeutzJeghers Syndrome: more than 100 fold
  - HNPCC: 4 fold
  - Ataxia telengectasia
  - PABL2 germline mutations: 6 fold
  - FAMMM: CDKN2A mutation (pancreatic cancer and melanoma)

- **Prevention & Screening**
  - Prevention: smoking cessation, avoid heavy alcohol consumption, weight reduction and healthy diet appear to lower the risk
  - Screening: No reliable screening tool available

- **Symptoms & Signs:**
  - **Common Symptoms:** epigastric/abdominal pain, Obstructive jaundice, malabsorption, weight loss, bowel obstruction symptoms, DM
  - **Common Signs:** jaundice, abdominal mass, hepatomegaly, Courvoisier's sign, ascites, cachexia
  - **Common Presentations:** many patients remain asymptomatic until their disease is more advanced. Tumors of the head of pancreas usually present earlier with obstructive jaundice.

2. Workup

Laboratory:

CA19-9

- Not specific or sensitive for pancreatic cancer (70-90%)
- The higher the more specific but less sensitive
- NOT used for Screening

- Also elevated in other malignancies: cancers of the biliary tree, less often gastric, ovarian, colorectal, rarely: lung, breast, uterine. Benign causes of elevation: acute cholangitis, cirrhosis, other cholestatic disease
- **Prognostic:** higher pre and post op CA19-9 carries worse prognosis and could be helpful in determining resectability. Nevertheless, CA 19-9 alone should not be used as the sole determinant of surgical resectability.

Diagnostic Imaging:
- CT scan with multiphase pancreatic protocol
- Trans abdominal US can be used for initial testing of patients with jaundice, but sensitivity decreases for small tumors
- MRI can be used if CT is contra indicated and, although it is more sensitive for differentiating pancreatitis from pancreatic cancer, it has not be shown to be superior to multiphase CT.
- EUS: can be useful for more detailed nodal information and small tumors

Diagnostic Procedures:
- Biopsy of highly suspicious pancreatic masses are often NOT needed prior to definitive surgery.
- Consideration for preoperative biopsy should be given to:
  - Suspicion of other etiology such as pancreatitis
  - Unresectable or borderline resectable on staging investigations to confirm the diagnosis
  - Plan to start Neo-adjuvant chemotherapy

Pathology & Molecular Biology
- Common Histology: (e.g., adenocarcinoma 80%, squamous cell carcinoma 10%)
- Common Metastatic Sites: liver, lung, hepatobiliary region

Relevant Molecular Biology:
- KRAS mutation in 80%
- CDKN2A: a cell-cycle control gene, is the most commonly inactivated tumor suppressor gene (>80%)
- Inactivation of tumor suppressor genes TP53 and SMAD4 are thought to occur later in the tumorigenesis process.

3. Staging

TNM 8th Edition

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*. This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 and <1 cm in greatest dimension
T1c	Tumor 1 to 2 cm in greatest dimension
T2	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

RESECTABLE: (T13, N01, M0), No involvement of celiac plexus or superior mesenteric artery
Bottom Line General Approach:

- Surgical resection (Whipple or distal pancreatectomy) followed by adjuvant chemotherapy (see options below)

BORDERLINE RESECTABLE:

- Evolving sub group of tumors that include no evidence of metastatic disease
- Venous involvement of SMV or portal vein with distortion of vein or short distance occlusion allowing for resection and reconstruction
- Venous involvement <180-degree circumference

Bottom line: Should be reviewed in multi-disciplinary rounds, consider systemic chemotherapy as extrapolation from locally advanced setting (eg. FOLFIRINOX if patient has a good performance status) to be followed by consideration of surgical resection.

LOCALLY ADVANCED/ UNRESECTABLE/ METASTATIC:

Bottom Line General Approach:

- If good performance status, palliative chemotherapy with Single agent Gemcitabine or FOLFIRINOX (5FU, Irinotecan and Oxaliplatin)
- Continue until unacceptable toxicity, significant clinical deterioration or clear disease progression.
- Palliative procedures should be considered (Biliary stents, gastric bypass, duodenal stents, celiac axis block, etc).
- Choice should be individualized based on patient factors such as performance status, side effect profile and availability.
- Best supportive care

Prognosis: median OS is 11.1 months with FOLFIRINOX, and 6.7 months with Gemcitabine alone, Without treatment, prognosis is poor

- Adjuvant Chemotherapy: Options include
- Gemcitabine + Capecitabine (Category 1)
- Modified FOLFIRINOX (Category 1)- includes Irinotecan is not on WHO EML
- Gemcitabine alone
- 5FU +leucovorin

Systemic Chemotherapy (locally advanced or in the metastatic setting)

- FOLFIRINOX (Category 1)
- Modified FOLFIRINOX
- Gemcitabine + albumin-bound-paclitaxel* (Category 1)
- Gemcitabine alone (Category 1)
- Capecitabine alone
- 5FU/Leucovorin

** Not on WHO EML*

D. GIST (Gastrointestinal Stromal Tumor)

1. Introduction

- Incidence: Rare tumor that accounts for less than 1% of all GI cancer, 10-20 cases per million populations per year.
- More common in: Men, black and middle age and elderly (mean age at diagnosis is 63).
- Location: GIST can occur in any part of GI tract, stomach 65%, small intestine 25%, others in rest of GI tract or in abdomen.
- Survival: 5-year overall survival is more than 75% in localized, 65% in regional and 40% in metastatic.

Risk Factors

Most of the GIST cases are sporadic.

Genetic:

- Familial GIST: mutations in KIT gene, multiple gastric and small intestine GIST, skin hyperpigmentation, dysphagia and paragangliomas.
- Neurofibromatosis type 1 (NF1): multiple, mainly small intestine and wild type KIT.

Prevention & Screening

- **Prevention:** Not known.
- **Screening:** No available data.

Symptoms & Signs

- **Common Symptoms:** Depends on the location of the tumor. Abdominal pain, GI bleeding, early satiety and other non-specific symptoms (N/V).
- **Common Signs:** Abdominal mass, bowel obstruction and incidental findings.

2. Workup

- **Laboratory:** CBC to check for anemia, LFT and kidney function.
- **Diagnostic Imaging:** CT or MRI, consider chest imaging, upper or lower endoscopy and EUS. PET will show metabolic activates in GIST but not routinely used.
- **Diagnostic Procedures:** FNA can be sufficient to make the diagnosis. Preferred core-biopsy tissue.

Pathology & Molecular Biology

- **Common Histology:** GIST typically presents as subepithelial tumors, spindle cell type 70%, epithelioid type 20% and mixed type 10%.
- Common Metastatic Sites: liver and peritoneum.
- **Molecular Biology:** 95% KIT positive (CD117), 70% CD34 positive. DOG-1 (Discovered On GIST -1) positive in almost all GISTs and used in negative KIT to confirm the diagnosis. Most GISTs have activating mutations in KIT or platelet-derived growth factor alpha (PDGRA) gene.
- Confirming the morphological diagnosis with IHC with the CD117 and/or DOG-1.

3. Staging

TNM:

Very Low Risk		Low Risk	Intermediate Risk	High Risk
Modified NIH	Any	Any	Gastric: 5.1–10	Any location: tumor rupture;
Consensus	location: <2	location:	cm and 5	>5 cm and >5 mitotic index;
Classification	cm and 5	2.1–5 cm	mitotic index;	>10 cm; >10 mitotic index
(used in the	mitotic index	and 5	5 cm and 6	Non-gastric: 5 cm and >5
SSGXVIII/AIO		mitotic	10 mitotic index	mitotic index; 5.1–10 cm and 5
study)		index		mitotic index
				Tumor rupture

Other risk stratifications commonly used

Very Low Risk		Low Risk	Intermediate Risk	High Risk
NIH consensus criteria	<2 cm and <5 mitotic index	2–5 cm and <5 mitotic index	5–10 cm and <5 mitotic index; <5 cm and 6–10 mitotic index	>5 cm and >5 mitotic index; >10 cm; >10 mitotic index
AFIP Gastric: 2 classification cm and any system mitotic index; (criteria used in 5 cm and 5 NCCN and mitotic index ESMO Non-gastric: guidelines) 2 cm and 5 mitotic index		**Gastric: >5 cm and 10 cm, and 5 mitotic index Non- gastric: >2 cm and 5 cm, and 5 mitotic index**	**Gastric:>10 cm and □5 mitotic index; >2 cm and □5 cm, and >5 mitotic index Jejunal or ileal: >5 cm and □10 cm, and □5 mitotic index**	**Gastric: >5 cm and >5 mitotic index Duodenal or rectal: >5 cm Non-gastric:>10 cm; >5 mitotic index**
Modified NIH	Any	Any	Gastric: 5.1–10	Any location: tumor rupture; >5
Consensus	location: <2	location:	cm and 5 mitotic	cm and >5 mitotic index; >10 cm;
Classification (used in the SSGXVIII/AIO study)	cm and 5	2.1–5 cm	index; 5 cm and	>10 mitotic index
	mitotic index	and 5	6–10 mitotic	Non-gastric: 5 cm and >5
		mitotic index	index	mitotic index; 5.1–10 cm and 5
				mitotic index
				Tumor rupture

Prognostic factors:

- The most important independent factor for GIST recurrence is high mitotic rate.
- Other factors include large tumor size, site and tumor rupture.
- Gastric GIST has the lowest risk for recurrence.
- Extra-GI GIST has the highest recurrence rate (Omentum, mesentery and retroperitoneum).
- Mutation of PDGFRA has a favorable outcome.
- Alteration of KIT exon 9, deletion in KIT exon 11 is associated with more tumor recurrence

4. Management

Surgery is primary therapy for localized disease. If complete resection is possible, proceed to surgery first.

LOCALIZED:
NEOADJUVANTTHERAPY: for resectable disease with significant morbidity or unresectable. There are no phase III randomized trials being done to assess preop Imatinib, however, a few phase II nonrandomized trials have been done. Neoadjuvant Imatinib can be considered for patients with unresectable GIST or where surgery will cause significant morbidity, and downsizing the tumor bulk will help to preserve organ function. The usual duration is 9-12 months of preoperative Imatinib (until plateau in response has been reached). Close monitoring with imaging studies is required to ensure therapy response every 3 months and evaluation for surgical resection.

ADJUVANT THERAPY: Surgical resection followed by adjuvant Imatinib is indicated in patients with intermediate or high risk of recurrence (Category 1). Survival (OS) benefit ONLY in HIGH-Risk group based on Modified NIH criteria. Intermediate group will derive DFS benefit but not OS.

Prognosis: Depends on risk of recurrence. (Use Memorial Sloan Kettering Nomogram to predict recurrence risk and prognosis)
Recommendations: Adjuvant Imatinib in resected GIST for 3 years is recommended.

5. Follow up

From the randomized clinical trials for adjuvant therapy: physical exam and blood work every 1-3 months, while on treatment CT 3-6 months, then every 6 months to complete 5 years then annually.

METASTATIC
Bottom Line General Approach:

- If the primary and metastatic site can be respected, combination of Imatinib and surgical resection is recommended.
- Palliative surgery and/ or XRT can be considered in symptomatic patients (e.g GI bleeding)
- Palliative Imatinib 400 mg PO OD as 1st line (Category 1), dose escalation when progressed to 800mg OD. Especially those with exon 9 mutation
  - 2nd line *Sunitinib** (Category 1)
  - 3rd line *Regorafenib** (Category 1)
- **Prognosis:** (median survival with Imatinib is 57 months and without treatment is 18)

** Not on WHO EML*

E. Colorectal Cancer

1. Introduction

Risk Factors:

- Environmental/Chemical/Infections: abdominal radiation, renal transplantation,
- Race – African at higher risk,
- Gender – men have greater mortality from colorectal cancer,
- Obesity, red and processed meat, tobacco, alcohol, use of androgen deprivation therapy, diabetes mellitus and insulin resistance
- Genetic: Familial adenomatous polyposis (FAP), Lynch syndrome (Hereditary non-polyposis colorectal cancer (HNPCC), MUTYH-associated polyposis (MAP), Peutz-Jeghers, Juvenile polyposis, personal or family history of sporadic colorectal cancers or adenomatous polyps, inflammatory bowel disease (ulcerative colitis and Crohn's disease) acromegaly

Protective factors:

- Exercise, high-fiber diet, ASA/NSAIDs/COX-2 inhibitors, and statins: evidence is mixed

Prevention & Screening

- **Prevention:** There is no established chemoprevention method. Although NSAIDs have been shown to have modest risk reduction in average- and high-risk individuals, clear recommendations for chemoprevention

- **Screening:**
  - **Average risk individuals:**
    - Age > 50 with no other additional personal or familial risk factors
    - FOBT or FIT testing every 1 to 2 years for asymptomatic individuals between age 50 to 75 years of age.
    - Positive FOBT, FIT or flexible sigmoidoscopy tests should be followed by endoscopy evaluation of the entire colon.
    - Colonoscopy every 10 years

  - **Inflammatory Bowel Disease:**
    - Guidelines differ slightly but generally recommend annual surveillance colonoscopy beginning after 8 to 10 years of IBD diagnosis
    - Colonoscopy should be repeated every 1 to 3 years

  - **Familial history:**
    - First-degree relative diagnosed age < 60 or >/= 2 first-degree relatives:
    - Screen with colonoscopy at age 40 or 10 years before the youngest relative's diagnosis.
    - Repeat colonoscopy every 5 years
    - First-degree relative diagnosed age > 60:
    - Same screening guidelines as for average risk individuals

- **Familial adenomatous polyposis:**
  - Annual flexible sigmoidoscopy or colonoscopy starting at age 10 to 12
  - Lynch syndrome (germline genetic mutations in MLH-1, MSH-2, MSH-6, PMS-1 and/or PMS-2: Screen with colonoscopy every 1 to 2 years beginning at age 20 to 25 years, or 2 to 5 years prior to the earliest age of colorectal cancer in the family, whichever comes first.

Signs and Symptoms

- **Common Symptoms:** hematochezia, melena, abdominal pain, iron deficiency anemia, change in bowel habits, occasionally signs of obstruction, rectal cancer can cause tenesmus, rectal pain, and diminished caliber of stools
- **Common Signs:** rectal bleeding, rectal mass on DRE
- **Common Presentations:** as above. Uncommonly, Streptococcus bovis or Clostridium septicum bacteremia are associated with colon cancer in 10 to 25% of patients.

2. Workup

Laboratory: preoperative CEA
Diagnostic Imaging: preoperative CT chest, abdomen and pelvis
Diagnostic Procedures: Complete colonoscopy for assessment of the entire bowel and to obtain tissue diagnosis, K-ras/N-ras/B-raf testing of tumors in the metastatic setting, Mismatch repair gene testing of tumors in localized disease (especially in stage II colon cancer) when affordable.

Pathology:

- **Common Histology:** Carcinomas are the most common: adenocarcinoma (>90%), adenosquamous carcinoma, spindle cell carcinomas, squamous cell (epidermoid) carcinoma, undifferentiated carcinoma.
- Other histologic types (neuroendocrine neoplasms, hamartomas, mesenchymal tumors, lymphomas) are rare.
- **Common Metastatic Sites:** regional lymph nodes, lungs, liver, and peritoneum. Colon cancer typically spreads to liver first because the venous drainage of the intestinal system is via the portal system. Rectal cancer may spread to lungs first because the inferior rectal vein drains into the inferior vena cava rather than to the portal system. Therefore, colon cancer drains into the portal system while rectal cancer drains systemically.
- **Relevant Molecular Biology:** K-ras/N-ras/B-raf testing of tumors, Mismatch repair genes testing of tumors, 18q deletions

3. Staging

TNM Staging (8th edition)

T Staging

T Category	T Criteria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into pericolorectal tissues
T4	Tumor penetrates to the surface of visceral peritoneum/directly invades other organs or structures

N Stage

N Category	N Criteria
N1	Metastasis in 1-3 regional lymph nodes or any number of tumor deposits are present and all identifiable lymph node are negative
N1a	One regional LN is positive
N1b	Two or three regional LNs are positive
N1c	No regional LNs are positive but there are tumor deposits in the : Subserosa Mesentary Nonperitonealized pericolic or perirectal/mesorectal tissues
N2	Metastasis in ≥4 regional lymph nodes
N2a	Four to six regional LNs are positive
N2b	Seven or more regional LNs are positive

M Stage

M Category	M Criteria
M1a/b	Metastasis confined to one organ or site/metastasis in more than one organ or site or the peritoneum
M1a	Metastasis confined to one organ or site
M1b	Metastasis in two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastasis.

4. Management

COLON CANCER - LOCALIZED / ADJUVANT / LOCALLY ADVANCED
Bottom Line General Approach:

- **Stage I:** segmental colectomy, observation alone no role for adjuvant therapy.

- **Stage IIA (T3N0):** segmental colectomy, consider 6 months adjuvant fluoro-pyrimidine based regimen in patients with high-risk (at least one of the high-risk features) T3N0 disease; 6 months of capecitabine or 5FU/Leucovorin, OR 3 months of CAPOX or FOLFOX regimens. For those with no high risk features consider observation or consider 6 months of capecitabine or 5FU/Leucovorin.
- Adjuvant chemotherapy in low-risk patients with microsatellite instability (MSI-high) is not recommended.

- **Stage IIB/C (T4N0):** segmental colectomy, consider 6 months of capecitabine or 5FU/ Leucovorin, OR 3 months of CAPOX or FOLFOX regimens; OR observation.

- High-risk features include: inadequate lymph node sampling (<12 nodes), T4 disease, clinical perforation, lymphovascular and/or perineural invasion, complete obstruction or poor differentiation.
- Patients with high levels of microsatellite instability have a better prognosis.

- **Stage III low risk:** T 1-3, N1: Segmental colectomy followed recommend CAPOX for 3 months or FOLFOX for 3-6 months. (preferred). Other options include capecitabine or 5FU/ Leucovorin for 6 months.

- **Stage III high risk:** T4, N1-2, any T, N2: Segmental colectomy followed CAPOX 3-6 months or FOLFOX 6 months.

Stage III colon cancer in patients > 70 years old: There is no clear benefit of the addition of oxaliplatin to adjuvant chemotherapy in patients > 70 years old. However, it is reasonable to consider single agent fluropyrimidines or combination therapies (FOLFOX/CAPOX) in select patients in this population.

There is usually no role for adjuvant radiotherapy.

Prognosis(SEER):
- 5 year survival with surgery alone
- Stage I – 85%
- Stage II T4aN0 – 80%
- Stage II T4bN0 (directly invades into or is adherent to other organs or structures) – 60%
- Node-positive (Stage III) – 30-50%

The prognosis of patients with localized colorectal cancer with defective mismatch repair (MSI-H/dMMR, whether secondary to HNPCC or sporadic MMR mutations) is better than that for patients with proficient mismatch repair (MSS/pMMR) localized colorectal cancer.

RECTAL CANCER -LOCALIZED / ADJUVANT / LOCALLY ADVANCED
Bottom Line General Approach:

Stage I: transabdominal resection (anterior resection –AR, low anterior resection –LAR or abdominoperineal resection –APR), and observation alone –no role for adjuvant therapy.
Stage II or III:
- For **non-fixed** tumors in the upper two-thirds of the rectum: neoadjuvant short-course radiation therapy (2500 cGy in 5 fractions)
- Followed by LAR or APR within 4 to 4 weeks of first radiation
- 6 months of adjuvant chemotherapy with 5FU/leucovorin or capecitabine (for stage II) or FOLFOX/CAPOX (for stage III disease or consider for high risk stage II).
- Adjuvant chemotherapy usually starts within 4-8 weeks of surgical resection.

- Long-course chemoradiotherapy may also be used for non-fixed stage III disease (see below).
- For **fixed** rectal tumors approaching the mesorectal margin and for tumors in the distal one-third of the rectum: neoadjuvant long-course radiation therapy (4500 cGy in 25 fractions with a possible boost of 540 cGy in 3 fractions) with concurrent chemotherapy (Capecitabine 825 mg twice daily on days of RT)
- Followed by LAR or APR within 5 to 12 weeks after completion of neoadjuvant therapy 4 months of adjuvant chemotherapy with 5FU/leucovorin or capecitabine (for stage II) or FOLFOX/CAPOX (for stage III disease or consider for high risk stage II).
- Adjuvant chemotherapy usually starts within 4-8 weeks of surgical resection.
- If a patient with rectal cancer undergoes upfront resection, referral to a comprehensive cancer centre is recommended for consideration of post-operative adjuvant chemoradiotherapy.
- Total neoadjuvant chemotherapy (TNT) with pre-operative short-course radiotherapy or long-course chemoradiotherapy PLUS 12-16 weeks of CAPOX or FOLFOX of chemotherapy (delivered before or after radiotherapy) may be considered. If TNT is given, no further adjuvant chemotherapy is recommended.

RECURRENT / METASTATIC COLORECTAL CANCER
Bottom Line General Approach:

Potentially resectable patients:
- In select patients, segmental resection of obstructing or bleeding colorectal primary lesions may be considered.
- Palliative radiotherapy may be considered.
- Liver-only metastasis or solitary/lobe-confined pulmonary mets may be considered for resection.
- Potentially resectable patients may be treated with neoadjuvant chemotherapy until optimal resectability. The criteria for liver resection are: - at least 2 adjacent lobes (caudate lobe excluded) free of tumor, biliary drainage intact, arterial inflow, non-thrombosed portal vein, 20% or more liver functional reserve.

Unresectable patients:
- Upon diagnosis of metastatic disease, patients' tumors should be tested for activating mutations in RAS (KRAS and NRAS), when available. Patients with known RAS mutations should NOT be treated with the EGFR inhibitors like Cetuximab; a combination of a VEGF inhibitor (Bevacizumab*) with standard chemotherapy (FOLFOX/CAPOX or FOLFIRI) may be used for these patients.
- Patients with RAS wild-type left-sided colorectal cancer, they should be treated with chemotherapy (FOLFOX/CAPOX or FOLFIRI) in combination with an EGFR inhibitor (cetuximab*) in the first line metastatic setting.
- In patients with RAS wild-type right-sided colorectal cancer, combination of a VEGF inhibitor (Bevacizumab*) with standard chemotherapy remains the standard first-line therapy for these patients. EGFR inhibitors may be added to standard chemotherapy in the second line.

- Other standard first-line palliative chemotherapy options include:
  - Capecitabine single-agent
  - 5-FU/Leucovorin
  - CAPOX
  - FOLFOX
  - FOLFIRI
  - FOLFOXIRI (in younger patient with excellent performance status, where rapid tumor response is desired)
  - *Cetuxumab** alone in RAS wild-type
  - *Cetuxumab** plus Irinotecan in RAS wild-type
  - *Cetuxumab** plus any chemotherapy combination above in RAS wild-type
  - *Bevacizumab** plus any chemotherapy combination

** Not on WHO EML*

Sequential vs Combination Chemotherapy Strategies:

- Sequential chemotherapy consists of a fluoropyrimidine monotherapy followed by either: Irinotecan monotherapy OR Combination chemotherapy which consists of a doublet of a fluoropyrimidine with irinotecan or oxaliplatin
- There is a statistically significant difference in overall survival in favor of combination chemotherapy over planned sequential chemotherapy. However, the magnitude of this difference may not be clinically significant. Additionally, sequential chemotherapy can minimize toxicities.
- Therefore, sequential chemotherapy and upfront combination chemotherapy are both acceptable standards of care and the choice should be made on a case-by-case basis.

Intermittent vs Continuous Chemotherapy Strategies

- Intermittent strategies of delivering first-line chemotherapy to patients with unresectable mCRC do not result in a clinically significant reduction in overall survival and improve or maintain quality of life in comparison to continuous chemotherapy. Therefore, consideration of intermittent chemotherapy strategies should be part of an informed discussion with patients.

Prognosis:

- Data from the Surveillance, Epidemiology, and End Results (SEER) database report 5-year survivals of: Stage IV – 8 percent

5. Follow Up

Stage I with full surgical staging:

- Colonoscopy at 1 year after surgery
- If advanced adenoma , repeat in 1 year.
- If no advanced adenoma , repeat in 3 years then every 5 years.

Stage II-IV:

- H & P every 3-6 month for 2 years, then every 6 months for a total of 5 years.
- CEA every 3-6 months for 2 years , then every 6 months for a total of 5 years ; if elevated then CT scan
- Chest/abdomen/pelvic CT
- Stage II, III: Every 12 months for a total of 5 years.
- Stage IV: Every 6 month x 2 years , then every 6-12 month for a total of 5 years.
  - Colonoscopy in 1 year after surgery except if no preoperative colonoscopy due to obstructing lesion , colonoscopy in 3-6 month
  - If advanced adenoma, repeat in 1 year.
  - If no advanced adenoma, repeat in 3 years then every 5 years.
  - PET/CT scan is not recommended

F. Anal Cancer

1. Introduction

Risk Factors:

- Environmental/Chemical/Infections: HPV (Serotypes 16 and 18) – mainly HPV 16
- History of anal warts
- History of cervical, vulvar or vaginal cancer
- History of multiple sexual partners, anal-receptive intercourse and sexually transmitted infections
- Immunosuppression (HIV)
- Cigarette smoking
- Chronic inflammation/fistulas in the context of inflammatory bowel disease
- Genetic: None known

Prevention:

- **Interventions to reduce HPV risk**
  - Vaccination against HPV – the quadrivalent HPV vaccine (HPV-6, 11, 16 and 18) reduced the rate of anal intraepithelial neoplasia in males (Palefsky et al.) HPV vaccine against anal HPV infection and anal intraepithelial neoplasia.
  - Safe sex interventions
  - Male circumcision
  - Smoking Cessation

Screening:

- No specific guidelines
- Strongest recommendation for screening for men with HIV who have sex with men. Also recommend for all men and women with HIV, women with genital dysplasia or cancers, anyone with perianal high-grade lesions, and recipients of solid organ transplants.

Options for screening include:

- Anal Papanicolaou test for cytology and/or HPV testing
- Digital anal exam
- High resolution anoscopy with staining with vinegar or Lugol's iodine

Signs & Symptoms

- **Common Symptoms:**
  - Anal itching, discharge, bleeding
  - Pain or pressure in the anal area that is not relieved by a bowel movement
  - Change in bowel habits: changes to the caliber, constipation, diarrhea or alternating between constipation and diarrhea
- **Common Signs:**
  - Lump or swelling in the anal area
  - Enlarged lymph nodes in the groin or anal area

2. Workup

- Include digital rectal exam and palpation of inguinal lymph nodes
- Pelvic exam for all women with cervical Pap smear
- Routine blood work, HIV serology, hepatitis screen
- Pelvic MRI
- CT chest, abdomen and pelvis
- Biopsy
- Fertility risk discussion and counseling should be undertaken in appropriate patients
- Most commonly squamous cell carcinoma and similar variants (cloacogenic, basaloid, transitional). Anal squamous cell carcinoma are further sub-classified by locations as anal canal or peri-anal cancers. Treatment recommendations below only apply to anal squamous cell carcinoma.
- Adenocarcinoma is managed like rectal cancer. Anal melanoma also accounts for a small percentage of anal cancers; please refer to melanoma guidelines for treatment recommendations.
- Note that lymphatic drainage goes to the peri-rectal, inguinal, and internal iliac nodes

3. Staging

TNM Staging - AJCC 8th Edition

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 LN 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
pM1	Distant metastasis, microscopically confirmed

4. Management

LOCALIZED AND LOCALLY ADVANCED (Squamous cell carcinoma)

- Consider surgery alone with a wide local excision for stage 0 (carcinoma in situ) and stage I (T1N0) for moderate to well-differentiated peri-anal cancers:
- Wide local excision should only be considered for stage I if negative margins can be achieved and continence can be preserved.
- Recommend primary chemoradiotherapy (as described for stage 1 disease) if sphincter preservation is not possible with wide local excision.
- Stage II-III should be treated with concurrent chemoradiation: RT plus Mitomycin*/5FU (preferred) or Mitomycin* /Capecitabine (preferred) or 5FU/Cisplatin. Allows for sphincter preservation, but no overall survival benefit.

45-54 Gy/25-30 fractions to the perineum and regional lymph nodes plus
Continuous infusion of 5-FU 4000 mg/m2 on D 1-4 and 29-32.
*Mitomycin** 10mg/m2 IV on D1 and D 29
Or
5 FU + Cisplatin +RT with Cisplatin given as 75mg/m2 d1 and 29 if *mitomycin** contraindicated
Or
Capecitabine + *Mitomycin** + RT

Capecitabine 825mg/m2 PO BID Monday to Friday on each day that RT is given, throughout the duration of RT (typically 28 treatment days)
Consider an RT boost for stage IIIB disease
Consider abdominoperineal resection for salvage treatment of residual disease
** Not on WHO EML*

Special considerations

HIV-infected and immunosuppressed patients should be managed the same as non-immunosuppressed patients if CD4 count > 200

RECURRENT / METASTATIC

Bottom Line General Approach

- Consider APR for locally recurrent disease
- Currently no randomized data to support decision
- Consider resection for oligometastatic disease
- Carboplatin AUC 5 IV day 1 + Paclitaxel 175mg/m2 day 1 repeat every 21 days is the preferred regimen
- Cisplatin 75mg/m2 and 5-FU 4000mg/m2 over 4 days every 28 days
- FOLFOX every 14 days
- Palliative radiation therapy may be considered in conjunction with palliative chemotherapy.

5. Follow-up

- DRE every 3-6 months for 5 years
- Inguinal node palpation every 3-6 moths for 5 years
- Anoscopy every 6-12 month x 3 years
- Chest/abdomen/pelvic CT with contrast annually for 3 years.

Prognosis:

- 5-year OS
- Localized = 80%
- Regional = 50%
- Poor prognostic features: T4, N2-3

H. Neuro-endocrine Tumors

1. Introduction

Neuroendocrine (NE) cells are located in almost every body tissue. NE cells are part of the Diffuse Endocrine System (DES) that can release hormones in response to a variety of stimuli to regulate normal physiological functions. Neuroendocrine Tumors (NETs) arise from NE cells. NETs are most commonly found in the gastrointestinal tract and pancreas. The term "carcinoid syndrome" refers to the collection of symptoms that are precipitated by secretory NETs. NETs can display variable biological behaviors, ranging from benign to very aggressive tumors.

Risk Factors:

- Environmental/Chemical/Infections: Whether there is an association between bronchial NETs and smoking is unclear. Causality has not been proven.
- Genetic: most are sporadic but bronchial NETs can rarely occur in the setting of multiple endocrine neoplasia type 1 (MEN1). Type 2 gastric NETs can occur in the context of MEN1. Most pancreatic NETs are sporadic but can be associated with MEN1, von Hippel Lindau, neurofibromatosis type 1, and tuberous sclerosis.

Prevention & Screening

- Prevention: nothing described.
- Screening: nothing described.

Symptoms & Signs

Common Symptoms/Signs/Presentations: Organized by site of origin of NET.

Stomach:

Type 1 – 70-80% of all gastric NETs. Arise from enterochromaffin-like cells (ECL cells). Associated with chronic atrophic gastritis and pernicious anemia. Patients may be asymptomatic or may present with abdominal pain, anemia, or reflux symptoms.

Type 2 – 5% of all gastric NETs. Occur in association with gastrinomas (Zollinger-Ellison syndrome), often in the setting of MEN1. Patients may present with hypergastrinemia symptoms of peptic ulcer disease.

Type 3 – 20% of all gastric NETs and are usually the most aggressive.

Local or hepatic mets is usually found on presentation. Fasting serum gastrin levels are usually normal in these patients.

Lung

Patients with bronchial NETs can present with a carcinoid syndrome (flushes, sweats, diarrhea) that is severe and prolonged. This usually occurs in patients that have liver mets as well. Flushes may be associated with disorientation, anxiety and tremor. The majority of tumours arise in the proximal airways and symptoms occur due to an obstructing mass causing bleeding or respiratory symptoms.

Beware of inducing a carcinoid crisis in attempts to biopsy. The patient may require pretreatment with a somatostatin analogue prior to biopsy if there is a risk of inducing a carcinoid crisis.

Bronchial NETs may be associated with a hilar or a perihilar mass on CXR. The minority of cases can present as a peripheral solitary pulmonary nodule. Some patients may present with a Cushing's syndrome.

Pancreas

50-75% of pancreatic NETs are non functioning while the rest are funtioning and may produce insulin, gastrin, glucagon, somatostatin or VIP. Gastrinomas and insulinomas are the two most common pancreatic NETs. See table below for features of selected syndromes.

Disease	Hormone produced	Site (most common)	Clinical features	Investigations (blood)
Carcinoid syndrome	Serotonin, others (histamine, substance P)	Small bowel	Flushing, diarrhoea, abdominal pain, carcinoid heart disease (tricuspid regurgitation, right heart failure)	CgA, urinary 5-HIAA
Insulinoma	Insulin	Pancreas	Whipple's triad: • symptoms of hypoglycaemia (eg, blurred vision, sweating, tremor, weakness, confusion, coma) • glucose <2.2mmol/L • relief of symptoms with administration of glucose	Fasting or random glucose 72-hour fast test (requires hospitalisation) Insulin, C-peptide Drug screen (to exclude factitious hypoglycaemia)
Gastrinoma (Zollinger–Ellison syndrome)	Gastrin	Duodenum Pancreas	Peptic ulcer, gastric reflux, diarrhoea	Fasting gastrin Gastroscopy/24h pH-metry Secretin test*
Glucagonoma	Glucagon	Pancreas	Rash (necrolytic migratory erythema), impaired glucose intolerance or diabetes	Glucagon
VIP-oma	Vasoactive intestinal peptide (VIP)	Pancreas	Profuse watery diarrhoea and resultant dehydration, hypokalaemia and achlorhydria (pancreatic cholera syndrome)	VIP Hypokalaemia
Somatostatinoma	Somatostatin	Pancreas	Triad of diabetes mellitus, steatorrhoea and gall stones, also associated with hypochlorhydria	Somatostatin

CgA = chromogranin A
5-HIAA = 5 hydroxyindole acetic acid
VIP = vasoactive intestinal peptide
*Secretin test: administration of exogenous secretin; test is positive if serum gastrin levels increase

Small bowel – many patients are asymptomatic at presentation and the small bowel NET is found incidentally. Among symptomatic patients, abdominal pain is the most common presenting symptom. Some patients may present with a bowel obstruction, intussusception, or bowel ischemia. Liver mets is very common. Can present with a carcinoid syndrome (see table 1).

Appendix – Most patients are asymptomatic. When the tumour occurs at the base of the appendix, they may cause bowel obstruction leading to appendicitis.

NETs arising from the colon, rectum and GU tracts are usually nonsecretory and NOT associated with a carcinoid syndrome, even when they metastasize.
Colon – usually asymptomatic unless the tumours are large. If there are symptoms, they are similar to colorectal adenocarcinoma symptoms of changes in bowel habits, obstruction or bleeding. Patients may also present with abdominal pain, anorexia or weight loss. The majority of colonic NETs are located in the right colon, particularly in the cecum.
Rectum – vast majority are asymptomatic and found incidentally on rectal exam or endoscopy.

GU – hindgut NETs arising from the renal or testicular systems have been described in case reports. These lesions typically present as an abdominal or testicular mass. Some can occasionally present with a carcinoid syndrome.

Ovary – Primary NETs are usually unilateral and often arise within a cystic teratoma or dermoid tumour. In contrast, metastatic ovarian NETs are usually bilateral, originate in the small intestine and can present with peritoneal carcinomatosis. The ovary drains directly into the systemic circulation so ovarian carcinoids can produce carcinoid syndrome without hepatic mets. Some ovarian carcinoids can produce a hormone that decreases gut motility and causes severe constipation.

2. Workup

Laboratory:
- Serum chromogranin A: useful marker for both functioning and nonfunctioning NETs
- 24hr urine 5-HIAA: useful for the diagnosis and follow-up of NETs, especially mid-gut NETs. Measure 24hr urine 5-HIAA even if not presenting with carcinoid syndrome symptoms. If elevated, patients need to be on surveillance for carcinoid heart disease.
- Other: specific to the secreted hormone – ex. Insulin for insulinoma, gastrin for gastrinoma, etc.
- Parietal cell antibodies for stomach NETs
- MEN1 is excluded with normal serum calcium, PTH and possibly pituitary hormones
- Calcitonin, somatostatin
- Serum acid phosphatase and HCG levels may be elevated in patients with hindgut NETs.

Pathology:
Well vs poorly differentiated appearance
Expression of NE markers such as synaptophysin and chromogranin on immunohistochemistry (IHC)
- Ki67 (+/- mitotic rate) to determine if G1, G2 or G3
- IHC staining for specific hormones as dictated by clinical presentation

Diagnostic Imaging:

- Anatomic imaging with CT or MRI.
- Octreotide scan (using 111Indium-penetreotide scintigraphy): useful for both functioning and nonfunctioning NETs. Octreotide scan avidity can predict response to octreotide therapy.
- MIBG (metaiodobenzylguanidine) scintigraphy: some NETs will take up MIBG and not octreotide.
- Consider Echocardiogram if concerned about carcinoid heart syndrome or elevated 24hr urine 5- HIAA.

- **Diagnostic Procedures:** may need to pursue endoscopy to obtain a tissue diagnosis. Beware of inducing a carcinoid crisis in attempts to biopsy suspected bronchial NETs. If there is a risk of inducing a carcinoid crisis, pretreat the patient with a somatostatin analogue.

- **Common Histology:** WHO Classification 2010 is used for digestive tract NETs; the 2004 is used for bronchial NETs.
  - **Digestive tract NETs:**
    - Neuroendocrine tumor grade 1 (G1) (carcinoid)
    - Neuroendocrine tumor grade 2 (G2)
    - Neuroendocrine carcinoma (large cell or small cell type)
    - Mixed adenoneuroendocrine carcinoma (MANEC)
    - Hyperplastic and preneoplastic lesions
  - **Bronchial NETs:**
    - Typical carcinoid (1-2%): < 2 mitotic figures per 10 HPF; no necrosis
    - Atypical carcinoid (0.1-0.2%): 2-10 mf/10HPF
    - Large cell neuroendocrine tumour (3%)
    - Small cell neuroendocrine tumour (20%) -> aka poorly differentiated
    - Common Metastatic Sites: liver, omentum, ovaries
    - Relevant Molecular Biology: none known.

3. Staging

TNM: There is a separate TNM staging system for NETs of the appendix, pancreas, stomach, small bowel/ampulla of Vater, and colorectal primary sites[3].
Other: European Neuroendocrine Tumour Society/World Health Organization Nomenclature and classification for NETs[2]

Well-differentiated:
Low grade (G1) – mitotic count <2 per 10 high power field (HPF), Ki-67 <3%
Intermediate grade (G2) – mitotic count 2-20 per HPF, Ki-67 3-20%

Poorly differentiated:
High grade (G3) – mitotic count >20 per 10 HPF, Ki-67 > 20%

4. Management

Treatment of NETs has be divided into:

- GastroEnteroPancreatic NETs (GEP-NETs) - The term "GastroEnteroPancreatic" (GEP- NETs) is now used to encompass the broad range of NETs arising from the GI tract or pancreas. GEP-NETs are subdivided into:
  - Pancreatic NETs
  - Midgut GEP-NETs (ie. Ileo-jejunal and appendix)
  - Other GEP-NETs (ie. Stomach and duodenal)
  - Colorectal NETs – arising from the colon or rectum.
  - Bronchial NETs – arising from the bronchopulmonary system.

GEP-NETs: PANCREATIC NETs

Bottom Line General Approach:

- **Role of surgery/local therapies:**

For pancreatic NETs (pNETs), surgery can be curative. Cytoreductive surgery can be considered in the presence of liver mets if the majority of the tumour can be safely removed. Consider cytoreductive surgery in the presence of liver mets to delay disease progression. Patients with extensive liver mets with functional pNET can also be considered for liver-directed therapies such as radiofrequency ablation, embolization, chemoembolization and radiolabeled microspheres.
Surgery can also be considered in cases of advanced symptomatology due to hormone excess state.

Chemotherapy and Targeted Agents
Well-differentiated pNETs:

- **First-line therapy**: Capecitabine and Temozolomide is effective in metastatic pNETs.
- **Second-line therapy:** Patients may be treated with targeted agents sunitinib or everolimus. Sunitinib and everolimus are generally considered after the failure of systemic chemotherapy. However, the choice and sequence of systemic therapy is determined by disease-related factors, patient preferences, potential therapy-related adverse effects and financial capacity.

Poorly-differentiated pNETs:

- Patients with poorly-differentiated pNETs should be treated with cisplatin and etoposide chemotherapy.
- The majority of patients present with advanced disease but some can present with localized disease amenable to surgical resection.
- Patients should be referred to medical oncology after surgery for consideration of adjuvant chemotherapy.

Prognosis: Well-differentiated pNETs have an overall survival rate of 80% at 5 years. Median survival for advanced well differentiated PNETs is 60 months. For poorly differentiated pNETs, median survival statistics are similar to what is quoted for other small cell cancers, with ~1 month without treatment, but 8- 10 months with chemotherapy.

GEP-NETs: MIDGUT NETs
Midgut NETs are those arising from the midgut (lower jejunum, ileum and appendix).

Bottom Line General Approach:
Role of surgery/local therapies:

- For midgut NETs confined to the bowel, surgery can be curative. Cytoreductive surgery can be considered in the presence of liver mets if the majority of the tumour can be safely removed. Consider removal of the primary tumour even in the presence of mets to prevent intestinal obstruction or ischemic complications.

- There is no indication for adjuvant or neoadjuvant chemotherapy for jejuno-ileal NETs.

- For appendiceal NETs, appendectomy can be curative if the tumour is located at the tip of the appendix, is well-differentiated and is <2cm. A right hemicolectomy is indicated if: tumour is 1- 2cm with positive or unclear margins or with deep meso-appendiceal involvement, vascular or perineural invasion is present, location of the tumour at the base of the appendix, histology is consistent with goblet cell carcinoid or mixed endocrine-exocrine tumour. Tumours >2cm should be treated with right hemicolectomy.

- Patients with goblet-cell carcinomas of the appendix should be referred after surgical resection for consideration of adjuvant chemotherapy with FOLFOX (similar to adjuvant treatment of colonic adenocarcinomas).

Chemotherapy and Targeted Agents

- **Well-differentiated midgut NETs:**

Chemotherapy is generally not used in well-differentiated midgut NETs as the response rates are < 10%. Agents that can be considered are: single-agent doxorubicin or 5-FU, dacarbazine.

- **Poorly-differentiated midgut NETs:**

For poorly-differentiated NETs, cisplatin plus etoposide chemotherapy may be effective.

- **Carcinoid heart disease**

Carcinoid heart disease should be followed with annual echocardiogram +/- MRI. Referral to a cardiac surgeon is encouraged in patients with tricuspid and/or pulmonary valvular heart disease. The role of octreotide in suppressing 5-HIAA levels to protect against heart damage is controversial.

Prognosis:

- The prognosis of patients with metastatic distal small bowel NETs with liver mets is 10yr OS of 15-25%.
- Most patients with appendiceal NETs present with localized disease and have 5yr OS of 85-95%.

OTHER GEP-NETs

Stomach NETs

Bottom Line General Approach:

Localized/Adjuvant/Locally Advanced Disease:

- **For type 1 and type 2:**

<1 cm: surveillance with OGD yearly

Multiple or >1 cm: endoscopic resection, then yearly OGD

- **Locally advanced or recurrent: resection or antrectomy**
- **For type 3 and poorly differentiated tumours**, partial or total gastrectomy with lymph node dissection. There is no standard for adjuvant or systemic treatment and depends on the clinical centre.
- **Recurrent disease despite local resection:** gastrectomy and LN dissection Somatostatin analogues can control disease for type 1 and type 2.
- **Metastatic Disease:**
  - Somatostatin analogues can control the secretory symptoms of the tumour
  - Well-differentiated stomach NETs: 5-FU chemotherapy is recommended.
  - Poorly-differentiated stomach NETs: platinum and etoposide.
- **Prognosis:** Type 1: recurrence-free survival of 24 months and 100% survival6. Types 2 and 3 are more likely to metastasize and so the prognosis is poorer, exact prognosis not well described.

Duodenal NETs

Bottom Line General Approach:

- Surgical removal of the tumour or pancreaticoduodenal resection/Whipple's procedure can be curative for localized disease.
- See "Metastatic Disease for stomach NETs" above as systemic treatment is similar for duodenal NETs.
- For gastrin-producing tumours, proton pump inhibitors should be used to control acid-related symptoms.
- **Prognosis:** The 5-year survival of duodenal NETs is felt to be similar to all GI foregut NETs which is 80–95% for local disease, 65–75% with regional involvement only, and 20–40% for the 5–10% of patients with liver or distant disease.

COLORECTAL NETs

These are NETs involving the colon and/or rectum.

Bottom Line General Approach:

Localized/Adjuvant/Locally Advanced Disease:

- Colonic NETs > 2cm in size, tumours with muscularis invasion, and G3 tumours should be treated according to colon adenocarcinoma guidelines (ie. Surgical resection with hemicolectomy).
- Rectal NETs > 2cm in size, T3 or T4 stage, with G3 grading, or lymph node-positive rectal tumours should be treated according to rectal adenocarcinoma guidelines (ie. Surgical resection with total mesorectal excision or abdominoperineal resection depending on distance from anal verge).

Adjuvant chemotherapy after surgery can be considered for G3/poorly-differentiated tumours with incomplete resection, although the evidence is lacking.

- **Metastatic Disease:**

Carcinoid syndrome is uncommon in colorectal NETs and should be treated with somatostatin analogues if occurring. Evidence is lacking for the use of somatostatin analogues as anti-tumour agents. Palliative surgery may be considered for debulking.

- **Well-differentiated colorectal NETs:**

Systemic chemotherapy is rarely indicated for G1 or G2 colorectal NETs. In the setting of progressive disease, chemotherapy may be considered. There may also be a role for temozolomide-based chemotherapy.

- **Poorly-differentiated colorectal NETs:** platinum and etoposide.

- **Prognosis:** Typically, years. Exact prognosis not well described.

BRONCHIAL NETs

Bottom Line General Approach:

- **Localized/Adjuvant/Locally Advanced Disease:**

Complete surgical resection with parenchymal sparing is recommended. Wide resection margins are not required. For elderly patients or patients who are poor surgical candidates, a bronchoscopic resection can be considered. Systematic lymph node dissection is recommended in lymph node positive disease. There is currently no role for adjuvant/neoadjuvant systemic treatment.

- **Metastatic Disease:**

Carcinoid syndrome can be treated with somatostatin analogues if occurring.

- **Well-differentiated colorectal NETs:**

Chemotherapy with capecitabine and temozolomide

- **Poorly-differentiated colorectal NETs:** platinum and etoposide.

- **Prognosis:** Typical Carcinoid: 94% 5yr OS. Atypical Carcinoid: 72% 5yr OS.

I. Hepato-Biliary Cancers

I.1. Hepato-Cellular Carcinoma

1. Introduction

The Hepato-Cellular Carcinoma (HCC) is the main liver malignancy, ranking among the ten most common causes of cancers in men and women, and representing a 1/3 of the cancer fatality cases overall.

Multiple risk factors have been established, with viral hepatitis (Hepatitis B and C), and chronic alcoholic liver disease among others. In African countries, aflatoxins have a leading position as causes of HCC.

The clinical presentation can vary from asymptomatic patients, to patients with – pain, jaundice, lethargy, ascites, hepatic encephalopathy and hematemesis from variceal bleeding.

Screening exists, and consists in focusing on patients at risk for HCC with – cirrhosis, hepatitis B/C, Alcohol history, Stage IV primary biliary cholangitis, history of exposure to Aflatoxin. For such patients, initial screening consists in abdominal ultrasound (with focus to the liver) +/- AFP.

If AFP is positive or ultrasound finds a nodule ≥10mm – additional workup is mandated

If AFP is negative and ultrasound finds a nodule <10mm – repeat ultrasound and AFP in 3-6 months

If AFP and ultrasound are negative – repeat both Ultrasound and AFP in 6 months

2. Workup

- History and Physical Examination
- FBC, LFT, RFTs, AFP, Hepatitis panel, PT or INR
- CT scan – abdominal triphasic CT scan. If detected, suspicious mass (reference to LI-RAD criteria) and Positive AFP – confirmed HCC; if not definitely HCC and positive AFP – biopsy is needed. Otherwise – return to screening
- Systemic scan – to rule out metastatic disease

3. Staging

T Staging

T Category	T Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2cm, or >2cm without vascular invasion
T1a	Solitary tumor ≤2cm
T1b	Solitary tumor >2cm without vascular invasion
T2	Solitary tumor >2cm with vascular invasion, or multiple tumors, none >5cm
T3	Multiple tumors, at least one of which is >5cm
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 gall-bladder or with perforation of visceral peritoneum

N Staging

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Regional lymph node metastasis

M Staging

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

Child-Pugh Score

Chemical and Biochemical Parameters	Scores (Points) for increasing Abnormality 1	2	3
Encephalopathy (grade)	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time Seconds over control INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Bilirubin (mg/dL) For primary biliary cirrhosis	<2 <4	2-3 4-10	>3 >10

Class A = 5-6 points; Class B = 7-9 points; Class C = 10-15 points

Class A – Good operative risk

Class B – Moderate operative risk

Class C – Poor operative risk

4. Management

Potentially resectable disease, operable by performance status

- Child Pugh Class A, B, no portal hypertension
- Suitable tumor location
- Adequate liver reserve
- Suitable liver remnant

Treatment – Refer for resection, if feasible; consider loco-regional options – with ablation (radiofrequency, percutaneous alcohol injection, microwave), or arterially directed therapy (Trans-arterial embolization, chemo-embolization).

Unresectable disease

With – inadequate hepatic reserve and tumor location: Evaluate whether patient is a candidate for transplant with the following (UNOS) criteria: Patient has a tumor 2-5cm in diameter or 2-3 tumors ≤3cm each, no macro-vascular involvement, no extra-hepatic disease

If eligible – refer for liver transplant

If not eligible – consider loco-regional therapy options or systemic therapy

Liver-confined disease, inoperable by performance status, comorbidity or with minimal or uncertain extra-hepatic disease, options are:

Refer for loco-regional therapy

Systemic therapy

Recurrent disease

If recurrent disease, generally switch to systemic treatment or best supportive care.

Metastatic disease or extensive liver tumor burden

Systemic therapy

Best supportive care

Systemic Therapy

- Sorafenib oral 200-400 mg twice a day, until disease progression or intolerable toxicity
- Levantinib oral 20-24 mg once a day, until disease progression or intolerable toxicity
- Second line – Nivolumab IV 240mg every 2 weeks or 480mg every 4 weeks, until disease progression or intolerable toxicity
- Second line – Pembrolizumab IV 200mg every 3 weeks or 600mg every 6 weeks, until disease progression OR 24 weeks if no disease progression, or intolerable toxicity.

5. Follow-up

Imaging every 3-6 months for 2 years, then every 6-12 months;

AFP, every 3-6 months for 2 years, then every 6-12 months

I.2. Gallbladder Cancer

1. Introduction

- Gallbladder cancer is a rare malignancy, with a high mortality rate. Common risk factors are gallstones, biliary cysts, carcinogen exposure, typhoid and Helicobacter Pylori infections.
- A majority of these malignancies are an incidental finding during surgery and pathologic review of an operated cholecystitis.

2. Workup

Workup depends on when the masses were found
Mass on imaging

- Multiphasic abdominal/pelvic CT/MRI with IV contrast
- Chest CT +/- contrast
- Liver function tests
- Assessment of hepatic reserve
- Consider CEA, CA 19-9 and staging laparoscopy

Incidental finding on pathologic review:
Cystic duct with positive node – Multiphasic abdominal/pelvic CT/MRI with IV contrast, chest CT +/- contrast;
T1b or greater – Same as above + consider staging laparoscopy

Incidental finding at surgery:
Same as above – imaging.

Patient with jaundice at presentation:

- History and Physical Examination
- LFTs
- Imaging (as above)
- Cholangiography
- Consider CEA, CA 19-9
- Consider staging laparoscopy and biliary drainage

3. Staging

TNM Staging

T Staging

T Category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2	Tumor invades the peri-muscular connective tissue on the peritoneal side, without involvement of the serosa (Visceral peritoneum) or tumor invades the peri-muscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades the peri-muscular connective tissue on the peritoneal side, without involvement of the serosa (Visceral peritoneum)
T2b	Tumor invades the peri-muscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extra-hepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extra-hepatic organs or structures

N Staging

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastases to 1-3 regional lymph nodes
N2	Metastases to 4+ regional lymph nodes

M Staging

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

Resectable disease (incidental finding at surgery or on imaging):

- Cholecystectomy + en bloc hepatic resection + lymphadenectomy +/- bile duct excision for malignant involvement
- If disease found incidentally on pathologic review – hepatic resection + lymphadenectomy +/- bile duct excision for malignant involvement
- If disease was found as patient came presenting first with jaundice – consider neo-adjuvant chemotherapy then surgery (as for incidental finding at surgery)

Post-resection status:

- Resected, R0 – negative margin, with negative margins or carcinoma in situ at margin – observe OR systemic therapy
- Resected, R1 – positive margin, with positive regional nodes – Systemic therapy
- Resected, R2 – gross residual disease – Treat as unresectable disease

Unresectable disease:

- Biopsy then MSI/MMR testing
- Systemic therapy
- Best supportive care

Systemic therapy

Neo-adjuvant therapy:

- Capecitabine oral 1000mg/m^2 twice D1-14 + Oxaliplatin IV 100 mg/m^2 on day 1, for a 21 day cycles for 3-6 cycles;
- Gemcitabine IV 1000mg/m^2 on Day 1 and 8 + Cisplatin IV 100 mg/m^2 on Day 1 for a 21 day cycles for 3-6 cycles;
- Gemcitabine IV 1000 mg/m^2 on Day 1 and 8 + Oxaliplatin IV 100 mg/m^2 on Day 1 for a 21 day cycles for 3-6 cycles;
- Single Agent – Capecitabine (same doses as above) and Gemcitabine (same doses as above)

Adjuvant treatment:

- Gemcitabine + Cisplatin (as above)
- Gemcitabine + Oxaliplatin (as above)
- Capecitabine + Oxaliplatin (as above)

Unresectable, Recurrent and Metastatic disease:

See other regimens not used before

If MSI-H/MMR positive tumors: Pembrolizumab IV 200mg every 3 weeks of 600 mg every 6 weeks

5. Follow-up

- Imaging every 3-6 months for 2 years, then every 6-12 months for up to 5 years, or as clinically indicated.

I.3. Cholangiocarcinoma

1. Introduction

Cholangiocarcinoma is a generally rare malignancy, but constitutes the 2nd most common intra-hepatic malignancy, with over 15% of all primary liver malignancies' cases. It is characterized by a high mortality rate.

There are two types of cholangiocarcinoma – **intra-hepatic, extra-hepatic tumors.** The extra-hepatic tumors are further categorized into 2 types – peri-hilar cholangiocarcinoma (Klatskin tumors) and distal biliary tract cholangiocarcinoma.

The common risk factors are:

- Primary Sclerosing Cholangitis
- Cholelithiasis
- Hepatitis B and C
- Diabetes, obesity, alcohol consumption, smoking

The common disease presentations are – Right upper quadrant pain, jaundice and signs of liver failure for an advanced disease

2. Workup (for both intra and extra-hepatic cholangiocarcinoma)

- History and Physical Examination
- FBC, LFTs
- Multiphasic abdominal/pelvic CT/MRI with IV contrast
- Chest CT +/- contrast
- Consider CEA, CA 19-9 and AFP
- Endoscopy (upper and lower – colonoscopy)
- Consider biopsy
- For extra-hepatic cholangiocarcinoma – consider IgG4 to rule out auto-immune cholangitis

3. Staging

a. Intra-hepatic bile duct tumor

TNM Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intra-ductal tumor)
T1	Solitary tumor without vascular invasion, ≤5cm or >5cm
T1a	Solitary tumor ≤5cm without vascular invasion
T1b	Solitary tumor >5cm without vascular invasion
T2	Solitary tumor with intra-hepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extra-hepatic structures by direct invasion

N Staging

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present

M Staging

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

b. Extra-hepatic Cholangiocarcinoma – Peri-hilar bile duct tumors

TNM Staging

T Staging

T Category	T Staging
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ /high grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals bilaterally with contralateral portal vein or hepatic artery involvement

N Staging

N Category	N Staging
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1-3 positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreato-duodenal, and portal vein, lymph nodes
N2	4+ positive lymph nodes from the sites described for N1

M Staging

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

c. Distal bile ducts tumors

TNM Staging

T Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ /high grade dysplasia
T1	Tumor invades the bile duct wall with a depth less than 5mm
T2	Tumor invades the bile duct wall with a depth of 5-12mm
T3	Tumor invades the bile duct wall with a depth greater than 12mm
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

N Staging

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1-3 regional lymph nodes positive
N2	4+ regional lymph nodes positive

M Staging

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

Intra-hepatic cholangiocarcinoma

- A.1. Resectable disease – consider staging laparoscopy; resection and regional lymphadenectomy
- A.2. Unresectable disease – MSI/dMMR status then – systemic therapy or best supportive care
- A.3. Metastatic disease – MSI/dMMR status then – systemic therapy or best supportive care

Post-resection:

- No residual disease, local disease (R0 resection) – observe, systemic therapy
- Microscopic margins (R1) or positive regional nodes – systemic therapy
- Macroscopic margins (R2) – treat as unresectable disease (see above)

Chemotherapy:

- Capecitabine oral 1000mg/m^2 twice D1-14 + Oxaliplatin IV 100 mg/m^2 on day 1, for a 21 day cycles for 3-6 cycles;
- Gemcitabine IV 1000mg/m^2 on Day 1 and 8 + Cisplatin IV 100 mg/m^2 on Day 1 for a 21 day cycles for 3-6 cycles;
- Gemcitabine IV 1000 mg/m^2 on Day 1 and 8 + Oxaliplatin IV 100 mg/m^2 on Day 1 for a 21 day cycles for 3-6 cycles;
- Single Agent – Capecitabine (same doses as above) and Gemcitabine (same doses as above)

Extra-hepatic cholangiocarcinoma

- B.1. Resectable disease – Consider pre-operative biliary drainage; surgical exploration; consider laparoscopic staging
- B.2. Unresectable disease – biliary drainage if indicated; biopsy; MSI/dMMR status then – systemic therapy OR best supportive care
- B.3. Metastatic disease – MSI/dMMR then – systemic therapy OR best supportive care

Post-resection status

- Resected, negative margins (R0) – negative regional nodes or Carcinoma in situ at margin – observe or systemic therapy
- Resected, positive margins (R1) or positive margins – Systemic therapy or best supportive care
- Resected with gross residual disease (R2) – treat as unresectable disease.

Chemotherapy:

- Capecitabine oral 1000mg/m^2 twice D1-14 + Oxaliplatin IV 100 mg/m^2 on day 1, for a 21 day cycles for 3-6 cycles;
- Gemcitabine IV 1000mg/m^2 on Day 1 and 8 + Cisplatin IV 100 mg/m^2 on Day 1 for a 21 day cycles for 3-6 cycles;
- Gemcitabine IV 1000 mg/m^2 on Day 1 and 8 + Oxaliplatin IV 100 mg/m^2 on Day 1 for a 21 day cycles for 3-6 cycles;
- Single Agent – Capecitabine (same doses as above) and Gemcitabine (same doses as above)

In case of recurrence:

- See other regimens not used before
- If MSI-H/MMR positive tumors: Pembrolizumab IV 200mg every 3 weeks of 600 mg every 6 weeks

5. Follow-up

- Consider imaging every 3-6 months for 2 years, then every 6-12 months for up to 5 years, or as clinically indicated.

GENITO-URINARY MALIGNANCIES

A. Renal Cell Carcinoma

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). Most of the symptoms are hidden for long, making patients present with a late disease.

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). There is a possible association with lymphoma.

2. Workup

In case of a suspicious mass

- History and Physical Examination
- Complete Blood Count, Comprehensive metabolic panel
- Urinalysis
- Abdominal +/- pelvic CT scan, chest X-ray/CT scan; If clinically indicated – Brain MRI
- Consider needle Biopsy
- If urothelial carcinoma is suspected (central mass) – consider urine cytology, ureteroscopy or percutaneous biopsy, with core needle biopsy.

Pathology

After nephrectomy, 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 (4-10%), oncocytic (rare), Sarcomatoid (1-6%, with poor prognosis).

3. Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 7 cms in greatest dimension, limited to the kidney
T1a	Tumor ≤ 4 cms in greatest dimension, limited to the kidney
T1b	Tumor > 4cms but ≤ 7 cms in greatest dimension, limited to the kidney
T2	Tumor > 7 cms in greatest dimension, limited to the kidney
T2a	Tumor > 7 cms but ≤ 10 cms in greatest dimension, limited to the kidney
T2b	Tumor > 10 cms in greatest dimension, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into T3 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)
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
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

4. Management

- **Stage I (T1a)**: Partial nephrectomy (Preferred) or Active surveillance or Radical nephrectomy (if nephron-sparing not indicated or feasible)
- **Stage I (T1b):** Partial nephrectomy or radical nephrectomy or active surveillance (in select patients)
- **Stage II:** Partial nephrectomy or radical nephrectomy
- **Stage III:** Radical nephrectomy or partial nephrectomy, if clinically indicated
- **Stage IV:**
  - Potentially surgically resectable primary* – consider tissue sampling then cytoreductive nephrectomy in select patients;
  - Surgically unresectable – Tissue sampling

Notes: * Individualize treatment based on symptoms and extent of metastatic disease

- **Stage IV,** relapsed, or recurrent disease with predominantly clear cell histology

4.1. Active Surveillance

Annual consultation with:

- Abdominal imaging (CT scan with contrast, MRI or ultrasound) within 6 month of surveillance initiation, then CT, MRI or Ultrasound at least annually;
- Chest imaging – Chest X ray or CT at baseline and annually as clinically indicated to assess for pulmonary metastases;
- Consider renal mass biopsy at initiation of active surveillance or at follow-up, as clinically indicated

4.2. Surgery for Renal Cell Carcinoma

Indications – partial nephrectomy (nephron-sparing surgery):

- Unilateral stage I-III tumors where technically feasible;
- Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer;
- Patients at relative risk for developing progressive chronic kidney disease due to young age or medical risk factors

Regional lymph node dissection is optional but recommended for patients with adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.

4.3. Systemic Treatment

4.3.1. First-line therapy for previously untreated patients low or intermediate risk:

- Sunitinib or Sorafenib.
  - Doses: Sunitinib oral 50mg once daily for 4 weeks followed by 2 weeks rest OR 37.5 mg once daily continuously if rapid progression during the 2 weeks rest;
  - Sorafenib oral 400mg BD continuously;
- Supportive care: Palliative radiation therapy, metastasectomy, and bisphosphonates for bony metastasis

4.3.2. 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.
  - Doses for Temsirolimus are: 25mg IV, once weekly for 4 weeks (4 weeks represent 1 cycle). Sunitinib and Sorafenib are given at doses specified above
- Patients with predominantly sarcomatoid renal cancers may respond to combination chemotherapy

4.3.3. Second line: Subsequent targeted therapy after tyrosine kinase inhibitors (i.e, sorafenib, sunitinib) and cytokine therapies:

- Axitinib. Doses are: 5mg orally, twice daily, can go up to 10mg twice daily, continuously

4.3.4. Third line:

Everolimus. Doses are: 10mg orally, once daily, and continuously

Stage IV, relapsed, or recurrent disease for patients with predominantly non–clear cell histology;

- Temsirolimus or Sorafenib or Sunitinib or Axitinib or Everolimus
- Gemcitabine and doxorubicin at doses: IV Doxorubicin 50mg/m^2 and Gemcitabine 1500mg/m^2 on Day 1, repeated every 14 days. OR
- Supportive care: palliative radiation therapy, metastasectomy, and bisphosphonates for bony metastasis

Nephrectomies with metastasectomy are beneficial to metastatic renal cancer patients.

4.4. Radiation therapy for Renal Cell Carcinoma

May be indicated for select patients who might benefit from palliative radiotherapy.

4.4.1. Radiation Planning

Patient in the supine position, 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 no surgery done), lymph node drainage sites, surgical clips; so if not possible to include scar in treatment volume, treat it with electrons to full dose.

5. Follow-up

Follow-up after partial or radical nephrectomy:

- Abdominal imaging: Baseline – abdominal CT, MRI or Ultrasound within 3-12 months of surgery, then annually for 3 years or longer as clinically indicated
- In case of positive margins, adverse pathologic features (sarcomatoid, high grade, positive margins) – needs a rigorous imaging schedule or technique modality
- Chest imaging: Chest X-ray or CT annually for at least 5 years; more rigorous imaging schedule or technique modality can be considered if positive margins or adverse pathologic feature.

B. Upper Genito-Urinary Tract Malignancies (renal pelvis, urothelial carcinoma)

1. Introduction

Upper genito-urinary tract malignancies are rare. Common symptoms include flank pain and frank hematuria, at times coupled with weight loss.

B.1. Renal Pelvis Carcinoma

B.1.1. Workup

- History and Physical examination
- Cystoscopy + Cytology
- Ureteroscopy and biopsy +/- selective washings
- Renal function tests, CBC, LFTs
- Chest imaging (X-ray or CT scan)

B.1.2. Staging (applies to ureteral carcinoma)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades
T2	Tumor invades the muscularis
T3	For renal pelvis only: tumor invades beyond the muscularis into peripelvic fat or the renal parenchyma For ureter only: tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs, or through the kidney into the perinephric fat

Clinical N Stage

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis≤ 2cm in greatest dimension, in a single lymph node
N2	Metastasis >2cm in a single lymph node; or multiple lymph nodes

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

B.1.3. Management

Primary management

- **Non-metastatic:**
  - Low Grade:
- Nephro-ureterectomy with cuff of bladder +/- perioperative intravesical chemotherapy

  - High Grade, large or parenchymal invasion:
- Nephro-ureterectomy with cuff of bladder + regional lymphadenectomy +/- perioperative intravesical chemotherapy
- Consider neoadjuvant chemotherapy in selected patients

- **Metastatic**

Systemic therapy - **similar to bladder cancer protocols (see section 4.3.3. under chemotherapy for bladder cancer).**

B.1.4. Follow-up

Adjuvant treatment for renal pelvis carcinoma:

- pT0, pT1: No adjuvant treatment needed – concomitant cytology with cystoscopy and consider cytology for high grade, every 3 months for 1 year, then at longer intervals
- pT2, pT3, pT4, pN+: Consider adjuvant chemotherapy – concomitant cytology with cystoscopy and cytology every 3 months for 1 year, then at longer intervals

B.2. Urothelial Carcinoma of the Ureter

B.2.1. Workup

- Similar as renal pelvis carcinoma

B.2.2. Staging

- Reference – above

B.2.3. Management

a. Upper location:

- Nephro-ureterectomy with cuff of bladder + regional lymphadenectomy if high grade and consider neoadjuvant chemotherapy in selected patients
- Endoscopic resection

b. Middle location:

- **Low Grade:** Nephro-ureterectomy with cuff of bladder OR Excision and ureteroureterostomy/ileal ureter in highly selected patients
- **High grade:** Nephro-ureterectomy with cuff of bladder + regional lymphadenectomy; consider neoadjuvant chemotherapy in selected patients

c. Distal location:

- Distal ureterectomy and regional lymphadenectomy if high grade and reimplantation of ureter; consider neoadjuvant chemotherapy in selected patients
- Nephro-ureterectomy with cuff of bladder + regional lymphadenectomy if high grade and consider neoadjuvant chemotherapy in selected patients

d. Metastatic disease:

- **Systemic therapy** - similar to bladder cancer protocols (see section 4.3.3. under chemotherapy for bladder cancer).

B.2.4. Follow-up

- Same as renal pelvis carcinoma

B.3. Urothelial Carcinoma of the Prostate

B.3.1. Workup

- History and Physical examination
- Digital Rectal examination (DRE)
- Cystoscopy (including bladder biopsy)
- Trans-Urethral Resection biopsies of prostate to include stroma
- PSA
- Needle biopsy if DRE is abnormal (in selected patients)
- Imaging of upper tract collecting system

B.3.2. Staging

- Combination of bladder and prostate cancer staging

B.3.3. Management

Mucosal prostatic urethra:

- **Mucosal prostatic urethra** – TURP and BCG, Follow-up imaging; if local recurrence: Cystoprostatectomy +/- urethrectomy
- **Ductal acini** – Chest Xray + abdominal and pelvic CT scan – Cystoprostatectomy +/- urethrectomy OR TURP + BCG; follow-up imaging, and if recurrence post TURP – cystoprostatectomy +/- urethrectomy;
- **Stromal invasion** – Chest Xray + abdominal and pelvic CT scan – cystoprostatectomy +/- urethrectomy +/- neo-adjuvant chemotherapy then consider adjuvant chemotherapy
- **Metastatic disease** – systemic therapy; regimens and doses are similar to bladder cancer regimens.

B.3.4. Follow-Up

Same as renal pelvis carcinoma

C. Bladder Cancer

1. Introduction

- 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.

2. Workup:

- History and Physical Examination
- Consider Cytology
- Cystoscopy, biopsy, examination under anesthesia (bimanual)
- Abdominal/pelvic imaging (CT, ultrasound or MRI) including upper urinary tract collecting system before TURBT;
- TURBT with random biopsies of normal appearing mucosa to exclude CIS (if trigone is involved, biopsy prostatic urethra)

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 invariably consists of cytologically high-grade tumor cells.

3. Staging

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
T1	Tumor invades the 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	Extra-vesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extra-vesical tumor invades directly into prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extra-vesical tumor invades pelvic wall, abdominal wall
N Category	**N Criteria**
NX	Lymph Nodes cannot be assessed
N0	No Lymph nodes metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph nodes)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph nodes metastasis to the common iliac lymph nodes
M Category	**M Criteria**
cM0	No distant metastasis
cM1	Distant metastasis
cM1a	Distant metastasis limited to lymph nodes beyond the common iliacs
cM1B	No lymph nodes distant metastasis

4. Management

Treatment categories of bladder cancer have been divided into superficial tumors (non-muscle invasive bladder cancer) and muscle invasive tumors and metastatic disease.

4.1. Management of Superficial tumors (non-muscle invasive bladder cancer) – Ta, T1, CiS

Surgery: Trans-Urethral Resection of Bladder Tumor (TURBT)

- **For cTa** - low grade: observation or intravesical therapy (BCG or Chemotherapy*)
- **For cTa** – high grade: if incomplete resection – repeat TURBT; if no muscle in specimen, strongly consider repeating TURBT. Intravesical therapy (BCG or Chemotherapy*) or observation.
- **For cT1** – Strongly advised to repeat TURBT:
  - In case of residual disease – intravesical BCG OR cystectomy;
  - If no residual disease – intravesical BCG or Intravesical chemotherapy* or observation in highly selected cases (low grade, small volume tumors with limited lamina propria invasion and no CIS);
  - If high grade disease – Consider Cystectomy
- **Any TiS** – Intravesical BCG

*The most commonly used options for intravesical chemotherapy are gemcitabine (preferred) and mitomycin;

NOTE:

1. Intravesical therapy should not be used in TURBT if extensive or bladder perforation is suspected.
2. The above bladder preservation protocol is applicable to transitional cell carcinoma; the standard of care in squamous cell carcinoma is radical cystectomy.

In case of recurrence or persistent disease

- **Cystoscopy positive** – TURBT + single dose of intravesical chemotherapy within 24 hours of TURBT (Gemcitabine or Mitomycin or Doxorubicin +/- 5-FU if available); based on tumor stage and grade: Adjuvant intravesical therapy or cystectomy.
- **Cytology Positive,** Imaging and Cystoscopy negative: Selected mapping biopsies with transurethral biopsy of prostate, cytology of upper tract; consider ureteroscopy:
  - IF bladder, prostate, and upper tract are negative: follow-up 3 monthly, if prior BCG – provide maintenance
  - IF bladder is positive – BCG – if no evidence of disease; maintenance BCG; if BCG unresponsive: Cystectomy;
  - IF prostate positive – treat as urothelial carcinoma of the prostate
  - IF upper tract positive – treat as upper GU tract tumors.

Note: Dose solutions:

- **Intravesical Mitomycin C** (Single Dose, Induction and Maintenance): 40mg; induction is given weekly for 6 doses, and maintenance is given monthly for a total of 10 months.
- **Intravesical Gemcitabine:** (Single Dose, Induction and Maintenance): 2000mg; induction is given weekly for 6 doses, and maintenance is given monthly for a total of 10 months.
- **Intravesical BCG** (Single Dose, Induction and Maintenance): 1 vial; induction is given weekly for 6 doses, and maintenance is given in 3 consecutive weeks at month 3, 6, 12, 18, 24, 30 and 36.

4.2. Management of Muscle Invasive Bladder Cancer

Patients are assessed for radical cystectomy or bladder preservation protocols, with a multimodality approach.

4.2.1. Cystectomy Candidates (T2 and greater)

- Consider Neoadjuvant chemotherapy (cisplatin-based) followed by radical cystectomy
- Consider Neoadjuvant chemotherapy (cisplatin-based) followed by partial cystectomy (patients with solitary lesion in a suitable location)
- Cystectomy alone for those not eligible to receive cisplatin-based chemotherapy

* Based on pathologic risk (pT3-4 or positive nodes or positive margins) consider adjuvant cisplatin-based chemotherapy or consider adjuvant RT if no neoadjuvant treatment was given.

- Concurrent chemo-radiotherapy then reassess tumor status in 2-3 months after full treatment.
  - If no tumor – observation
  - If tumor present – if TiS, Ta or T1 – consider intravesical BCG or surgical consolidation or treatment as metastatic disease

4.2.2. Non-cystectomy candidates (T2 and greater)

- Concurrent chemo-radiotherapy
- RT
- TURBT

In either of the cases – reassess tumor status in 2-3 months after treatment:

- If no tumor – observation
- If tumor present – systemic therapy or concurrent chemo-radiotherapy or RT alone (if RT was not used) or best supportive care

Bladder preservation options:

- TURBT alone - solitary lesion, < 2 cm, minimal muscle invasion, no CiS
- TURBT followed by chemotherapy alone
- Partial cystectomy
- Chemo-radiotherapy - 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

4.2.3. Recurrent 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

4.3. Chemotherapy options in bladder cancer (per cases)

4.3.1. Neoadjuvant chemotherapy for stage II, III and non-metastatic stage IV disease (dose details are below under section 4.3.3.)

- Cisplatin Eligible: Gemcitabine + Cisplatin
- Cisplatin Ineligible:
  - Gemcitabine + Carboplatin
  - Gemcitabine

4.3.2. Concurrent chemo-radiotherapy for stage II, III and non-metastatic stage IV disease

- Cisplatin + RT

4.3.3. Chemotherapy for metastatic disease

- Gemcitabine + Cisplatin
- Docetaxel

Note: Dose solutions for chemotherapy

- Weekly Cisplatin (+ RT) = 40mg/m^2
- Neoadjuvant Gemcitabine + Cisplatin = Gemcitabine 1250mg/m^2 for D1 and D8, and Cisplatin at 70mg/m^2 for D1 only; repeat every 21 days for a maximum of 4 cycles prior to surgery
- Neoadjuvant Gemcitabine + Carboplatin (for Cisplatin ineligible patients) = Gemcitabine 1250mg/m^2 for D1 and D8, and Carboplatin at AUC of 5-6 for D1 only; repeat every 21 days for a maximum of 4 cycles prior to surgery
- Gemcitabine alone = Gemcitabine 1250mg/m^2 for D1 and D8; repeat every 21 days for a maximum of 4 cycles prior to surgery
- Docetaxel (Metastatic disease) = 75mg/m^2 every 3 weeks until disease progression or intolerance

4.4. Radiation therapy for bladder cancer

4.4.1. Radiation Planning

- Simulation to be done with patient in supine position with immobilization and empty bladder;

4.4.2. Radiation delivery and Dose Solutions

a. Definitive radiation therapy

– Treat the whole bladder with or without pelvic nodal irradiation (depending on N status) with 39.6 – 50.4 Gy in conventional fractionation

- **N0:** Elective treatment to the lymph nodes is optional and should take into account patient comorbidities and the risks of toxicity to adjacent/organs at risk; boost either the whole or partial bladder between 60-66 Gy.
- **N1+:** Consider boosting grossly involved LNs to the highest achievable dose; Alternative – 55 Gy in 20 fractions or integrated boost to sites of gross disease.

b. Adjuvant radiation therapy

- For patients with pT3/T4 pN0-2 bladder cancer following radical cystectomy with ileal conduit, consider adjuvant pelvic RT. Treatment to encompass areas at risk for harboring microscopic residual disease, based on pathologic findings at resection, cystectomy bed and pelvic lymph nodes with doses in range of 45-50.4Gy. Involved resection margins and areas of extranodal extension could be boosted to 54-60 Gy if feasible based on normal tissue constraints.

c. Palliative radiation for metastatic or recurrent bladder cancer

- Treatment fields to encompass the whole bladder and all sites of gross disease +/- uninvolved regional lymph nodes. Regional lymph nodes include the hypogastric, obturator, internal and external iliac, perivesical, sacral, and presacral nodes. For involved nodal disease, the common iliac nodes are a site of secondary involvement

5. 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.

D. Prostate Cancer

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, younger men are being diagnosed, with the black race being a strong predilection factor.
Symptoms are usually related to Lower Urinary Tract obstruction symptoms, with hesitancy, dribbling, urgency, and hematuria in advanced stages.
Routine screening is 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 groups should take place starting at age 45.

2. Workup

- History and Physical Examination
- Perform Digital Rectal Exam (DRE) to confirm clinical stage
- Perform and/or collect PSAs and calculate PSA density and PSADT
- Laboratory tests with testosterone, FBC, RFT and LFT
- Obtain and review diagnostic prostate biopsies; biopsy best obtained with Trans-Rectal Ultrasound (>8 separate cores is recommended, the highest GS is used)
- Pelvic CT or MRI and metastatic work-up 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.

3. Staging

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	Extra-prostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicles
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum,bladder, levator muscles, and/or pelvic wall

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

Notes:
1. Pathological and Clinical T stages are similar from T2 up to T4;
2. Positive surgical margins should be indicated by an R1 descriptor, indicating residual microscopic disease.

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

Risk Stratification and Staging Workup

Risk Group	Clinical/Pathologic features	Imaging
Very Low	T1c And Grade group 1 and PSA <10 ng/mL and Fewer than 3 prostate biopsy fragments/cores positive, ≤ 50% cancer in each fragment/core and PSA density < 0.15 ng/mL/g	Not indicated
Low	T1-T2a and Grade group 1 and PSA <10 ng/mL	Not indicated
Intermediate	Has no high-or very high risk features and has one or more intermediate risk factors (IRF): T2b-T2c Grade Group 2 or 3 PSA 10-20 ng/mL	(See below)

Favorable Intermediate	1 IRF and Grade group 1 or 2 and <50% biopsy cores positive	Pelvic +/-abdominal imaging recommended if nomogram predicts >10% of pelvic lymph node involvement*
Unfavorable intermediate	2 or 3 IRFs and/or Grade group 3 and/or ≥50% biopsy cores positive	Same as above
High	T3a or Grade group 4 or grade group 5 or PSA ≥ 20 ng/mL	Metastatic work-up Pelvic +/- abdominal imaging recommended if nomogram predicts >10% of pelvic lymph node involvement*
Very High	T3b-T4 or Primary Gleason pattern 5 or >4 cores with grade group 4 or 5	Metastatic work-up Pelvic +/- abdominal imaging if nomogram predicts >10% of pelvic lymph node involvement*

NOTE: The prostate cancer prediction nomograms – use the online Partin Tables: (https://www.hopkinsmedicine.org/brady-urology-institute/specialty_areas/prostate_cancer/risk_assessment_tools/partin-tables.html)

4. Management

4.1. Newly diagnosed local prostate cancer

a. Very Low Risk

- **For patients with life expectancy§ ≥ 20 years, management options are:**
  - Active surveillance*
  - Definitive radiation therapy
  - Radical Prostatectomy; consider adjuvant radiation therapy if presence of adverse features (positive surgical margins, seminal vesicle invasion, extracapsular extension) and detectable PSA (as per AUA criteria) post Radical Prostatectomy

- **For patients with life expectancy between 10-20 years:**
  - Active surveillance*

- **For patients with life expectancy < 10 years**
  - Observation

§ Life expectancy estimation – use current national life expectancy age from the WHO (https:app.who.int/gho/data/view.main.60000?lang=en)

*Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. It includes:

- PSA no more often than every 6 months unless clinically indicated;
- DRE no more often than every 12 months unless clinically indicated;
- Repeat prostate biopsy based upon faster PSA doubling time (≤ 3 years)

Observation involves monitoring the course of disease with the expectation to deliver

palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent

b. Low Risk

- **For life expectancy ≥ 10 years, management options are:**
  - Active surveillance
  - Definitive radiation therapy
  - Radical Prostatectomy; consider adjuvant radiation therapy if presence of adverse features (positive surgical margins, seminal vesicle invasion, extracapsular extension) and detectable PSA (as per AUA criteria) post Radical Prostatectomy

- **For life expectancy < 10 years:**
  - Observation

c. Intermediate Risk

c.1. Favorable Intermediate Risk

For life expectancy ≥ 10 years, management options are:

- Active surveillance
- Definitive external beam radiation therapy. Monitor PSA (Phoenix Criteria):
  - If PSA nadir – regular monitoring on follow-up
  - If PSA nadir + 2ng/mL – consider radical prostatectomy
- Radical Prostatectomy +/- Pelvic Lymph Node Dissection if predicted probability of lymph node metastasis ≥ 2%
  - If no adverse features or lymph node metastases – monitor PSA (AUA criteria):
    - Undetectable PSA after radical prostatectomy – regular monitoring on follow-up*
    - PSA persistence/recurrence – Salvage external beam radiation therapy +/-ADT* (4-6 months);
  - If Presence of adverse features (positive surgical margins, seminal vesicle invasion, extracapsular extension), and no lymph node metastasis, consider adjuvant/salvage radiation therapy +/- ADT (4-6 months). Monitor PSA (AUA criteria), with the same endpoints as above;
  - If lymph node metastasis present: ADT +/- adjuvant radiation therapy or observation. Monitor PSA (AUA criteria), with the same endpoints as above;

For patients with life expectancy <10 years:

- Definitive external beam radiation therapy alone. Monitor PSA (Phoenix criteria):
  - PSA nadir - regular monitoring on follow-up
  - PSA nadir + 2ng/mL consider radical prostatectomy
- Observation

c.2. Unfavorable Intermediate

For patients with life expectancy ≥ 10 years:

- Radical Prostatectomy +/- Pelvic Lymph Node Dissection if predicted probability of lymph node metastasis ≥ 2 years;

- If no adverse features or lymph node metastases – monitor PSA (AUA criteria):
  - Undetectable PSA after radical prostatectomy – regular monitoring on follow-up*
  - PSA persistence/recurrence – Salvage radiation therapy +/-ADT (4-6 months);

(**ADT includes medical or surgical ADT*)

- If presence of adverse features positive surgical margins, seminal vesicle invasion, extracapsular extension) and no lymph node metastasis: Radiation therapy +/- ADT (4-6 months) or observation
- If lymph node metastasis present: ADT +/- External Beam Radiation Therapy or Observation

- External Beam Radiation Therapy +/- ADT (4-6 months). Monitor PSA (Phoenix criteria):
  - PSA nadir - regular monitoring on follow-up
  - PSA nadir +2ng/mL, consider radical prostatectomy

For patients with life expectancy < 10 years:

- External Beam Radiation Therapy +/- ADT (4-6 months). Monitor PSA (Phoenix criteria):
  - PSA nadir - regular monitoring on follow-up
  - PSA nadir +2ng/mL, consider radical prostatectomy
- Observation

d. High or Very High Risk

For patients with life expectancy > 5 years:

- External Beam Radiation Therapy +ADT for 1.5 – 3 years, then monitor PSA (Phoenix criteria)
  - PSA nadir - regular monitoring on follow-up
  - PSA nadir +2ng/mL, consider radical prostatectomy
- Radical Prostatectomy + Pelvic Lymph Node Dissection;
  - If no adverse features or lymph node metastases – monitor PSA (AUA criteria):
    - Undetectable PSA after radical prostatectomy – regular monitoring on follow-up*
    - PSA persistence/recurrence – Salvage radiation therapy +/-ADT (4-6 months);
  - If presence of adverse features positive surgical margins, seminal vesicle invasion, extracapsular extension) and no lymph node metastasis: Radiation therapy +/- ADT (4-6 months) or observation
  - If lymph node metastasis present: ADT +/- External Beam Radiation Therapy or Observation

For patients with ≤ 5 years and asymptomatic:

- Observation
- ADT
- External Beam Radiation Therapy +/- ADT

4.2. Locally Recurrent Prostate Cancer

a. If radical prostatectomy was the initial therapy and:

- Increasing PSA
- Positive DRE
  - Risk Stratification +/- PSA density
  - Consider MR – spine, chest, abdominal and pelvic CT
  - Prostate bed biopsy.
  - If studies are negative for distant metastases:
    - External Beam Radiation Therapy +/- ADT
    - Observation
  - If studies are positive for distant metastases
    - Observation
    - Systemic therapy

b. If External Beam Radiation Therapy was the initial therapy, and:

- PSA persistent or recurrence
- Positive DRE:
  - Risk stratification +/- PSA density
  - Consider MR – spine, chest, abdominal and pelvic CT
    - If studies are negative for distant metastases:
    - Radical Prostatectomy + Pelvic Lymph Node Dissection – if feasible
    - Observation; if non-metastatic progression occurs:
- Systemic therapy for castration naïve disease OR
- Systemic therapy for M0 castration resistant disease
  - If studies are positive for distant metastases:
    - Systemic therapy for castration naïve disease OR
    - Systemic therapy for M1 castration resistant disease

4.3. Disease progression post local treatment

4.3.1. Non metastatic disease

a. M0 castrate naïve disease

- Observation
- ADT

If progression occurs on PSA and/or metastatic work-up:

- Switch to systemic therapy

b. M0 castrate resistant disease

- ADT to maintain castrate serum levels of testosterone (<50 ng/dL):
  - If PSA doubling time > 10 months:
    - Observe
    - Other secondary hormone therapy
    - If PSA doubling time < 10 months:
    - Apalutamide (if available) – at dose of 240 mg daily

– Enzalutamide (if available) – at dose of 160 mg daily
– Other secondary hormone therapy
° If no PSA increase – maintain same treatment and continue monitoring
- In both the above cases – with PSA increase, perform metastatic work-up:
° No metastasis – maintain or change current treatment and continue monitoring
° If metastasis present – Systemic treatment for M1 castrate resistant disease

4.3.2. Metastatic disease

a. Castration naïve disease
- ADT and Docetaxel (75 mg/m^2) +/- Prednisone for 6 cycles or
- ADT and Abiraterone (1000 mg OD) + Prednisone or
- ADT and External Beam Radiation Therapy to the primary tumor for low volume M1 or
- ADT alone.

In case of progression, treat as M1 castrate resistant disease.

b. Castration resistant disease
- Continue ADT to maintain castrate levels of serum testosterone (<50 ng/dL)
- Bone antiresorptive therapy with Zoledronic Acid if bone metastases are present – at dose of 4mg once monthly
- Palliative radiation therapy for painful bone metastases
- Best supportive care

In case the primary histology is adenocarcinoma:
- Imaging for visceral metastasis:
° If no visceral metastases:
– Abiraterone + Prednisone – doses specified above
– Docetaxel +/- Prednisone – doses specified above
– Other secondary hormone therapy

Note: Either Docetaxel or Abiraterone can be second lines of treatment in case of failure of the other.

° If visceral metastases present:
– Docetaxel +/- Prednisone – doses specified above
– Abiraterone + Prednisone – doses specified above
– Other secondary hormone therapy

Note: Either Docetaxel or Abiraterone can be second lines of treatment in case of failure of the other.

In case the primary histology is small cell/neuroendocrine prostate cancer:
- First and subsequent therapy options:
° Chemotherapy:
– Cisplatin + Etoposide – at doses: Cisplatin 75-80mg/m^2 + Etoposide 80-100mg/m^2 every 3-4 weeks, for 6 cycles
– Carboplatin + Etoposide – at doses: Carboplatin AUC 5-6 + Etoposide 100mg/m^2 every 3 weeks, for 4-6 cycles

– Docetaxel+Carboplatin – at doses: Docetaxel 60-75mg/m^2 + Carboplatin AUC 4-6 every 3 weeks, for 6 cycles

° Best supportive care

4.4. Treatment Modalities

4.4.1. 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.

4.4.2. Androgen Deprivation Therapy (ADT)

- Neoadjuvant ADT for radical prostatectomy is strongly discouraged;
- ADT should not be used as monotherapy in localized prostate cancer unless there is a contraindication to definitive local therapy such as a low life expectancy at disease presentation or comorbidities;
- ADT can be given before, during and/or after radiation, to prolong survival in selected radiation managed patients (depending on risk group). Options are:
  - ° Combined Androgen Blockade: First generation anti-androgen (2 weeks prior to LHRH agonist to prevent testosterone flare) + LHRH agonist. The commonly used combination is Bicalutamide (50 mg tablets OD, 2 weeks) then Goserelin (10.8 mg subcutaneous every 3 months). Duration is dependent on risk group;
- ADT in metastatic disease can be used for both castrate naïve and castrate resistant disease as a combination – with doses of Bicalutamide tablets 150 mg OD, continuously and Goserelin 10.8 mg subcutaneous every 3 months; Caution is taken in case there are competing co-morbidities;
- Surgical castration is an alternative to medical ADT;
- Abiraterone, when indicated, is given at a dose of 1000 mg daily and should be given with concurrent steroid (oral prednisone) at a dose of 5 mg twice or 10 mg once daily.

4.4.3. Radical Prostatectomy

- 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.

4.4.4. Radiation Therapy

a. Radiation Planning

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 for simulation
Gold marker seeds, if available, are placed in the base and apex of the prostate, 7-10 days prior to simulation.

b. Radiation Dose

- Prophylactic dose to the pelvic lymph nodes is 1.8 Gy/fraction to 45 Gy total. Involved lymph nodes receive 54-56 Gy or higher with IMRT Prophylactic dose to the seminal vesicles is 54 Gy. With a simultaneous integrated boost technique, the dose to the prostate reaches 74-78 Gy in 2 Gy/fraction, with doses to the lymph nodes and seminal vesicles kept at 54-56 Gy.
- Alternative fractionation (hypofractionation) with 60 Gy in 20 fractions (3 Gy/fraction) is encouraged in settings of locally advanced prostate cancer as a primary treatment.
- In the postoperative setting, the prostate bed is typically treated to 64-66.6 Gy at 1.8 Gy per fraction, but may be boosted higher if local residual disease is documented.

4.4.5. Systemic Treatment

- **Options include:**
  - Docetaxel intravenous injection at 75 mg/m^2 +/- daily oral prednisone (5mg BD or 10 mg OD for 21 days), given every 3 weeks, for a total of 6 cycles, in combination with ADT.
  - In patients with bone metastasis, addition of Zoledronic Acid is advised. The generic dose is 4 mg, intravenous injection every 3 to 4 weeks or every 12 weeks. Dose also depends on renal function, and it is not recommended if creatinine clearance is < 30mL/min.

5. Follow-up

- H&P
- DRE every year, but may be omitted if PSA is undetectable.
- 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 months).
- The AUA criteria definition of PSA failure following surgery is controversial and values ≥0.2, ≥0.3, and ≥ 0.4 ng/mL have been used. The standard value for PSA failure 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;
- The "Phoenix Definition" (current ASTRO/RTOG definition) of PSA failure after EBRT, with or without short-term ADT, 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 (usually radical prostatectomy) are declared failures at the time of positive biopsy or salvage therapy administration (whichever comes first).

E. Testicular Cancer

1. Introduction

- There are two types of testicular tumors: seminoma and non-seminoma tumors. The non-seminoma type 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 non-seminoma tumor.
- **Risk Factors:** Undescended testis, first-born, pre/perinatal estrogen exposure, polyvinyl chloride exposure, advanced maternal age, Down's Syndrome, Klinefelter's syndrome (47 XXY), CIS, HIV/AIDS.

2. Workup

With any suspicious testicular mass:

- History and Physical Examination
- Alpha-Fetoprotein, beta-hCG, LDH
- Chemistry profile: if available, consider measuring the baseline levels of gonadal function
- Testicular ultrasound
- Chest, abdomen and pelvic CT scan if ≥stage II

3. Staging

TNM Classification (8th edition)

Clinical 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 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 < 3 cm in size
pT1b	Tumor ≥ 3 cm 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 wihout lymphovascular invasion
pT3	Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumor invades scrotum with or without lymphovascular invasion

Clinical N Category	N criteria
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph nodes metastasis
cN1	Metastasis with a lymph node mass 2cm or smaller in greatest dimension OR Multiple lymph nodes, none larger than 2cm in greatest dimension
cN2	Metastasis with a lymph node mass larger than 2cm but not larger than 5cm in greatest dimension OR multiple lymph nodes, any one mass larger than 2cm in greatest dimension
cN3	Metastasis with a lymph node mass larger than 5cm in greatest dimension
Pathological N Category	**N Criteria**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2cm or smaller in greatest dimension and less than or equal to 5 nodes positive, none larger than 2cm in greatest dimension
pN2	Metastasis with a lymph node mass larger than 2cm but not larger than 5cm in greatest dimension; or more than 5 nodes positive, none larger than 5cm; or evidence of extra-nodal extension of tumor
pN3	Metastasis with a lymph node mass larger than 5cm in greatest dimension

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-retroperitoneal nodal or pulmonary metastases
M1b	Non-pulmonary visceral metastases

S Category	S Criteria
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 x Upper normal limits and hCG (mIU/mL) <5,000 and AFP (ng/mL) <1,000
S2	LDH 1.5-10 x Upper normal limits or hCG (mIU/mL) 5,000-50,000 or AFP (ng/mL) 1,000 – 10,000
S3	LDH >10x Upper normal limits or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000

When T is..	And N is..	And M is..	And S is…	Then the stage group is..
pTis	N0	M0	S0	0
pT1-4	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

Risk Status	Nonseminoma	Seminoma
Good risk	Testicular or retroperitoneal primary tumor and No non-pulmonary visceral metastases and Post-orchiectomy markers – all of: AFP <1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and Non non-pulmonary visceral metastases and Normal AFP Any hCG Any LDH
Intermediate risk	Testicular or retroperitoneal primary tumor And No non-pulmonary visceral metastases and Post-orchiectomy markers – any of: AFP 1,000 – 10,000 ng/mL hCG 5,000 – 50,000 iu/L LDH 1.5 – 10 x upper limit of normal	Any primary site and Non-pulmonary visceral metastases and Normal AFP Any hCG Any LDH
Poor risk	Mediastinal primary tumor Or Non-pulmonary visceral metastases or Post-orchiectomy markers – any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis

4. Management

4.1. Primary treatment

– Discuss sperm banking, if available, and if clinically indicated;
– Radical inguinal orchiectomy;
– Consider inguinal biopsy of contralateral testis if:

- Ultrasound showing intra-testicular mass concerning of testicular cancer (biopsy not recommended for microcalcifications)
- Cryptorchid testis
- Marked atrophy
- Suspicious mass

Diagnosis is made as follows:
- **Pure seminoma:** pure seminoma histology and AFP normal; may have elevated beta-hCG)
- **Non-seminomatous germ cell tumor:** includes mixed seminoma/non-seminoma tumors and seminoma histology WITH elevated AFP

4.2. Pure seminoma management

4.2.1. Stage IA, IB
Options include:
- Surveillance* for pT1-T3 tumors (strongly preferred)
- Adjuvant Single agent carboplatin (AUC=7 x 1 cycle or AUC=7 x 2 cycles)
- Adjuvant Radiation Therapy

4.2.2. Stage IS
Options include:
- Adjuvant radiation therapy
- Surveillance*

Note: * 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

4.2.3. Stage IIA and IIB
Options include:
- Adjuvant Radiation therapy – including para-aortic and ipsilateral lymph nodes to a dose of 30 Gy (IIA) or 36 Gy (IIB – selected, non bulky, ≤3cm cases) in conventional fractionation
- Primary chemotherapy: BEP (Bleomycin, Etoposide and Cisplatin) for 3 cycles or EP (Etoposide and Cisplatin) for 4 cycles.

4.2.4. Stage IIC and III

1. Good risk:
- Primary chemotherapy: BEP x 3 cycles or EP x 4 cycles

2. Intermediate risk:
- Primary chemotherapy: BEP x 4 cycles or Etoposide, Ifosfamide, mesna and Cisplatin (VIP) x 4 cycles.

4.2.5. Stage IIA, IIB, and III after primary chemotherapy

- Chest, abdominal, pelvic CT scan and serum tumor markers:
  - If no residual mass or residual mass ≤ 3cm and normal serum AFP and b-hCG
    - Surveillance
  - If residual mass > 3cm and normal serum AFP and b-hCG:
    - Surveillance
    - Resection of residual mass or biopsy. If negative for viable seminoma – surveillance, if positive for viable seminoma:
  - If complete resection add 2 cycles of adjuvant chemotherapy (EP, VIP)
  - If incomplete resection – 2nd line of chemotherapy (Paclitaxel, Ifosfamide and Cisplatin or Vinblastine, Ifosfamide and Cisplatin)

4.2.6. Follow-up for Seminoma

Clinical Stage I seminoma (post-orchiectomy):

- History and Physical Examination – every 3-6 months at year 1, every 6 months from year 2, every 6-12 months at year 3, and annually from year 4 to 5. Serum tumor markers are optional, and testicular ultrasound is indicated for any equivocal exam;
- Abdominal +/- pelvic CT scan – at the same frequency as above; Chest CT scan indicated for symptomatic patients

Clinical Stage I seminoma (post-adjuvant chemotherapy or radiation therapy):

- History and Physical Examination – every 6-12 months in year 1, every 6-12 months in year 2, annually from year 3 to 5. Serum tumor markers are optional, and testicular ultrasound is indicated for any equivocal exam;
- Abdominal +/- pelvic CT scan – done annually from year 1 to 3; Chest CT scan indicated for symptomatic patients

Clinical Stage IIA, non-bulky IIB seminoma: Surveillance after radiotherapy or chemotherapy:

- History and Physical examination – every 3 month in year 1, every 6 months from year 2 to 5. Serum tumor markers are optional, and testicular ultrasound is indicated for any equivocal exam;
- Abdominal +/- pelvic CT scan – done at month 3 then 6-12 month in year 1, and annually from year 2 to 3, then as clinically indicated afterwards; Chest CT scan done at every month 6 from year 1 to 2

Clinical Stage IIB, IIC and Stage III seminoma: Surveillance after chemotherapy:

- History and Physical examination and serum markers – every 2 months from year 1 to 2, then every 6 months from year 3 to 4, then annually;
- Abdominal and pelvic CT scan done every 4 months in year 1, every 6 months in year 2, and annually from year 3 to 4
- Chest CT scan done every 2 months in year 1, every 3 months in year 2, and annually from year 2 to 5

4.3. Non-Seminoma management

4.3.1. Stage IA, IB, IS:

For stage I, without risk factors, options include:

- Surveillance
- Primary chemotherapy: BEP x 1 cycle

For stage I with risk factors, options include:

- Primary chemotherapy: BEP x 1 cycle

For stage IS:

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

4.3.2. Stage IIA, IIB

- If markers are negative – chemotherapy: BEP x 3 cycles or EP x 4 cycles;
- If persistent tumor marker elevation – add chemotherapy (BEP x 3 cycles or EP x 4 cycles);
- If with stage IIB there is lymph node metastasis with lymphatic drainage sites – consider open nerve sparing retro-peritoneal lymph node dissection

4.3.3. Stage IIC, IIIA, IIIC and brain metastases

1. Good risk

- Chemotherapy with EP x 4 cycles or BEP x 3 cycles

2. Intermediate risk

- Chemotherapy with BEP x 4 cycles or VIP x 4 cycles
- Non seminoma stage IIIB: BEP x 4 cycles
- If Bleomycin cannot be tolerated because of pneumonitis, VIP is recommended
- If brain metastases are present on brain CT scan, patients should receive primary chemotherapy plus radiation. Surgery should be performed if clinically indicated (Brain CT scan indicated b-hCG > 5,000 IU/L, extensive lung metastasis, choriocarcinoma, neurologic symptoms, non-pulmonary visceral metastasis, or AFP > 10,000 ng/mL)
- After primary chemotherapy is completed, an abdominal and pelvis CT scan and tumor markers assays are indicated. The following options apply in presence of:
  - Complete response:
    - Surveillance
    - Open nerve-sparing retro-peritoneal lymph node dissection
  - If residual disease is present but tumor markers are normal:
    - Resect all residual disease
  - If resection specimens shows only necrotic tissue or teratoma – no further therapy is recommended, apply active surveillance
  - If residual specimen is embryonal, yolk sac, choriocarcinoma, or seminoma elements:
    - EP x 2 cycles
    - Paclitaxel, Ifosfamide and Cisplatin (TIP) x 2 cycles
    - VIP x 2 cycles
    - Vinblastine, Ifosfamide, mesna and Cisplatin (VeIP) x 2 cycles.

4.3.4. Recurrent disease

- If prior chemotherapy was used:
  - Early relapse – recurrence ≤ 2 years after completion of primary treatment:
    - Chemotherapy, conventional-dose therapy (VeIP or TIP)
    - Consider surgical salvage if solitary site
    - Recommend sperm banking if clinically indicated
  - Late relapse – recurrence > 2 years afer completion of primary treatment:
    - Surgical salvage, if resectable
    - Chemotherapy, conventional-dose therapy (VeIP or TIP)
    - Recommend sperm banking
- Palliative chemotherapy and radiation: If surgery cannot be done, patients can be considered for palliative chemotherapy (3rd line) or palliative radiation; Gemcitabine + Oxaliplatin (GEM-OX) has shown efficacy in relapsed cisplatin-refractory disease and may offer a chance for long term survival.

4.3.5. Follow-up for Non-Seminoma

Clinical Stage I with and without risk factors:

- History and Physical examination: every 2 months for year 1, every 3 months for year 2, every 4-6 months for year 3, every 6 months for year 4 and annually for year 5
- Abdominal +/- pelvic CT scan: every 4-6 months for year 1, every 6 months for year 2, and annually for year 4;
- Chest CT scan: at month 4 and 12 for year 1, and annually from year 2 to 5

Clinical Stage IA/B after 1 cycle of adjuvant chemotherapy (BEP):

- History and Physical examination: every 3 months for year 1 and 2, every 6 months for year 3 and 4, and annually for year 5
- Abdominal +/- pelvic and chest CT scan: annually from year 1 to 5;

Clinical Stage II-III after complete response to chemotherapy:

- History and Physical examination: every 2 months for year 1, every 3 months for year 2, every 6 months for year 3, every 6 months for year 4, every 6 months for year 5
- Abdominal +/- pelvic and chest CT scan: every 6 month for year 1 and 2, and annually from year 3 to 5

4.4. Radiation Therapy

4.4.1. Radiation planning:

- Fertility assessment and sperm banking to be considered (needs to be performed prior to imaging and delivery of adjuvant therapy)
- Simulate in supine position. 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 the field to include left renal hilar nodes. If prior inguinal surgery, treat contralateral inguinal and iliac regions
- Timing – once wound has fully healed

4.4.2. Radiation Dose

- Generally: 20 Gy at 2Gy/fraction, and alternatively, 25.5 Gy at 1.5Gy/fraction; boost IIA nodes to 30 Gy and IIB nodes to 36 Gy

4.5. Chemotherapy

- BEP - Bleomycin, Etoposide, Cisplatin (Platinum) (strongly preferred as tolerance allows):
  - Etoposide 100 mg/m² IVon days 1-5
  - Cisplatin 20 mg/m² IV on days 1-5
  - Bleomycin 30 units IV weekly on days 1, 8 and 15 or days 2, 9 and 16; repeat every 21 days
- EP - Etoposide, Cisplatin (Platinum):
  - Etoposide 100 mg/m² IV on days 1-5
  - Cisplatin 20 mg/m² IV on days 1-5; repeat every 21 days
- VIP - Etoposide (VP-16), Ifosfamide, Cisplatin (Platinum):
  - Etoposide 75 mg/m² IV on days 1-5
  - Cisplatin 20 mg/m² IV on days 1-5
  - Ifosfamide 1200 mg/m² IV on days 1-5 with mesna protection; repeat every 21 days
- TIP - Paclitaxel (Taxane), Ifosfamide, Cisplatin (Platinum):
  - Paclitaxel 250 mg/m² IV on days 1-5
  - Cisplatin 25 mg/m² IV on days 2-5
  - Ifosfamide 1200 mg/m² IV on days 2-5 with mesna protection; repeat every 21 days
- VeIP - Vinblastine, Ifosfamide, Cisplatin (Platinum):
  - Vinblastine 0.11 mg/kg IV push on days 1-5
  - Ifosfamide 1200 mg/m² IV on days 2-5 with mesna protection
  - Cisplatin 20 mg/m² IV on days 2-5; repeat every 21 days
- GEMOX - Gemcitabine, Oxaliplatin:
  - Gemcitabine 1000-1250 mg/m² IV over 30 minutes on days 1 and 8 followed by
  - Oxaliplatin 130 mg/m² IV over 2 hours on day 1; repeated every 21-day cycle until disease progression or unacceptable toxicity

5. Follow-up

After RT for stage I seminoma

H&P, labs (AFP, b-HCG, LDH), and Chest X-Ray 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

F. Penile Cancer

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.

2. Work-up

- History and Physical Examination
- Consider cystourethroscopy with biopsy and bimanual exam under anesthesia if lesion is deep
- CBC, RFTs, LFTs, with alkaline phosphatase
- Ultrasound, MRI (penis), inguinal ultrasound, abdomen and pelvis CT scan
- HIV screening
- Biopsy of the lesion

3. Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (penile intraepithelial neoplasia)
Ta	Non-invasive 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)

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 Extra-Nodal Extension (ENE)
pN2	≥ 3 unilateral inguinal metastases or bilateral metastases, no ENE
pN3	ENE of lymph node metastases or pelvic lymph node metastases

M Staging

M Category	M Criteria
M0	No distant metastasis
M1	Distant Metastasis

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

4. Management

4.1. Treatment of primary tumor

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

4.1.1. Treatment T1s/Ta

– Topical therapy (5-FU) or Imiquimod or
– Circumcision
– Wide local excision
– Complete Glansectomy
– Moh's surgery

4.1.2. Treatment of T1, grade 1-2 (Early limited lesions, for RT alone – lesions should be T1-2, < 4cm)

– Wide local excision
– Partial penectomy
– Glansectomy, in select cases
– Radiation therapy, in select cases

Note: Consider – penis preservation (preferred): Circumcise first, then EBRT.

4.1.3. Treatment of T1, grade 3-4

– Wide local excision
– Total penectomy
– Radiation therapy
– Chemoradiotherapy, if not eligible for surgery

Note: Surgery – save for salvage; partial or radical penectomy; consider prophylactic inguinal node dissection with tumors extending onto shaft of penis/poorly differentiated; if node positive, need inguinal and pelvic lymph node dissection

4.1.4. Treatment of T2 or greater

– Partial or total penectomy
– Radiation therapy
– Chemoradiotherapy, if not eligible for surgery

Note: 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.

4.1.5. Treatment of T4 with invasion of other adjacent structures

– Neoadjuvant chemotherapy followed by surgery in patients with complete/partial response;
– Palliative EBRT

4.1.6. Treatment of metastatic disease

– Systemic chemotherapy
– Radiation therapy
– Chemoradiotherapy
– Best supportive care

4.1.7. Treatment of local recurrence after conservative treatment

– Salvage surgery

4.2. Principles of treatment

4.2.1. Topical therapy

Tis or Ta disease:

1. Imiquimod 5%, apply at night, three times per week for 4-16 weeks;
2. 5-FU cream 5%, apply twice daily for 2-6 weeks.

4.2.2. Surgery

a. Conservative surgery (penile organ-sparing approach)

- Wide local excision – for patients with skin confined lesions, with little or no invasion
- Surgical margins for wide local excision depend on the location of the penile tumor
- Circumcision may be reasonable for tumors of the distal prepuce
- Glansectomy to be considered for select patients with distal tumors on the glans or prepuce

b. Penectomy

- Partial penectomy to be considered the standard for high-grade primary penile tumors, provided a functional penile stump can be preserved and negative margins are obtained;
- Total penectomy – when invasion into corpora cavernosum, necessary to achieve negative margins

4.2.3. Chemotherapy

Preferred: 5-FU+ Cisplatin

- Continuous infusion 5-FU 800-1000 mg/m2/d IV on days 1-4 or days 2-5
- Cisplatin 70-80 mg/m2 IV on day 1; repeat every 3-4 weeks

4.2.4. Radiation Therapy

T1-2, N0 (tumor <4cm):

- EBRT (post-circumcision): total dose: 65-70 Gy with conventional fractionation with appropriate bolus to primary penile lesion with 2-cm margins
- EBRT with concurrent chemotherapy: total dose: 65-70 Gy with conventional fractionation with appropriate bolus to primary penile lesion with 2-cm margins
- Consider prophylactic EBRT to inguinal nodes in patients who are not surgical candidates or who decline surgical management

T1-2, N0 (tumor ≥4cm)

- Circumcision then EBRT with concurrent chemotherapy: 45-50.4 Gy to a portion of/or whole penile shaft depending on bulk and extent lesion + pelvic/inguinal nodes, then boost to primary lesion with 2-cm margins (total 65-70 Gy)

T3-4, N+ (surgically unresectable):

- Circumcision then EBRT with concurrent chemotherapy: 45-50.4 Gy to the whole penile shaft, pelvic lymph nodes, and bilateral inguinal lymph nodes, then boost primary lesion with 2-cm margins and gross lymph nodes (total 60-70 Gy)

Primary site margin positive following penectomy:

- Post –surgical EBRT: If no gross disease: 45-60 Gy to the primary site and scar; if gross disease present: follow guideline for T3-4, or N+
- Treat bilateral inguinal lymph nodes and pelvic lymph nodes if no or inadequate lymph node dissection

Adjuvant chemo-radiotherapy:

- Inguinal and/or pelvic lymph node positive
- Recommended for palpable bulky inguinal lymph nodes or enlarged pelvic lymph nodes; consider for palpable non-bulky inguinal lymph nodes (pN2-3) disease or for local recurrence to inguinal region
- Inguinal and pelvic lymph nodes EBRT to 45-50.4 Gy
- Boost gross nodes and areas of extracapsular extension to a total dose of 65-70 Gy

Treat primary site of disease if positive margin.

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.

GYNECOLOGICAL CANCERS

A. Epithelial Carcinoma of the Ovary, fallopian tube and peritoneum

1. Introduction

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

2. Workup

- History and General Physical
- Examination Baseline: FBP, RFT, LFT, CA-125, CEA, AFP
- Chest X-ray, Abdominal pelvic Ultrasound, CT-Scan (Abdomen and Pelvis) – if abdominal ultrasound is unclear on origin of tumor
- Ascitic fluid/peritoneal and pelvic washing cytology – if neoadjuvant chemotherapy is planned, and adds little to staging when done intra-operatively. If surgery is planned prior to chemotherapy, paracentesis is not indicated
- Histology of oophorectomy specimen

3. Staging

(The staging is surgical)

T Staging

T Category	T Staging
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to ovaries (one or both), or fallopian tubes
T1a	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	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	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
T1c1	Surgical spill
T1c2	Capsule rupture before surgery or tumor on ovarian or fallopian tube surface
T1c3	Malignant cells in ascites or peritoneal washings
T2	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
T2b	Extension to and/or implants on other pelvic tissues
T3	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	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes
T3c	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)

N Staging

N Category	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	Positive retroperitoneal lymph nodes only (histologically confirmed)
N1a	Metastasis up to and including 10 mm in greatest dimension
N1b	Metastasis more than 10 mm in greatest dimension

M Staging

Clinical M category	M Criteria
cM0	No distant metastasis
cM1	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	Pleural effusion with positive cytology
cM1b	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
Pathologic M Category	M Criteria
pM1	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	Pleural effusion with positive cytology, microscopically confirmed
pM1b	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

Note: The AJCC stage groups are similar to those of FIGO

4. Management

Treatment recommendations

- **Stage 1A/B Grade 1&2:** Cytoreductive surgery with surgical staging when possible > Observation
- **Stage IB- Grade 3:** Cytoreductive surgery > Adjuvant chemotherapy Stage IC/II: Cytoreductive surgery > Adjuvant chemotherapy
- **Stage III:** Neoadjuvant chemotherapy > Surgery > Adjuvant chemotherapy - surgical cytoreduction with adjuvant chemotherapy is also an option
- **Stage IV:** Manage abdominal disease as stage III +/- Palliation

a. Chemotherapy – first line

- Choice of regimen
- Carboplatin (AUC 6) and Paclitaxel (175 mg/m^2): given on day 1 of each 21-day cycle for a total of six cycles.

b. Chemotherapy for recurrent disease

- **The choice of a second-line regimen** depends on the disease-free interval.
- **If Disease-Free Interval ≥6 months (platinum-sensitive disease):** remission from completion of primary treatment - retreatment with:
  - IV Carboplatin (AUC 6) and IV Paclitaxel (175 mg/m^2): given on day 1 of each 21-day cycle for a total of six cycles. or
  - IV Docetaxel 100mg repeat every 3 weeks
  - IV Gemcitabine 1000mg D1 ,8 , 15 every 4 weeks or D1 , D8 every 3 weeks

- **If Disease-Free Interval < 6months (Platinum resistant)**
  - IV Docetaxel 100mg repeat every 3 weeks
  - IV Gemcitabine 1000mg D1, 8 and 15 every 4 weeks or D1, 8 every 3 weeks

A.1. Ovarian Germ Cell Tumors

Complete staging surgery

- Stage I dysgerminoma or Stage I, grade I immature teratoma
- Observe
- Any stage embryonal tumor or any stage yolk sac tumor or stage II-IV dysgerminoma or stage I , grade 2 or 3 or stage II-IV immature teratoma or any stage non gestational choriocarcinoma
- Chemotherapy
  - Imaging as clinically indicated
  - Complete clinical response then observe
  - Residual tumor on imaging; markers normal
- Consider surgical resection or observe or additional chemotherapy x 2 cycles
  - Persistent elevated markers with definitive residual disease
- TIP (Paclitaxel/Ifosfamide/Cisplatin)

Chemotherapy for Malignant Cell and Sex Cord Stromal Tumors

- BEP (Bleomycin + Etoposide + Cisplatin)
- IV Cisplatin 20mg/m2 D1 to D5
- IV Etoposide 100mg/m2 D1 to D5
- IV Bleomycin 30 units D1, 8 , 15

Repeat cycle every 3 weeks for 3-4 cycles depending on residual disease at time of surgery

5. Follow-up

- First and second years: 3 monthly followup:
- Physical Examination
- Laboratory investigations: FBP, RFT, LFT, CA-125 for germ cell tumors and sex cord stromal tumors follow specific tumor markers
- Imaging investigations: Chest XRay, Ultrasound (abdomen and pelvis), CT- Scan (abdomen and pelvis) when indicated for suspicion of recurrence
- Year 3 and onward: 6 monthly follow- up - same details

B. Cervical Cancer

1. Introduction

Cervical cancer is the leading cause of cancer death in women worldwide. Persistent human papilloma virus infection is the most important factor in the development of cervical cancer.
Clinical Presentation:

- Asymptomatic in Early stage of the disease
- Majority present with abnormal vaginal bleeding (post-coital, inter- menstrual, post-menopausal)
- Foul smelling discharge, pelvic pain and incontinence (Vesico-Vaginal Fistula or Recto-Vaginal Fistula) - symptoms of late disease.

2. Workup

- History and physical examination (H&P)
- Laboratory tests: FBC, LFTs, RFTs, HIV testing
- Cervical biopsy for pathologic review; pap smear wherever applicable, and preferably where pathologists are available
- Imaging

Stage I

- Consider Chest xray .If an abnormality is seen ,then chest CT without contrast may be performed
- Consider Chest/abdomen/pelvic CT in FIGO stage IB1-IB2
- Chest/abdomen/pelvic CT in FIGO stage IB3

For patients who underwent total hysterectomy with incidental finding of cervical cancer, chest/abdomen/pelvic CT to evaluate for metastatic disease and pelvic MRI to assess pelvic residual disease.

Stage II-IV

- Kidney/hydronephrosis can be assessed by US or IVP
- Chest/abdomen/pelvic CT to evaluate for metastatic disease.

3. Staging

AJCC

T Category	T Criteria
Tx	Primary tumor cannot be assessed
T0	Evidence of primary tumor
T1	Cervical carcinoma confined to the uterus (extension to corpus should be disregarded)
T1a	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	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	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	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	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	Tumor without parametrial invasion
T2a1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	Tumor with parametrial invasion
T3	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	Tumor extending to the pelvic wall and/or causing hydronephrosis or non functioning kidney
T4	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)

Note: 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.

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

FIGO

- **Stage I** - The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
- **Stage IA** - Invasive carcinoma that can be diagnosed only by microscopy with deepest invasion <5 mm.
- **Stage IA1** -Measured stromal invasion of <3 mm.
- **Stage 1A2** -Measured stromal invasion of ≥3.0 mm and <5.0 mm.
- **Stage IB** – Invasive carcinoma with measured deepest invasion ≥ 5mm, lesion limited to the cervix
- **Stage IB1** – Invasive carcinoma ≥ 5mm depth of stromal invasion, and <2cm in greatest dimension
- **Stage IB2** – Invasive carcinoma ≥ 2cm and <4cm in greatest dimension
- **Stage IB3** – Invasive carcinoma ≥ 4cm in greatest dimension

- **Stage II** - Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina.
- **Stage IIA** – Involvement limited to the upper 2/3 of the vagina without parametrial invasion.
- **Stage IIA1** – Invasive carcinoma <4 cm in greatest dimension.
- **Stage IIA2** – Invasive carcinoma ≥4.cm in greatest dimension.
- **Stage IIB** - With parametrial invasion but not to the pelvic sidewall.
- **Stage III** - The tumor involves the lower third of the vagina and/or extends to the pelvic sidewall and/or causes hydronephrosis or non functioning kidney and/or involves the pelvic and/or paraaortic lymph nodes
- **Stage IIIA** - Tumor involves the lower third of the vagina with no extension to the pelvic wall.
- **Stage IIIB** - Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.
- **Stage IIIC**- Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations) *
- **Stage IIIC1**-Pelvic lymph node metastasis only
- **Stage IIIC2**-Para-aortic lymph node metastasis
- **Stage IV** - The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum
- **Stage IVA** - Spread of the growth to adjacent organs.
- **Stage IVB** - Spread to distant organs.
- **Stage IA1**- Satisfies IA criteria and measured stromal

4. Management

Stage 1A1, no LVSI

Cone biopsy if not already done

- Negative margins & inoperable
  - Observe or
  - Brachytherapy in selected cases
- Negative margins & operable
  - Observe
  - Extrafascial hysterectomy(abdominal or vaginal)
- Unknown margins
  - Repeat cone biopsy
- If negative treat as negative margins above
  - If positive Extra-fascial or modified radical hysterectomy +/- pelvic LN dissection if margins are positive for carcinoma dependent on total depth of invasion of both cone biopsies
- Positive margins and not a surgical candidate-Brachytherapy+/- pelvic EBRT
- Positive margins and operable
  - Extra-fascial or modified radical hysterectomy +/- pelvic LN dissection if margins are positive for carcinoma

- Positive margins and inoperable
  - Brachytherapy+/- pelvic EBRT

STAGE 1A1, with LVSI and Stage 1A2

- Modified radical hysterectomy+pelvic lymph node dissection (consider SLN mapping or
- Pelvic EBRT + brachytherapy

Stage IB1,IB2 and Stage IIA1

- Radical hysterectomy+pelvic lymph node dissection +/-neoadjuvant chemotherapy for stage IIA1 if deemed unresectable upfront +/- Postoperative concurrent chemo-radiotherapy if positive pelvic nodes and/or positive surgical margin and/or positive parametrium or
- Pelvic EBRT+brachytherapy +/- concurrent platinum containing chemotherapy

Stage IB3 and stage IIA2

Definitive pelvic EBRT+Concurrent platinum containing chemotherapy+brachytherapy (preferred) or

- Radical hysterectomy+pelvic lymph node dissection+/- neoadjuvant chemotherapy or
- Pelvic EBRT+ Concurrent platinum-containing chemotherapy + brachytherapy+ selective adjuvant hysterectomy

Stage IIB, III, IVA

- Definitive pelvic EBRT+Concurrent platinum containing chemotherapy+brachytherapy or
- Pelvic EBRT+ Concurrent platinum-containing chemotherapy+ tailored EBRT boost (if no brachytherapy available)

Note: Post

Recurrent and Metastatic disease

Local/regional recurrence

- No prior RT or failure outside of previously treated field
  - Consider surgical resection if feasible
  - Individualized EBRT+systemic therapy +/- brachytherapy

If second recurrence then

  - Systemic therapy or best supportive care

- Prior RT
  - Individualized EBRT +/- systemic therapy or
  - Systemic therapy
  - Best supportive care
- Metastatic disease
  - Systemic therapy +/- individualized RT
  - Best supportive care

Radiotherapy details

Definitive Radiotherapy

- Primary tumor and regional lymphatics at risk are typically treated with External Beam Radiotherapy with 40-50Gy in 1.8-2Gy/fraction.
- The primary tumor is then boosted using brachytherapy with additional 30-40Gy to point A. Fractionations are as follow;
  - 5.5Gy x 5 fractions for early disease and
  - 6Gy x 5 fractions for large tumors.
- Involved nodes can be boosted with additional 10-15Gy of highly conformal EBRT.
- EBRT conformal boost can be used in absence of brachytherapy to a dose equivalent to that of brachytherapy. Caution should be taken for organs at risk.

Chemotherapy details

Chemoradiation

- IV cisplatin 40mg/m2
- IV carboplatin if patient is cisplatin intolerant
- Neoadjuvant/adjuvant chemotherapy, the same regimen is used as the first line for recurrent and metastatic disease.
- IV carboplatin AUC =5-6 or IV cisplatin /IV Paclitaxel 175mg/m2.
- Use AUC of 6 ; if prior pelvic radiation therapy , use AUC of 5

5. Follow-Up

- Interval history and physical exam
  - Every 3-6 months for 2 years (3 months for those treated with curative intent)
  - Every 6-12 months for 3-5 years then (6 months for those treated with curative intent)
  - Annually based on patient's risk of disease recurrence
- Imaging as indicated based on symptoms or examination findings suspicious for recurrence
- Laboratory assessment as indicated – FBC, LFTs, RFTs
- Consider hormone replacement therapy in selected cases
- Patient education regarding lifestyle, exercise, sexual health etc
- Biopsy if indicated.

C. Vulva Cancer

1. Introduction

Clinical Presentation:

- Lump or vulva mass
- Presence of leukoplakia and other dystrophic change
- Itching is a common manifestation and may become ulcerative

2. Workup

- History and physical examination (H&P)
- Laboratory tests: FBC, LFTs, RFTs, HIV testing
- Any suspicious lesion should be biopsied for pathologic review
- Cervical cancer screening
- Imaging
  - Chest Xray and if an abnormality is seen , then chest CT without contrast may be performed.
  - Consider pelvic MRI to aid in surgical and/or radiation treatment planning.
  - Consider Chest/abdomen/pelvis CT for T2 or larger tumors or if metastasis is suspected

3. Staging

T Staging

T Category	T Staging
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	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	Lesions 2 cm or less, confined to the vulva and/or perineum, and with stromal invasion of 1.0 mm or less
T1b	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	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	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

N Staging

N Category	N Staging
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 with one or two lymph node metastases each less than 5 mm, or one lymph node metastasis ≥5 mm
N1a	One or two lymph node metastases each less than 5 mm
N1b	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	3+ lymph node metastases each less than 5 mm
N2b	Two or more lymph node metastases ≥5 mm
N2c	Lymph node(s) with extra-nodal extension
N3	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.

M Staging

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 Staging
cM0	No distant metastasis (no pathological M0; use clinical M to complete stage group)
cM1	Distant metastasis (including pelvic lymph node metastasis)
pM1	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

FIGO STAGING

- **Stage I** - Tumor confined to the vulva
  - **Stage IA**- Tumor size ≤2 cm and stromal invasion ≤1 mma
  - **Stage IB**- Tumor size >2 cm or stromal invasion >1 mma
- **Stage II** - Tumor of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes
- **Stage III** - Tumor of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node
  - **Stage IIIA** - Tumor of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm
  - **Stage IIIB** - Regionalb lymph node metastases >5 mm
  - **Stage IIIC** - Regionalb lymph node metastases with extracapsular spread
- **Stage IV** - Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases
  - **Stage IVA** - Disease fixed to pelvic bone, or fixed or ulcerated regionalb lymph node metastases
  - **Stage IVB** - Distant metastases

4. Management

4.1. Early Stage (T1, smaller T2)

T1a<1mm invasion

- Partial superficial vulvectomy and observe if negative margins

T1b >1mm invasion or T2 or T1 with unknown depth of invasion

- Radical partial vulvectomy & ipsilateral +/- bilateral (central lesions) inguinofemoral lymph node evaluation and/or lymphadenectomy.
  - Negative margins
    - Observe
    - Adjuvant EBRT based on other risk factors
  - If Positive margins
    - Re-excise and if negative margins
    - Observe or adjuvant EBRT based on other risk factors
  - If positive margins
    - Adjuvant EBRT
  - Unresectable without exenterative approach
    - Adjuvant EBRT
  - Positive Lymph nodes
    - EBRT+/-concurrent chemotherapy

Locally advanced (Larger T2, T3)

- Radiographically negative nodes
  - EBRT+ Concurrent chemotherapy to primary tumor/inguinofemoral LNs/pelvic nodes
  - Inguinofemoral lymphadenectomy
    - Positive LNs
  - EBRT+ concurrent chemotherapy to primary tumor/inguinofemoral LNs/pelvic nodes
    - Negative LNs
  - EBRT+ concurrent chemotherapy to primary tumor (+/-Selective inguinofemoral LN coverage)
- Radiographically positive (includes pelvic confined M1, LN disease)
  - Inguinofemoral Lymphadenectomy
    - Positive LNs
      - EBRT+concurrent chemotherapy to primary tumor/inguinofemoral LNs/pelvic nodes
    - Negative LNs
      - EBRT+concurrent chemotherapy to primary tumor (+/-Selective inguinofemoral LN coverage)
  - Inguinofemoral lymphadenectomy not performed
    - Consider FNA for enlarged LN
    - EBRT+Concurrent chemotherapy to primary tumor/inguinofemoral LNs/ pelvic nodes

Recurrent/residual tumor

- Vulva confined recurrence (nodes clinically negative) not previously irradiated
  - Partial or total radical vulvectomy +/- unilateral or bilateral inguinofemoral lymphadenectomy. Depending or surgical outcomes
  - Observe (For negative margins and negative LNs)
- Positive margins or LNs surgically positive
  - EBRT+/-Concurrent chemotherapy
  - Complete response – then follow up
- Gross residual vulvar tumor
  - Resection
- Vulva confined recurrence (nodes clinically negative) previously irradiated
  - Partial or total radical vulvectomy+/- unilateral or bilateral inguinofemoral lymphadenectomy. Depending or surgical outcomes
    - Observe (For negative margins and negative LNs)
  - Positive margins or LNs surgically positive
    - EBRT+/-Concurrent chemotherapy
    - EBRT+/- concurrent chemotherapy
- Complete response then follow-up
- Gross residual disease
  - Resection

- Vulva confined recurrence (nodes clinically negative) previously irradiated
  - Assess for resectability
    - Resectable
      - Partial or total radical vulvectomy for gross residual disease
    - Unresectable
      - Chemotherapy or best supportive care
- Metastatic disease beyond pelvis (any T, any N, M1 beyond pelvis)
  - EBRT for locoregional control/symptom palliation and or
  - Systemic therapy
  - Best supportive care

Radiotherapy Details

- The target tissues should be treated once daily, 5 days per week.
- Doses range from 45-50.4Gy in 25-28 fractions (1.8Gy /fraction) for adjuvant therapy to 59.4-64.8Gy in 33-36 total fractions (1.8Gy/fraction) for unresectable disease.
- For bulky or persistent primary disease or large nodes that are unresectable may be boosted to 70Gy

Suggested dosing to areas of risk:

- Gross Primary vulva disease = 60-70Gy
- Primary surgical bed (post-op,negative margins)=45-50Gy
- Primary surgical bed (post op close or positive margins)=54-60Gy
- Clinically and /or radiographically uninvolved inguinofemoral LNs=45-50Gy
- Inguinalfemoral LNs (positive,no extracapsular extension[ECE] or gross residual disease)=50-55Gy
- Inguinofemoral LNs(ECE)=54-64Gy
- LNs (gross residual or unresectable disease) =60-70Gy

Systemic Therapy

Chemoradiation

- IV cisplatin 40mg/m^2 Weekly
- Chemotherapy for advanced, recurrent/metastatic disease
- IV paclitaxel 175mg/m^2 over followed by V carboplatin AUC 5 -6 or IV cisplatin 50mg/m^2 Repeated every 3 weeks for predetermined cycles.

OR

- IV paclitaxel 175mg/m^2 over followed by
- IV carboplatin AUC 5-6 or IV cisplatin 50mg/m^2
- IV Bevacizumab 15mg/kg
- Repeated every 3 weeks for predetermined cycles.
- Use AUC of 6 ; if prior pelvic radiation therapy , use AUC of 5

5. Follow- up

Interval history and physical exam:

- Every 3-6 months for 2 years
- Every 6-12 months for 3-5 years then
- Annually based on patient's risk of disease recurrence
- Imaging as indicated based on symptoms or examination findings suspicious for recurrence
- Cervical/vaginal cytology screening as indicated.
- Laboratory assessment – FBC, LFTs, RFTs
- Consider hormone replacement therapy in selected cases
- Patient education regarding lifestyle , exercise , sexual health etc
- Among patients with HIV, optimize HIV care

D. Uterine Cancers

D. 1. Endometrial Carcinoma

1. Introduction

This is predominantly a disease of older women, typically for women above 60-65 years of age, but can occur at any age. Adenocarcinoma is the most common histological type. Risk factors for endometrial carcinoma include obesity, diabetes, high fat diet, early age at menarche, nulliparity and late age at menopause, advanced age and use of tamoxifen.
Clinical Presentation: Abnormal uterine bleeding for premenopausal women or post-menopausal bleeding.

2. Workup

- History and Physical Examination
- FBP, RFT, LFTs,
- Curettage biopsy is recommended
- Chest /abdomen/pelvic CT
- For patients who underwent TH with incidental finding of uterine sarcoma or incompletely resected uterus/adnexa perform chest/abdominal/pelvic CT or chest without contrast to evaluate for metastatic disease.
- Endometrial Biopsy to confirm diagnosis

3. Staging

TNM Classification
T Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to the corpus uteri, including endocervical glandular involvement
T1a	Tumor limited to the endometrium or invading less than half the myometrium
T1b	Tumor invading one half or more of the myometrium
T2	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus. Does NOT include endocervical glandular involvement
T3	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
T3b	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

N Staging

N Category	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 to pelvic lymph nodes
N1mi	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to pelvic lymph nodes
N1a	Regional lymph node metastasis (greater than 2.0 mm in diameter) to pelvic lymph nodes
N2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

Note: 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	M Criteria
cM0	No distant metastasis
cM1	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	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone), microscopically confirmedIt 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

FIGO STAGING

- **Stage I** - Confined to the uterine corpus and ovary
  - IA - Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
  - IA1 - Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
  - IA2 - Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
  - IA3 - Low-grade endometrioid carcinomas limited to the uterus and ovaryc
  - IB - Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSId
  - IC - Aggressive histological typese limited to a polyp or confined to the endometrium
- **Stage II** - Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
  - IIA - Invasion of the cervical stroma of non-aggressive histological types
  - IIB - Substantial LVSId of non-aggressive histological types
  - IIC - Aggressive histological typese with any myometrial involvement
- **Stage III** - Local and/or regional spread of the tumor of any histological subtype
  - IIIA - Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
  - IIIA1 - Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)c
  - IIIA2 - Involvement of uterine subserosa or spread through the uterine serosa
  - IIIB - Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
  - IIIB1 - Metastasis or direct spread to the vagina and/or the parametria
  - IIIB2 - Metastasis to the pelvic peritoneum
  - IIIC - Metastasis to the pelvic or para-aortic lymph nodes or bothf
  - IIIC1 - Metastasis to the pelvic lymph nodes
  - IIIC1i - Micrometastasis
  - IIIC1ii - Macrometastasis
  - IIIC2 - Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
  - IIIC2i - Micrometastasis
  - IIIC2ii - Macrometastasis
- **Stage IV** - Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
  - IVA - Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
  - IVB - Abdominal peritoneal metastasis beyond the pelvis
  - IVC - Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

4. Management

Disease limited to the uterus (endometrioid histology)

- Suitable for surgery
  - °Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) and surgical staging then adjuvant treatment as per stage
- Not suitable for primary surgery
  - °EBRT+/- Brachytherapy or
  - °Consider hormone therapy in select patients

Gross cervical involvement (endometrioid histology)

- Medically operable/suitable for surgery
  - °TAH/BSO or modified radical hysterectomy and surgical staging followed for adjuvant treatment (Stage III-IV)
- Not medically suitable for primary surgery
  - °EBRT+/-Brachytherapy+/-systemic therapy and surgical resection if rendered operable

Suspected extrauterine disease

- Suitable for primary surgery
  - °No evidence of extrauterine disease then treat as limited to uterus as above

Abdominal/pelvic confined disease

- °TAH/BSO +Surgical staging/debulking (Consider preoperative chemotherapy

Distant metastasis

- °Systemic therapy and /or EBRT
- °Consider palliative TB/BSO

- Not suitable for primary surgery

Locoregional disease

- °EBRT+/-Brachytherapy+/-systemic therapy or best supportive care
- °Hormonal therapy

Distant metastasis

- °Systemic therapy and re-evaluate for surgical resection and/or RT based on response.

Adjuvant treatment for surgically staged

STAGE IA

- °G1, G2

- Observation preferred or
- Consider vaginal brachytherapy if lymphovascular space invasion(LVSI) and/or age >60 years
  - °G 3
- Vaginal brachytherapy preferred or
- Consider observation if no myoinvasion or
- Consider EBRT if high intermediate risk (HIR)

STAGE IB

- °G1,
- Vaginal brachytherapy preferred or consider EBRT if no VB or
- Consider observation if no other adverse risk factors
- °G2
- Vaginal brachytherapy preferred or
- Consider EBRT if HIR or
- Consider observation if no other adverse risk factors
- °G 3
- RT (EBRT and/or vaginal brachytherapy

STAGE II

- °G1-3
- EBRT (preferred) and/or vaginal brachytherapy +/- systemic therapy or
- Systemic therapy

STAGE III, V

- Systemic therapy +/- EBRT+/- vaginal brachytherapy

Incompletely surgically staged

- Stage IA, G1-2 and no LVSI and age <60 or Stage IA, G3 and age <60 and no myometrial invasion
  - °Observe
- Stage IA , G3 or stage IB , G1-2 and Age >60 and no LVSI
  - °Consider imaging then
    - – Vaginal brachytherapy or Observation if vaginal brachytherapy unavailable
- Stage IA, G1-3 and LVSI , Stage IB , G1-2 and LVSI , stage IB ,G3+/-LVSI and stage II

Imaging

- °Negative: Treat as stage I or Stage II
- °Suspicious /Positive
- °EBRT

Other histologies

Serous carcinoma or clear cell carcinoma or undifferentiated/dedifferentiated carcinoma or carcinosarcoma

- Consider CA 125 and imaging

Suitable for primary surgery (TH/BSO and surgical staging)

Stage I

- Systemic therapy + vaginal brachytherapy (preferred)
- EBRT + VB or
- Vaginal brachytherapy in select cases of non-invasive disease
- Observe

Stage IB, II, III, IV

- Systemic therapy +/-EBRT+/- VB

Not suitable for primary surgery

- Systemic therapy and /or EBRT +/- Brachytherapy then re-evaluate for surgery
  - Surgical resection then consider additional systemic therapy
  - If unresectable consider best supportive care

D.2. Uterine Sarcoma

Low grade Endometrial Stromal Sarcoma (ESS)
Stage I
- TAH/BSO (Preferred) or observe especially if menopausal or prior BSO

Stage II, III, IVA
- TAH/BSO +/- anti estrogen hormone therapy +/-EBRT

Stage IVB
- TAH/BSO +/- anti-estrogen hormone therapy +/- palliative EBRT

High grade ESS, Undifferentiated Uterine Sarcoma (UUS), Undifferentiated Leiomyosarcoma (ULMS)

- Stage I: Observe
- Stage II, III: Consider systemic therapy and/or consider EBRT
- Stage IVA: Systemic therapy and/or EBRT
- Stage IVB: Systemic therapy +/- palliative EBRT

5. Follow-Up

- Physical exam every 3-6 month for 2 years
- Physical exam every 6 months until 5 years, then annually
- CA 125 if initially elevated
- Imaging as clinically indicated
- Patient education regarding symptoms of potential recurrence, lifestyle, obesity, exercise, smoking cessation and sexual health.

Recurrence
Locoregional recurrence (no distant metastasis)
- No prior EBRT to site of recurrence
  - EBRT+/-Brachytherapy +/-systemic therapy and/or surgical resection or best supportive care
- Prior EBRT to site of recurrence
  - Systemic therapy or best supportive care

Chemotherapy Regimen
Cytotoxic therapy for High-Risk Disease inoperable, metastatic or recurrent disease is:
- IV Paclitaxel 175mg/m² followed by
- IV Carboplatin AUC 6
- Repeat every 3 weeks for 6 cycles.

For carcinosarcoma

- IV Paclitaxel 135mg/m² and Carboplatin AUC 6

For Uterine sarcoma

- IV doxorubicin
- Aromatase inhibitors for low grade ESS for ER/PR +
  - Anastrozole
  - Exemestane
  - Letrozole

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.

E. Vaginal Cancer

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.

2. Workup

- FBC, LFTs, RFTs, HIV testing
- Bimanual and rectal exam, speculum exam with Colposcopy and directed biopsies
  - Tissue biopsy
  - 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.

3. Staging

TNM Staging

T Staging

T Category	T Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to the vagina
T1a	Tumor confined to the vagina, measuring ≤2.0 cm
T1b	Tumor confined to the vagina, measuring >2.0 cm
T2	Tumor invading paravaginal tissues but not to pelvic sidewall
T2a	Tumor invading paravaginal tissues but not to pelvic wall, measuring ≤2.0 cm
T2b	Tumor invading paravaginal tissues but not to pelvic wall, measuring >2.0 cm
T3	Tumor extending to the pelvic sidewall* and/or causing hydronephrosis or nonfunctioning kidney
T4	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.

N Staging

N Category	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	Pelvic or inguinal lymph node metastasis

M Staging

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…
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

FIGO STAGING

- **Stage I** - Limited to the vagina
- **Stage II** - Invading paravaginal tissues, but not to pelvic sidewall
- **Stage III** - Extending to the pelvic wall and/or the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney; with or without metastases to inguinal lymph nodes
- **Stage IV** - Extending beyond the true pelvis and/or involving the bladder or rectal mucosa and/or distant metastases (lung or bones); with or without metastases to nearby lymph nodes

4. Management

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
High grade I or any II (>0.5 cm thick and > 2cm, high grade I	EBRT to whole pelvis ± inguinal LN to 45 Gy .
III	EBRT to whole pelvis to 45–50 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, frog-legged with custom immobilization, full bladder, PO contrast. Consider bladder full and empty scans to generate vaginal ITV.Consider IV contrast. Place markers at tumor for delineation and fuse with MRI to define tumor extent

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.

Systemic Therapy

- **Chemoradiation**
  - IV cisplatin 40mg/m² Weekly

Chemotherapy for advanced, recurrent/metastatic disease

- IV paclitaxel 175mg/m² over followed by
- IV carboplatin AUC 5 or IV cisplatin 50mg/m²
- Repeated every 3 weeks for predetermined cycles.

Or

- IV paclitaxel 175mg/m² over followed by
- IV carboplatin AUC 5 or IV cisplatin 50mg/m²
- IV Bevacizumab 15mg/kg
- Repeated every 3 weeks for predetermined cycles.

5. Follow-up

- Interval history and physical exam
  - Every 3-6 months for 2 years (3 months if initial treatment was surgical resection)
  - Every 6-12 months for 3-5 years (6 months if initial treatment was surgical resection) then
  - Annually based on patient's risk of disease recurrence
- Imaging as indicated based on symptoms or examination findings suspicious for recurrence
- Cervical cytology screening as indicated.
- Laboratory assessment – FBC, LFTs, RFTs
- Consider hormone replacement therapy in selected cases
- Patient education regarding lifestyle, exercise, sexual health etc
- Among patients with HIV, optimize HIV care

F. Gestational Trophoblastic Neoplasia

1. Introduction

Malignant gestational trophoblastic disease (GTD) is the persistence of gestational trophoblastic tissue, usually following a molar pregnancy. Malignant GTD includes invasive mole and choriocarcinoma, but since treatment is usually the same for both, exact histologic diagnosis is usually not necessary.
The presence of malignant GTD can become apparent clinically (for example, through persistent bleeding following a pregnancy or evidence of disease or metastases on physical exam), radiologically (for example, through persistent molar tissue noted on pelvic ultrasound or evidence of metastases on other imaging), or hormonally (through a persistently elevated beta HCG level).

2. Workup

Diagnosis is confirmed by the presence of a **persistently elevated or rising** beta HCG level >= 3 weeks after evacuation of a molar pregnancy. Note: Evacuation of the uterus must occur to rule out other explanations for persistently elevated HCG or bleeding after a pregnancy, such as retained products of conception, unless invasive mole suspected by ultrasound or MRI.. Ectopic pregnancy should also be considered.

Diagnosis is supported by:

1. Clinical symptoms such as persistent abnormal vaginal bleeding or evidence of metastases on physical exam;
2. Persistent molar tissue on pelvic ultrasound or evidence of metastases on imaging;
3. Pathologic diagnosis of molar tissue upon repeated evacuation of the uterus. However, pathologic diagnosis is NOT required for diagnosis and to initiate treatment. Invasive moles and suspected vaginal metastasis should NOT be biopsied due to risk of severe hemorrhage.

Histologic types:

- Invasive mole
- Choriocarcinoma
- Placental site trophoblastic tumor (PSTT) Epithelioid trophoblastic tumor (ETT)

Investigations

- Serum β-hCG level
- FBC, LFT, RFT, TSH, T3, T4
- Abdominal and Pelvic US
- CXR (CT of chest if lung mets suspected but not confirmed on CXR)
- Abdominal and Pelvic USS or CT Scan Brain MRI
- Brain MRI if metastatic disease confirmed and symptoms of brain mets
- Tissue sample for histology CSF hCG level

3. Staging

TNM Classification – T Staging

T Category	T Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to uterus
T2	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	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
cM1a	Lung metastasis
cM1b	All other distant metastases
pM1	Distant metastasis, microscopically confirmed
pM1a	Lung metastasis, microscopically confirmed
pM1b	Distant metastasis, microscopically confirmed

Prognostic Factors Required for Stage Grouping Risk Score

Risk Score	0	1	2	4
Age (Years)	<40	≥40		
Antecedent (pregnancy	Hydatiform Pregnancy	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 metastases identified		1-4	5-8	>8
Previous failed chemotherapy			Single Medicine	2+ medicines

FIGO STAGING - Should be reported as stage and score from chart above Stage: Score

- **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

4. Management

- **Surgery:** For women not desiring future fertility, hysterectomy should be performed, especially for women with choriocarcinoma.
- **Chemotherapy:** The use of adjunctive chemotherapy is advisable in patients with malignant GTN because of the probability of occult metastases.

Pre-chemotherapy evaluation and monitoring during chemotherapy:

1. All patients should start a family planning method (oral contraceptives, implants, or injection) prior to starting chemotherapy.
2. Check (FBC), ALAT/ ASAT, and creatinine prior to each cycle of chemotherapy.
3. Check beta-HCG prior to each cycle of chemotherapy.
4. Hold or delay chemotherapy if there are the following side effects:
   - Neutropenia (absolute neutrophil count < 1500)
   - Hepatotoxicity (ALAT or ASAT > 2x the upper limit of normal)
   - Renal toxicity (creatinine > 1.5x the upper limited of normal)
   - Severe gastrointestinal distress or oral ulcerations

Chemotherapy regimens by stage:
Stage 1 or low-risk (WHO score <=6) Stage II or III:

1. Methotrexate 0.4 mg/ kg PO once a day for five days every two weeks; OR
2. Methotrexate 0.4 mg/ kg IM (max 25 mg/ day) once a day for five days every two weeks

Monitoring:

- Check beta-HCG level prior to every treatment course (every two weeks)
- Repeat 5-day treatment course until beta-HCG levels have been normal (negative) for 2 consecutive measurements, then give two more 5-day course.
- The disease should be considered resistant to single-agent chemotherapy and EMA/CO should be initiated (see below) if:
  - Beta-hCG level plateau of 3 values over a 4-week duration (plus/minus 10%)
  - Beta-hCG level increase >10% of 2 values recorded over a 2-week duration.

Stage IV or high-risk (WHO score ≥ 7) Stage II or III or resistance to single-agent Chemotherapy:

Combination chemotherapy with EMA/CO: etoposide, methotrexate, and dactinomycin (Day 1-2) followed by cyclophosphamide and vincristine (Day 8) for 14-day cycles;

- Etoposide: 100 mg/m^2 IV over 30 minutes on days 1 and 2
- Methotrexate: 100 mg/m^2 IV push followed by 200 mg/m^2 IV over 12 hours on day 1
- *Leucovorin:* 15 mg orally every 12 hours for four doses, starting 24 hours after start of MTX
- Dactinomycin: 0.5 mg IV bolus on days 1 and 2
- Cyclophosphamide: 600 mg/m^2 IV on day 8
- Vincristine: 1.0 mg/m^2 IV on day 8

Monitoring:

- Check beta-HCG level prior to every treatment course (every two weeks)
- Repeat the above regimen every two weeks until remission, i.e. normal (negative) beta-HCG levels (negative) and disappearance of clinically evident disease, and then continue for an additional 3 cycles (six weeks).

EMA/EP (or EP/EMA) regimen is considered the most appropriate therapy for patients who have responsed to EMA/CO but have plateauing low hCG levels or developed re-elevation of hCG after a complete response to EMA/CO

- EMA/EP: Etoposide, Methotrexate, Dactinomycin/Etoposide, Cisplatin(repeat every 2 weeks)
- Etoposide: 100 mg/m^2 IV over 30 minutes on days 1 and 2
- Methotrexate: 100 mg/m^2 IV push followed by 200 mg/m^2 IV over 12 hours on day 1
- Leucovorin: 15 mg orally every 12 hours for four doses, starting 24 hours after start of MTX
- Dactinomycin: 0.5 mg IV bolus on days 1 and 2
- Etoposide 100mg/m^2 IV on day 8
- Cisplatin 75 mg/m^2 IV on day 8
- Filgrastim 300mcg SC for 3-5 days following chemotherapy during each cycle.

Therapy for Methotrexate -Resistant High risk GTN

TP/TE: Paclitaxel, Cisplatin/Pacliatxel, Etoposide (Repeat every 2 weeks)

- Paclitaxel 135mg/m^2 IV infusion on Day 1
- Ciplatin 75mg/m^2 IV on Day 1

Alternating every 2 weeks with:

- Paclitaxel 135mg/m^2 on Day 15
- Etoposide 150mg/m^2 IV on Day 15
- Filgrastim 300mcg SC for 3-5 days following chemotherapy during each cycle.

5. Follow-up

Patients who have completed chemotherapy and have hormonal and radiographic evidence of remission can be followed every month x **3 months**, and then every **3 months**, for one year. Beta HCG should be checked at each visit.

****Family Planning****

All patients with active malignant GTN, including those who are on treatment, must be on effective family planning methods. Patients with non-metastatic disease should continue family planning for **12 months** following completion of chemotherapy. Patients with metastatic disease should continue family planning for **24 months** following completion of chemotherapy.

HAEMATOLOGICAL NEOPLASMS

Hematological malignancies

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 common subtopics:

1. Hodgkin Lymphoma (HL)
2. Non- Hodgkin Lymphoma (NHL)
3. Acute Myelogenous Leukemia (AML)
4. Acute Lymphoblastic Leukemia (ALL)
5. Chronic Myelogenous Leukemia (CML)
6. Chronic Lymphocytic Leukemia (CLL)
7. Multiple Myeloma (MM)

A. Hodgkin lymphoma

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, and
- Lymphocyte-depleted

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

Clinical Presentation:

- Enlarging, painless lymph nodes
- Mediastinal mass with respiratory compromise
- Abdominal mass with early satiety or other abdominal symptoms
- May also present as extranodal disease (bone, liver, spleen, lung)
- Pruritus
- "B" symptoms: fever, night sweats, or >10% weight loss

2. Workup

- History and Physical exam including B symptoms (fever >380c, drenching night sweats, or >10% weight loss), alcohol intolerance, pruritus , fatigue , performance status, examination of lymphoid regions , spleen and liver
- Tissue diagnosis: Core needle biopsy of lymph node or Excisional lymph node biopsy(recommended) or Incisional biopsy of extra-nodal site of involvement or

Note: fine needle aspirate (FNA) is NOT adequate to make the diagnosis

- Histologic and immunohistochemical evaluation by Pathology
- Laboratory work up: Full blood count and differential, Creatinine , Liver function tests , HIV test , Hepatitis B and C serologies , Lactate dehydrogenase (LDH) Pregnancy test in women with childbearing potential

- Bone marrow examination for staging if there cytopenias
- Pneumococcal, meningococcal vaccines, if splenic RT contemplated
- CSF cytology in all patients with neurologic symptoms and all HIV+ patients (if available)
- Radiological work up
- CXR
- Staging CT chest/abdomen/pelvis
- Echocardiogram to assess baseline cardiac function (for patients who will be receiving doxorubicin)

3. Staging

Ann Arbor

Stage	Criteria
I	Involvement of a single lymph node region (e.g cervical , axillary , inguinal , mediastinum) or of a single extralymphatic organ such as the spleen , thymus or waldeyer's ring
II	Involvement of 2 or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be "lateralized" and when involved on both sides, constitute stage II disease. For the purpose of defining the number of anatomic regions, all nodal disease within the mediastinum is considered to be a single lymph node region, and hilar involvement constitutes an additional site of involvement. The number of anatomic regions should be indicated by a subscript (eg, II-3).
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may be subdivided stage III-1 or III-2: stage III-1 is used for patients with involvement of the spleen or splenic hilar, celiac, or portal nodes; and stage III-2 is used for patients with involvement of the paraaortic, iliac, inguinal, or mesenteric nodes.
IV	Diffuse or disseminated involvement of 1 or more extranodal organs or tissue beyond that designated "E," with or without associated lymph node involvement.

International Prognostic Score

One point is given for each of the characteristics below (increasing score represents increasing degrees of risk):

- Serum albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- Male gender
- Age >45 years
- Stage IV disease
- White blood cell count ≥15,000/microL
- Absolute lymphocyte count <600/microL and/or <8 percent of the total white blood cell count.

Unfavorable risk factors for stage I-II

The EORTC (European Organisation for Research and Treatment of Cancer) prognostic model, in which the presence of one or more of the following features constitutes unfavorable prognosis:

- Age >50 years
- Large ("bulky") mediastinal adenopathy
- Erythrocyte sedimentation rate (ESR) ≥50 mm/hour and no B symptoms (or ESR ≥30 mm/hour in those who have B symptoms)
- ≥4 regions of involvement
- Bulky disease —Bulky disease defined as mediastinal disease as at least one-third of the maximum thoracic width or any individual tumor mass ≥10 cm in maximum diameter.

4. Management

4.1. Classic Hodgkin's Lymphoma

Stage I-II favorable (non-bulky)

- ABVD x 2 cycles + ISRT 20Gy or
- ABVD x 4 cycles

- **Stage I-II Unfavorable (non-bulky)**
- ABVD x 4 cycles and restage with CT and if ;
  - °Complete or partial response
    - – ISRT 30Gy or
    - – ABVD X 2 cycles (a total of 6 cycles)
  - °Stable disease
    - – Biopsy and if;
      - Negative treated complete or partial response as above
      - Positive :Treated as refractory
  - °Progressive
    - – Consider biopsy to rule out other histology or treat as refractory

Stage I-II Unfavorable (Bulky mediastinal disease or >10 cm adenopathy)

- ABVD x 4 cycles and restage with CT and if ;
  - °Complete
    - – ISRT 30Gy or
    - – AVD X 2 cycles (a total of 6 cycles)
  - °Partial response
    - – ISRT 30Gy and then follow up or
    - – ABVD X 2 cycles (a total of 6 cycles) then restage if:
      - Complete response
        - Consider ISRT 30Gy
      - Partial response
        - ISRT 30Gy

- Stable disease
  - Biopsy and if;
    - Negative treated partial response as above
    - Positive
      - Treated as refractory
- Progressive
  - Consider biopsy to rule out other histology or treat as refractory

Stage III-IV

- ABVD x 4 cycles and restage with CT and if ;
  - Complete
    - AVD X 2 cycles + ISRT 30Gy to initially bulky sites
  - Partial response
    - AVD X 2 cycles + ISRT 30Gy to initially bulky sites
  - Stable disease
    - Biopsy and if;
      - Negative treated partial response as above
      - Positive
        - Treated as refractory
  - Progressive
    - Consider biopsy to rule out other histology or treat as refractory

4.2. Nodular Lymphocyte- predominant HL

CS IA, IIA (Non bulky)

- ISRT (Preferred for stage IA or contiguous stage IIA) or Observe. Restage with CT and if ;
  - Response;
    - Continue observe or
    - ISRT (if no prior RT)
  - Stable or progressive then biopsy and if;
    - Negative then observe if asymptomatic
    - Positive
      - Treat as refractory

CS IB, IIB or CS IA and IIA bulky or non-contiguous

- Chemotherapy (ABVD) + Rituximab x 4 cycles + ISRT 30Gy and re-evaluate with CT if;
  - Response;
    - Observe if asymptomatic or
    - ISRT (if no prior RT)
  - Stable or progressive then biopsy and if;
    - Negative then observe if asymptomatic
    - Positive :Treat as refractory

CS III-IV

- Chemotherapy (CHOP) + Rituximab x 6 cycles +/- ISRT and then restage with CT
  - Complete or partial response then
    - CHOP+Rituximab x 2 more cycles +/- ISRT 30Gy
  - Local RT (palliation of locally symptomatic disease)

4.3. Refractory or Relapsed disease

Biopsy proven refractory or relapsed disease

- Second line (with Brentuximab vedotin (Bv) or Bv+Bendamustine or Bv + Nivolumab) and then transplant or
- Best Supportive care

4.4. Chemotherapy details

ABVD

- Doxorubicin: 25 mg/m^2 IV on days 1 and 15
- Bleomycin: 10 U/m^2 IV on days 1 and 15
- Vinblastine: 6 mg/m^2 IV on days 1 and 15
- Dacarbazine: 375 mg/m^2 IV on days 1 and 15

Repeat cycle every 28 days for 6 cycles, using terminology of part A for day 1 therapy and part B for day 15 therapy, e.g., cycle 1A, 1B, etc.

Criteria to initiate next treatment:

• Platelet count >100,000

• Absolute neutrophil count >200 and no active infection

Supportive care with antiemetics is essential. Dexamethasone 12 mg should also be given prior to chemotherapy as an antiemetic.

Pregnancy and Breastfeeding

If possible, chemotherapy should be delayed until the 2nd trimester, and can be safely administered during the 2nd trimester if necessary. Chemotherapy should not be administered during breastfeeding (patient and infant should be provided formula).

5. Follow Up

- H & P every 3-6 month for 1-2 year, then every 6-12 months until year 3, then annually
- Patients in clinical remission should be seen about every 3 months with full blood count and differential, chemistry profile if clinically indicated.
- Clinically suspected relapse should be confirmed by biopsy if possible CT in select patients (bulky disease, IPS>4

B. Non-Hodgkin's Lymphomas

1. Workup

- History and physical examination: Attention to node bearing areas, including Waldeyer's ring , and to size of liver and spleen.
- Performance status
- B symptoms
- Blood: FBC/ RFTs / LFTs / Serum electrolytes / LDH / HIV serology / Hepatitis B&C , uric acid
- Bilateral bone marrow, trephine biopsies and Immunohistochemistry:
- Nodal or tru-cut biopsy.
- FNAC or bone marrow biopsy with flow cytometry may be sufficient to make a diagnosis in a selected few patient
- Contrasted CT scan of neck, chest, abdomen and pelvis and if indicated, head and nasopharynx (if there is disease in these sites).
- If CT is 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)

2. Staging

Lugano Classification for Hodgkin and Non-Hodgkin Lymphoma

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 2+ 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 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 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.

3. General Management

If a bulky tumor, anticipate tumor lysis syndrome and admit the patient for the 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

3.1. Indolent lymphomas

3.1.1. 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
FLIPI -1 CRITERIA

- Age >60 years
- Ann Arbor Stage III-IV
- Hemoglobin level <12g/dL
- Serum LDH level >ULN
- Number of nodal sites >5

Risk group according to FLIPI Chart

Low	0-1
Intermediate	2
High	>3

Management
Grade 3 follicular lymphoma is treated like diffuse large B-cell lymphoma (DLBCL) Asymptomatic patients with grade 1 and 2 FL can be eligible for watchful waiting. Single-agent Rituximab is an option.
Stage I and II:

- Stage I (<7cm) or contiguous Stage II (<7cm)
  - ISRT and if
    - CR or PR then follow up
    - No response then treat as Stage III , IV

- Stage I(>7cm) or contiguous stage II (>7cm) or non contiguous Stage II
  - Anti-CD 20 monoclonal antibody +/- chemotherapy and if;
    - CR then follow up
    - PR & NR consider ISRT if CR or PR then follow and if NR then treat as Stage III , IV
  - Anti-CD 20 monoclonal antibody +/- chemotherapy +/ISRT and if ;
    - CR or PR follow up
    - NR then treat as Stage III , IV
  - Observation

Stage III, IV

Indication for treatment:

- Symptoms
- Threatened end organ function
- Cytopenia secondary to lymphoma
- Bulky disease
- Steady or rapid progression

If not any indication then observation and do follow up.

If indication present:

- Consider CT scan neck/chest/abdomen/pelvis with contrast and then any of the following.
  - CHOP at least 6 cycles
  - Bendamustine or
  - Rituximab 375mg/m2 weekly for 4 cycles or
  - CVP (cyclophosphamide, vincristine , prednisone)
- 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 pre biopsy
- 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

3.1.2. 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 for Gastric MALT Lymphoma

Stage I or II Pylori positive

- Currently accepted antibiotics for H.Pylori
  - Evaluate with endoscopy and if ;
    - Lymphoma positive then

- ISRT for persistent disease or
- Rituximab
  - Lymphoma negative
    - Follow up

Stage I1 or I2 or Stage II H pylori negative
- ISRT or
- Rituximab

Stage IIE or II2 or stage IV
- Observation if no treatment indication
- First line therapy if treatment indicated
  - Bendamustine + Rituximab
  - R CHOP
  - RCVP

Management for Nongastric MALT Lymphoma

Stage I-II
- ISRT or
- Surgery for certain sites or
- Rituximab in selected cases or
- Observation in selected cases

Stage IV
- ISRT or
- Observation in selected cases or
- Manage per advanced stage NMZL

3.1.3. 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 recommended.

3.2. Indolent T-cell Lymphomas

3.2.1. Mycosis fungoides
Introduction

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.

Treatment
- Topical corticosteroids: for localized or generalized 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, Cyclophosphamide, Methotrexate (>100mg/ week)

3.3. Aggressive lymphomas

3.3.1. Diffuse Large B-Cell Lymphoma
This is a neoplasm of large B lymphoid cells that has a diffuse growth pattern. Typical immunohistochemical profiles are 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
Stage I, II with good Performance Status (0-2)
- **Non bulky (<7.5cm), CD20+ or not done**
  - RCHOP x 3 cycles + ISRT or
  - RCHOP x 6 cycles +/- ISRT

- **Non bulky (<7.5cm), CD20-**
  - CHOP x 3 cycles + ISRT or
  - CHOP x 6 cycles +/- ISRT

- **Bulky (>7.5cm), CD20+ or not done**
  - RCHOP x 6 cycles +/- ISRT

- **Bulky (>7.5cm), CD20-**
  - CHOP x 6 cycles +/-

If poor performance status, then prephase Rituximab + Prednisone for CD20+ or ISRT for CD 20 - If there is improvement then treat as PS 0-2. Best supportive care if no clinical improvement.

Stage III, IV
- Performance Status 0-2
  - CD 20+ or not done – RCHOP x 6 cycles
  - CD20 – CHOP x 6-8 cycles
- Performance Status 3-4
  - CD 20+ or not done – Prephase: Rituximab + Prednisone
  - CD20 – ISRT
- If there is improvement then treat as PS 0-2. Best supportive care if no clinical improvement.

Follow Up

Clinical
- H & P and labs every 3-6 months for 5 years and then yearly or as clinically indicated

Imaging
- Neck/C/A/P CT-scan with contrast no more often than every 6 months for 2 year after completion of treatment, then only as clinically indicated.

Relapsed/Refractory Disease Management
- Second line therapy or
- Palliative ISRT or
- Best supportive care

3.3.2. Adult Burkitt Lymphoma
- This generally is rare and has poor prognosis, unlike BL in children. The standard of care for BL in adults is yet to be defined.
- CHOP is not an adequate therapy

Induction therapy

Low risk

CODOX-M (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by systemic methotrexate + rituximab (Cycle A x3) + Growth factor support.

High risk

CODOX-M alternating with IVAC (Ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) + rituximab (Cycle A alternating with cycle B x2—a total of 4 cycles).

Chemotherapy generally used in Lymphomas

Recommended Chemotherapy Regimens in Lymphoma:

- Cyclophosphamide,Vincristine and Prednisolone(CVP)
- Cyclophosphamide,Adriamycin,Vincristine and Prednisolone (CHOP) or
- CHOEP - with addition of Etoposide used for aggressive T-cell lymphomas

Rituximab in either of the above regimen if CD 20 positive.

Intrathecal Chemotherapy

- Methotrexate Ara C
- **CMV** (Cyclophosphamide, Methotrexate and Vincristine)
- Palliative regime for indolent and aggressive NHL
- **FC** (Fludarabine and Cyclophosphamide).
- 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 the 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

Complications

Tumor Lysis Syndrome

- Lymphoblastic lymphoma/leukaemia and Burkitt's 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:
  - Hyperuricemia
  - Hyperkalaemia
  - Hyperphosphatemia
  - Hypocalcaemia

Management

- Anticipate and prevent TLS Start Allopurinol
- Do baseline bloods – RFT, urate, Ca, Mg, Ph, K Prehydrate.
- Monitor labs 6 hourly for high-risk patients and 12 hourly for moderate risk.

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.

C. Acute Myeloid Leukemia (AML)

1. Introduction

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.

2. Workup

- 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)
- Confirmation of Acute promyelocytic leukaemia (APML) using molecular studies such as the detection of PML-RARA fusion gene (or its chimeric protein product) is necessary, and also helpful as a predictive element

3. Classification

There are four main groups of AML recognized by the WHO classification system:

- 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.

4. 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)

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
All-Trans Retinoic Acid is an important agent in all three phases of APML 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 ≤10 x 109/L)
- High risk: WBC > 10 x 109/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

D. Acute Lymphoblastic Leukemia (ALL)

1. Introduction

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%.

2. 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 evaluation e.g., MUGA scan or echocardiogram or cardiac MRI.
- Transplant – eligible patients and their siblings should be HLA typed.

3. 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.

4. 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

E. Chronic Myelogenous Leukemia (CML)

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the uncontrolled production of mature and maturing granulocytes. CML is associated with the fusion of two genes, BCR (on chromosome 22) and ABL1 (on chromosome 9), typically resulting from the t (9;22) (q34; q11) reciprocal translocation that gives rise to the Philadelphia (Ph) chromosome. The BCR-ABL1 fusion gene encodes a dysregulated tyrosine kinase that drives CML.

Screening: No routine screening is recommended.

Common Findings at Presentation:

Splenomegaly, fatigue, weight loss, night sweats, anemia, and granulocytosis. Atypical presentation may include isolated thrombocytosis, visual disturbances.

2. Workup

The diagnosis of CML is first suspected based on typical findings in the blood and often bone marrow, and then confirmed by demonstration of the BCR-ABL1 fusion gene or its products.

Full Blood Count: Typical findings are leukocytosis, usually with a full spectrum of granulocytes and their precursors, including eosinophilia and basophilia, often associated with thrombocytosis and mild anemia. Accelerated phase is marked by decreasing platelet counts, increasing basophil counts, and an increase in circulating blasts. Blast crisis may be either lymphoid or myeloid and is marked by increasing blasts in the bone marrow and worsening cytopenias.

- **Peripheral Blood Smear:** Direct visualization of granulocytes and the full spectrum of granulocytes and their precursors. Absolute basophilia is a universal finding, and absolute eosinophilia is seen in most cases.
- **Bone Marrow Aspiration and Biopsy:** Granulocyte hyperplasia with a maturation pattern similar to the peripheral smear. (Bone marrow aspiration and biopsy is often included in the initial work-up for CML, though not required for diagnosis.)
- **Genetic Testing**: the BCR-ABL1 fusion gene or its products must be demonstrated in order to diagnose CML, typically by one of the following methods:
  - **Cytogenetics:** conventional karyotyping may be used to detect the Philadelphia chromosome in peripheral blood or bone marrow samples.
  - **Fluorescence in situ hybridization (FISH):** FISH utilizes DNA probes to directly detect the BCR-ABL1 fusion gene in peripheral blood or bone marrow samples.
  - **Reverse transcriptase polymerase chain reaction (RT-PCR):** RT-PCR is a highly sensitive technique that uses specific primers to amplify BCR-ABL1 fusion mRNA transcripts from peripheral blood or bone marrow samples. The most common BCR-ABL1 fusion transcripts in CML encode proteins that weigh 210 kilodaltons (p210), seen in 90% of CML. A p190 transcript is seen in a small minority (9%), and a p230 transcript is seen rarely (<1%). The standard RT-PCR technique for diagnosis of CML is qualitative RT-PCR, which utilizes multiple different primers to identify a patient's specific fusion transcript.

- **GeneXpert BCR-ABL Assay** is a quantitative RT-PCR technique available in Rwanda. GeneXpert uses a specific primer to detect and quantify the p210 BCR-ABL1 transcript in a peripheral blood sample. The result is reported as a percentage ratio of BCR-ABL1 to normal ABL. This technique may be used for both diagnosis of CML and monitoring of response to therapy.
    - All patients with clinically suspected CML should have GeneXpert BCR-ABL testing.
    - The WBC must be less than 200,000 for GeneXpert to be accurate. If the WBC is greater than 200,000 initially, hydroxyurea should be administered for cytoreduction (see guidelines below).
    - Patients with clinically suspected CML and a negative GeneXpert result should undergo further genetic testing, such as qualitative RT-PCR, since GeneXpert does not detect p190 or p230 transcripts, which are responsible for <10% of CML.

3. Staging:

CML usually progresses from a relatively indolent disease to a more aggressive disorder. Treatment of CML depends on the specific disease phase. There are three general phases (WHO definition):

- **Chronic phase:**
    - Less than 10% blasts in the peripheral blood and bone marrow.
- **Accelerated phase:**
    - 10 to 19% blasts in the peripheral blood or bone marrow
    - Peripheral blood basophils ≥ 20%
    - Persistent thrombocytopenia (platelets <100,000/microL), unrelated to therapy
    - Persistent thrombocytosis (platelets >1,000,000/microL), unresponsive to therapy
    - Progressive splenomegaly and increasing WBC, unresponsive to therapy
- **Blast crisis:**
    - ≥20% blasts in the peripheral blood or bone marrow
    - Large foci or clusters of blasts on the bone marrow biopsy
    - Extramedullary blast proliferation (e.g. myeloid sarcoma, also known as granulocytic sarcoma or chloroma)

Recommended Staging Evaluation:

- Physical examination including assessment of spleen size
- Full blood count with differential
- Formal peripheral blood smear to quantify blasts, if available
- Bone marrow aspiration and biopsy if WBC is ≥300,000 at time of presentation
    - If WBC is <300,000 at time of presentation, the patient can be considered chronic phase and imatinib may be initiated once bcr-abl confirmed (bone marrow aspiration and biopsy is not necessary).
- Imaging is not needed.

4. Treatment

The goal of treatment for CML may be:

- Potential cure with allogeneic hematopoietic cell transplantation if available
- Long-term disease control without cure using tyrosine kinase inhibitors (TKIs) i.e., imatinib (Gleevec)
- Palliative therapy with cytotoxic agents i.e., hydroxyurea

Cytoreduction with Hydroxyurea

Indications for cytoreduction:

- To reduce the WBC below 200,000 for GeneXpert testing (pre-diagnosis)
- For the relief of systemic symptoms or symptomatic splenomegaly (pre-diagnosis or after imatinib failure)
- Added to TKI in accelerated or blast phase
- Note: in general, hydroxyurea should be discontinued once imatinib is initiated

Guidelines for cytoreduction:

- Typical starting dose for adults is hydroxyurea 1g BID with allopurinol 300 mg QD
- The dose can be reduced as the WBC count decreases
- Labs should be checked every 2 weeks given myelosuppressive effect of hydroxyurea

Initial Treatment for Confirmed CML

- Prior to starting imatinib (Gleevec), patients should have baseline full blood count, Cr/urea, AST/ALT, and pregnancy test if applicable
- For chronic phase CML:
  - Start imatinib 400 mg PO daily (adult) or 340 mg/m2 PO daily (pediatric; not to exceed 400 mg per day)
    - Patients must be counseled on the importance of strict medication adherence
    - Imatinib is teratogenic. Effective contraception must be used; women of childbearing potential (female patients and female partners of male patients) must not become pregnant during imatinib therapy.
- If WBC is >100,000 at time of imatinib initiation, or if there is clinical concern for hyperuricemia (renal failure or a history of gout), allopurinol may be used for protection from tumor lysis syndrome

For accelerated or blast phase CML:

- Start or increase dose to imatinib 600 mg PO daily (adult); use 340 mg/m2 PO daily for pediatrics, with maximum dose 600 mg per day
- Add hydroxyurea and allopurinol

Guidelines for Monitoring

- Until complete hematologic response (CHR) is achieved, patients should have:
  - Clinic visit every 2-4 weeks
  - Full blood count every 2-4 weeks
  - Cr/urea and AST/ALT every 2-4 weeks

- Once CHR is achieved, patients should have:
  - Clinic visit every 2-3 months
  - Full blood count every 2-3 months
  - Cr/urea and AST/ALT every 2-3 months
  - Pregnancy test every 3 months
  - Molecular monitoring with GeneXpert BCR-ABL Assay every 12 months for 3 years

Response Assessment

- Complete hematologic response (CHR):
  - Platelets <450 x109/L
  - WBC <10 x109/L
  - Differential: no immature granulocytes, basophils <5%
  - No palpable spleen
  - Note: CHR must be achieved in the absence of hydroxyurea
- Target molecular response:
  - <1% transcripts on quantitative GeneXpert BCR-ABL Assay
  - Patients with >1% transcripts have worse prognosis (see management guide below)
- Clinical failure:
  - Failure to achieve CHR after 3 months (refractory)
  - Loss of CHR at any point (relapse)
  - Progression from chronic to accelerated or blast phase

Guidelines for Clinical and Molecular Failure

- If a patient has clinical failure on imatinib 400 mg/day:
  - Ensure medication adherence and increase to maximum dose of 600 mg PO daily
- If a patient develops clinical failure OR fails to achieve target molecular response on maximum dose imatinib:
  - Mutational analysis should be performed on peripheral blood;
  - If appropriate based on mutation status, initiate dasatinib 100 mg PO daily.

Guidelines for Toxicity Monitoring and Dose Reductions

In chronic phase CML (initial dose 400 mg/day in adults or 340 mg/m^2/day in children):
a. If ANC <1 x109/L and/or platelets <50 x10^9/L, withhold imatinib until ANC ≥1.5 x10^9/L and/or platelets ≥75 x10^9/L and resume treatment at original starting dose
For recurrent neutropenia and/or thrombocytopenia, withhold until recovery and reinstitute at a reduced dose:
i. Adults: if initial dose 400 mg/day, reduce to 300 mg/day
ii. Children: if initial dose 340 mg/m^2/day, reduce to 260 mg/m^2/day
In accelerated phase or blast crisis (initial dose 600 mg/day in adults):
b. If ANC <0.5 x10^9/L and/or platelets <10 x10^9/L, establish whether cytopenia is related to leukemia (bone marrow aspirate or biopsy).
i. If unrelated to leukemia: reduce dose to 400 mg/day. If cytopenia persists for an additional 2 weeks, further reduce dose to 300 mg/day.
ii. If cytopenia persists for 4 weeks and is still unrelated to leukemia, without treatment until ANC ≥1 x10^9/L and/or platelets ≥20 x10^9/L, then resume at 300 mg/day.

F. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

1. Introduction

CLL and SLL are similar diseases, one with primarily a peripheral blood and bone marrow manifestation (CLL) and the other presenting primarily as lymphadenopathy without significant peripheral blood involvement (SLL). Both have the same immunophenotype and molecular genetics. They are distinguished by lymphocyte count: in CLL, the lymphocyte count is >5,000 cells/mm3, and in the lymphocyte count is below this threshold.
Screening: No routine screening is recommended.

Common findings at presentation
- Incidentally elevated white blood cell count with lymphocytosis
- Generalized enlarging, painless lymph nodes
- Splenomegaly or hepatomegaly
- "B" symptoms: fever, night sweats, or > 10% weight loss

2. Workup

Diagnostic work up:
- Full blood count with differential to assess absolute lymphocyte count
- Peripheral blood smear to confirm circulating small lymphocytes (if available)
- Peripheral blood for flow cytometry with lymphoma panel (if available)
- Tissue biopsy:
  - Core needle biopsy of lymph node or
  - Excisional lymph node biopsy or
  - Incisional biopsy of extra-nodal site of involvement
  - *Fine Needle Aspiration (FNA) is NOT adequate to make the diagnosis.*

Pathology: standard histology with immunohistochemistry (IHC) if available
- Bone marrow aspirate and biopsy (only if evidence of severe cytopenias)

Additional laboratory investigations: creatinine, liver function tests, LDH, pregnancy test (if applicable)

Radiological work up if there is evidence of significant adenopathy:
- Chest Xray and abdominal ultrasound (minimum)
- CT scan for staging of the neck, chest, abdomen, and pelvis (recommended)

3. Staging

Document a detailed lymph node exam and abdominal exam for organomegaly including negative findings. Staging categories below are based on physical exam and imaging findings.

RAI STAGE

Stage	Criteria
Stage 0	Lymphocytosis in blood or bone marrow
Stage I	Lymphocytosis + enlarged lymph nodes
Stage II	Lymphocytosis + enlarged liver or spleen with or without LAD
Stage III	Lymphocytosis + anemia (Hgb <11.0 g/dL) with or without enlarged liver, spleen, or lymph nodes
Stage IV	Lymphocytosis + thrombocytopenia (plt <100,000/microL) with or without anemia or enlarged liver, spleen, or lymph nodes

BINET STAGE

Stage	Criteria
Stage A	Two or less lymphoid bearing areas enlarged*
Stage B	Three or more lymphoid bearing areas enlarged*
Stage C	Presence of anemia (Hgb <10.0 g/dL) or thrombocytopenia (platelet count <100,000/microL)

* Five lymphoid bearing areas are possible: cervical, axillary, inguino-femoral, spleen, and liver.

Poor Prognostic Factors

- High Rai or Binet stages
- Lymphocyte doubling time <12 months
- Elevated LDH
- Elevated beta-2 microglobulin

Transformation

About 1% of CLL cases per year will transform to Diffuse Large B Cell lymphoma (Richter's transformation) or classical Hodgkin lymphoma (rarely). Usually this is heralded by B symptoms and growth of one lymph node or extranodal mass out of proportion to other sites of disease. Biopsy should be performed on the most suspicious mass/node; if aggressive histology is confirmed then treatment for that histology should be initiated rapidly. However, the prognosis is poor, and palliative care is an option.

4. Treatment

Observation

Most CLL patients can be followed expectantly without institution of therapy, often for many years. They should be seen every 3-6 months, with history and physical (including detailed lymph node and abdominal exam) and lab work to follow lymphocyte count and evaluate for cytopenias.

Therapy should be initiated when any of the following treatment indications are met:

- Progressive marrow failure (neutropenia, anemia or thrombocytopenia)
- Bulky or rapidly enlarging lymphadenopathy that is organ-threatening, or symptomatic splenomegaly
- Symptoms ("B", fatigue, pain)
- Lymphocyte doubline time < 6 months
- Progressive lymphocytosis with an increase of >50% over 2 months
- Autoimmune anemia and /or thrombocytopenia that is poorly responsive to steroids/ standard therapy.
- Disease related to

First Line Treatment Options

Bottom Line: Treatment goals are to achieve symptomatic control of the disease and prevent complications. No single standard treatment and treatment depends on agae and cytogenetics ie presence f 11q or 17p deletion. Treatment options include:

- Purine analogs (Fludarabine)
- Alkylating agents (Chlorambucil, Bendamustine , Cyclophosphamide)
- Monoclonal antibodies against CD20 (Rituximab)
- Combination of the above

Alternate the above regimen if there is relapse.

5. Follow-up

- Patients in clinical remission should be seen about every 3 months with full blood count and differential
- Clinically suspected relapse should be confirmed by biopsy if possible

G. Multiple Myeloma

1. Introduction

Risk Factors:

- Environmental/Chemical/Infections: Radiation, benzene, organic solvents, herbicides, insecticides
- Genetic: Genetic predisposition, older age, immunosuppression, gender (male > female), ethnicity (African American)

Prevention and Screening:

- Patients with myeloma likely had an MGUS preceding myeloma diagnosis.

Clinical Presentation:

(CRAB= calcium elevated, renal failure, anemia and bone lesions)

- Common Symptoms: Anemia, bone pain, fatigue/general weakness, weight loss
- Common Signs: Elevated creatinine, hypercalcemia, normocytic anemia
- Common Presentations: Radiculopathy, pathologic fracture, cord compression

2. Workup

- **Laboratory**: CBC, albumin, total protein, Calcium, Creatinine, B2microglobulin, LDH, calcium, LFT, SPEP with immunofixation, Free Light Chain assay (kappa, lambda, FLC ratio), 24hr UPEP, NT-proBNP, troponin
- **Diagnostic Imaging:** Skeletal survey, MRI (to rule out cord compression if back pain or neurologic symptoms) echo/cardiac MRI (if suspicion of cardiac amyloidosis)
- **Diagnostic Procedures:** Bone marrow biopsy and aspirate (for morphology, flow cytometry, immunostains and cytogenetics). If suspected amyloidosis perform Congo red staining, fat pad biopsy or organ specific biopsy.
- **Pathology & Molecular Biology**
  - Common Histology:
    - Peripheral Blood Smear: rouleaux, normocytic anemia, circulating plasma cells
    - Bone marrow aspirate: mature plasma cells with immunohistochemistry positive for CD79a, CD138, CD38
  - Relevant Cytogenetics: FISH for prognosis
    - Poor prognosis: t(14;16), t(4;14), del17p, hypodiploidy
    - Standard prognosis: t(11;14), hyperdiploidy

3. Classification

2014 International Myeloma Working Group (IMWG) diagnostic criteria for MM and related plasma cell disorders

Disorder	Disease Definition
Non-IgM MGUS	All 3 criteria must be met: Serum M protein (non-IgM type) <3g/dL Clonal bone marrow plasma cells <10% Absence of end-organ damage, such as CRAB, that can be attributed to the plasma cell proliferative disorder Ca (corrected) > 0.25mmol/L **C**a (corrected)>0.25mmol/L upper limit of normal or >2.75mmol/L **R**enal impairment: Creatinine>176µmol/L **A**nemia:Hemoglobin < 100g/L or 20g/L below lower limit of normal **B**one lesions: lytic lesions or osteoporosis with compression fractures Others: symptomatic hyper-viscosity, amyloidosis, recurrent bacterial infections (>2/year)
IgM MGUS	All 3 criteria must be met: Serum IgM monoclonal protein <3g/dL Bone marrow lymphoplasmacytic infiltration <10% No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder
Light Chain MGUS	All criteria must be met: Abnormal FLC ratio (<0.26 or >1.65) Increased level of the appropriate involved light chain No immunoglobulin heavy chain expression on immunofixation Absence of end organ damage that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells <10% Urinary monoclonal protein <500mg/24hr
Smoldering MM (SMM)	Both criteria must be met: Serum M protein (IgG or IgA) ≥3g/dL, or urinary monoclonal protein ≥500mg/24hr and/or clonal bone marrow plasma cells 10-60% Absence of myeloma defining events (CRAB) or amyloidosis
MM	Both criteria must be met: Clonal bone marrow plasma cells ≥10% or biopsy proven bony or extramedullary plasmacytoma Any one or more of the following myeloma defining events: Hypercalcemia: serum Ca >0.25mmol/L higher than upper limit of normal or >2.75mmol/L Renal insufficiency: CrCl <40mL/min or Scr>177umol/L Anemia: Hb >2g/dL below lower limit of normal or Hb <10g/dL Bone lesions: one or more osteolytic lesions on skeletal survey, CT, or PET-CT Clonal bone marrow plasma cell ≥60% Involved: uninvolved serum FLC ratio ≥100 ≥2 focal lesions on MRI studies (at least 5mm) t(4;14) or p53 deletion

Solitary Plasmacytoma	All 4 criteria must be met: Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end organ damage such as CRAB that can be attributed to a lymphoplasma cell proliferative disorder
Solitary Plasmacytoma with minimal marrow involvement	All 4 criteria must be met: Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Clonal bone marrow plasma cells <10% Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end organ damage such as CRAB that can be attributed to a lymphoplasma cell proliferative disorder

International Staging System (ISS):

Stage	B2M (mg/L)		Albumin (g/L)	Median Survival (months)
I	< 3.5	And	≥ 35	62
II	≥ 3.5 to <5.5	And/or	<35	44
III	β2M ≥ 5.5			29

Durie-Salmon Staging:

Stage	Criteria	Myeloma Cell Mass ($X10^{12}$cells/m^2)
I	All of the following: Hb >100, normal Calcium, no lytic bone lesions, IgG<50g/L, IgA <30 g/L, Urine M-protein <4 g/24h	<0.6
II	Neither I nor III	0.6-1.2
III	One of more of the following: Hb<85, Ca >3mmol/L, IgG>70g/L, IgA>50g/L, Urine M-protein >12g/24h	>1.2

IMWG Response Criteria

Classification	Criteria
Stringent Complete Response (sCR)	• CR as defined below • Normal FLC ratio • Absence of clonal cells in BM by IHC or immunofluorescence
Complete Response (CR)	• Negative immunofixation on the serum and urine • Disappearance of any soft tissue plasmacytomas ≤ 5% plasma cells in BM • Normal FLC ratio of 0.26 to 1.65 on 2 consecutive assessments
Very Good Partial Response (VGPR)	• Serum/urine M protein detectable by IF but no on electrophoresis • ≥90% decrease in serum M protein plus urine M protein level <100mg/24h • ≥90% decrease in the difference between involved and uninvolved FLC

Partial Response (PR)	• ≥50% reduction of serum M protein and reduction in 24h urinary M protein by ≥90% or to <200mg/24h • If serum and urine M protein are unmeasurable a ≥50% decrease in the difference between involved and uninvolved FLC required • If serum and urine FLC unmeasurable, ≥50% reduction in plasma cells required • In addition to above, if present at baseline, a ≥50% reduction in size of soft tissue plasmacytoma
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR or progressive disease

4. Treatment

Transplant Eligible (≤65 years)

Bottom Line General Approach:

- **Induction:** Pre-transplant induction with a triple drug regimen that includes a novel agent such as bortezomib or lenalidomide. Triple drug regimen such as CyBorD (Cyclophosphamide, Bortezomib, Dexamethasone) or VRD (Bortezomib, Lenalidomide, Dexamethasone).
- **VRD** is an option for high-risk disease (17p deletion of t(4;14)).
- **ASCT:** High dose melphalan +/- bortezomib followed by autologous stem cell transplantation
- **Consolidation:** Post transplant consolidation (ie) VRD, bortezomib – not standard practice, not usually funded in Canada
- **Maintenance:** Maintenance until disease progression with lenalidomide or bortezomib

Relapsed/Refractory Disease

- General Considerations:
- Always consider for clinical trial
- Components of initial therapy: Novel agents? ASCT?
- Degree and duration of response to primary therapy: PR, VGPR, CR? >6mo, >1yr?
- Previous toxicities: myelosuppression, peripheral neuropathy, renal insufficiency
- Type of relapse: aggressive, indolent
- Age and performance status: elderly, frail
- Comorbidities
- Patient Preference

Definitions

- **Refractory**: Nonresponsive while on primary or salvage therapy OR progresses within 60days of last therapy
- **Relapsed:** Disease recurrence in absence of current therapy after response established (25% rise in M protein, new plasmacytoma, or hypercalcemia)
- **Relapsed & Refractory:** Nonresponsive while on salvage therapy OR progresses within 60days of last therapy in those who have achieved response at some point

Newer Generations of Antimyeloma Drugs

Mechanism/Target	Drugs
Immunomodulatory Drugs	Pomalidomide
PIeK/AKT/mTOR Inhibitors	Everolimus
Alkylating plus purine analog	Bendamustine
Monoclonal Antibodies	**Daratumumab** (anti CD38)

Other Treatment Considerations

Anemia

- Rule out Iron deficiency
- Transfusion support
- Consider Erythropoietin

Pain

- Tylenol, hydromorphone, fentanyl patch, radiation, kyphoplasty, bisphosphonates
- Avoid NSAID (renal insufficiency)

Neuropathy

- Mild: reduce dose
- Severe affecting ADLS: stop treatment
- Consider duloxetine, pregabalin, gabapentin

Infection

- Septra (1st 3months post chemotherapy or after ASCT)
- Acyclovir (bortezomib, ASCT)
- Vaccinate (influenza, pneumococcal, no live vaccines)
- IVIG if low IgG

Bone

- Bisphosphonates reduce bone complications and inhibit bone resportion by suppression of osteoclast activity. Monthly Pamidronate or Zoledronic acid for 2 years in all patients
- Pretreatment dental evaluation, yearly dental checkups, avoid dental extractions à risk of Osteonecrosis of the jaw

Thromboprophylaxis

- Thrombosis common with Immune Modulators (Lenalidamide, thalidomide) and concurrent use of steroids
- Risk factors: Obesity, previous VTE, Immobilization, Surgery, EPO, Hyperviscosity, comorbidities (Cardiac, CKD, DM, acute infection)
- High Risk: 2 or more risk factors, treat with LMWH or warfarin
- Low Risk: No or 1 risk factor, treat with ASA 81mg.

HEAD AND NECK CANCERS

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 cancer of unknown primary (CUP).

2. 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 initial diagnostic approach for a suspicious neck mass with a fine- needle aspiration (FNA) is acceptable but open or core needle biopsies are preferred and confirmatory. Open biopsy for metastatic disease is not recommended.

A. Nasopharyngeal Cancer

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 (4th-5th 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.

Risk factors are:

- EBV
- Salt preserved fish
- Preserved foods
- Low fruit/vegetable diet
- Tobacco smoke
- Family history

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. Special attention on the head and neck exam. Mirror examination as clinically indicated.

- **Imaging:**
  - Chest X-ray
  - Abdo/pelvic Ultrasound (Liver metastasis) Head and neck CT scan and/or MRI to evaluate skull base erosion
  - Nasopharyngoscopy (to visualize the primary and take a biopsy)
  - As clinically indicated:
    - Dental, nutritional, speech and swallowing, and audiology evaluation
    - Consider ophthalmologic and endocrine evaluation.
  - Bone scan when indicated

- **Pathology:** Definitive diagnosis is confirmed by endoscopic guided biopsy of the primary tumor. Immunohistochemistry may be needed to further confirm the diagnosis. P16 as HPV surrogate should be done where possible

3. Staging

Staging is based on the clinical presentation and Physical examination Imaging reports (Endoscopy, CT Scan/MRI etc)

TNM Staging system:

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

Clinical N Stage

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

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

Surgery

- Due to the 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.

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 systemic therapy/RT followed by adjuvant chemotherapy or induction chemotherapy followed by chemo/RT or concurrent systemic therapy/RT not followed by adjuvant chemotherapy.
- **Stage IVC:** Palliative care with systemic platinum-based combination chemotherapy followed by RT or concurrent systemic therapy/RT as clinically indicated or observation or concurrent systemic therapy/RT.

Note: If induction chemotherapy is not given, adjuvant chemotherapy should be given if it can be tolerated by the patient.

Local Recurrence: Chemotherapy, surgery or re-irradiation.

Radiotherapy details (IMRT/VMAT)

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.

CT Simulation

- 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.

Radiation dose:

Definitive:

RT alone (for T1, N0 or patients who are not eligible to receive chemotherapy)

- **PTV**
  - High risk: Primary tumor and involved lymph nodes
    - 66Gy (2.2Gy/fraction) to 70-70.2Gy (preferred) (1.8-2Gy/fraction) daily Monday- Friday in 6-7 weeks or
    - 66.96Gy (2.12Gy/fraction) daily Monday- Friday in 6-7 weeks
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Concurrent Chemoradiation

Preferred for patients eligible for chemotherapy

- **PTV**
  - High risk: Primary tumor and involved lymph nodes
    - 66 -70.2Gy (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks; typically 70-70.2Gy (1.8-2Gy/fraction); daily Monday- Friday in 7 weeks.
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Chemotherapy details:

- **Concurrent chemotherapy:**
  - Platinum based mostly IV Cisplatin 40mg/m² weekly or 100mg/m² every three weeks.

- **Induction Chemotherapy**
  - For patients with advanced nasopharyngeal carcinoma - PF or TPF (Taxane, Platinum and 5 FU). At least 3 cycles are given.

- **Adjuvant /Sequential Chemotherapy:**

In curative intent concurrent chemoradiation is indicated with Cisplatin / 5FU

If induction chemotherapy was not given then adjuvant chemotherapy is recommended with the same regimen as induction above.

- TPF: IV Docetaxel 75mg/m² D1 /IV 5 FU 750mg D1-D5/IV Cisplatin 75mg/m² D1 for at least 3 cycles or ,
- TP: IV carboplatin AUC 5 or 6 D1/IV Paclitaxel 175mg/m2 D1 for at least three cycles

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.

5. Follow up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow up includes the following:

- H & P exam (including a complete head and neck exam; mirror and fiberoptic examination)
  - Year 1: every 1-3 months
  - Year 2: every 2-6 months
  - Year 3-5: every 4-8 months
  - > 5 years: every 12 months
- Imaging:
  - Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 months of treatment
  - Chest x ray or CT scan as clinically indicated for patients with smoking history
  - Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination.
  - Routine annual imaging (great use of pretreatment imaging modality) may be indicated in areas difficult to visualize on exam.
- Thyroid -stimulating hormones (TSH) every 6-12 months or as indicated if the neck irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intraoral radiation treatment.
- Supportive care and rehabilitation
  - Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated.
  - Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is indicated.
  - Ongoing surveillance for depression
  - Smoking cessation and alcohol counseling as clinically indicated.

B. Laryngeal Cancer

1. Introduction

Laryngeal cancer is one of the most common cancers of the head and neck. Worldwide laryngeal cancer cases are estimated to be around 238,000 and around 106,000 die annually. Laryngeal cancer is predominantly found in men and mostly in those with a history of tobacco smoking and alcohol intake.
Larynx is divided into three major anatomical 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.

Clinical Presentation

- Hoarseness
- Stridor
- Difficulty in breathing
- Neck mass
- Odynophagia
- Cough

2. Workup

- **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.

3. Staging

Supraglottis

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Tumor *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 (eg, 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 (eg, 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.

Glottis

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Tumor *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 (eg, 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.

Subglottis

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Tumor 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 (eg, 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.

Clinical N Stage

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 Metastases 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(+)

NOTE: A designation of «U» or «L» may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE (–) or ENE (+).

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

a. 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 for organ preservation.
- Total Laryngectomy and neck dissection. Adjuvant radiotherapy or chemo radiotherapy is considered depending on the surgical adverse effects.

b. 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 site

Stage III-IVB

- Concurrent Chemoradiation for organ preservation.
- Total Laryngectomy and neck dissection. Adjuvant radiotherapy or chemo radiotherapy is considered depending on the surgical adverse effects.

c. 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 for organ preservation.
- 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.

d. 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.

e. CT Simulation

- 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

Radiation dose for IMRT/VMAT — 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. Treatvthe 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.

Radiotherapy Details
Definitive:

- **RT alone**
  - Tis, N0 : 60.75 Gy (2.25Gy/fraction) to 66Gy (2Gy/fraction)
  - T1,N0 : 63Gy (2.25/fraction – preferred) to 66Gy (2Gy/fraction)
  - T2, N0 "65.25 (2.25Gy/fraction) to 70Gy (2Gy/fraction)
  - >T2,N1:
- **PTV**
  - High risk: Primary tumor and involved lymph nodes
    - 66Gy (2.2Gy/fraction) to 70-70.2Gy (preferred) (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks
    - Concomitant boost accelerated RT
      - 72 Gy/ 6 weeks (1.8Gy/fraction ,large filed ; 1.5 Gy boost as second daily fraction during last 12 treatment days
  - 66.96Gy (2.12Gy/fraction) daily Monday- Friday in 6-7 weeks
    - Low to intermediate risk: Sites of suspected subclinical spread
  - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Concurrent Chemoradiation
Preferred for patients eligible for chemotherapy

- **PTV**
  - High risk: Primary tumor and involved lymph nodes
    - 66-70.2Gy (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks; typically 70Gy (2Gy/fraction);daily Monday- Friday in 7 weeks.
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Postoperative
RT alone or concurrent Systemic Therapy/RT if adverse features

- Preferred interval between resection and postoperative RT is </= 6 weeks.
- PTV
  - High risk: Adverse features such as positive margins
    - 60-66Gy (2Gy/fraction); daily Monday -Friday in 6-6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

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 IV Cisplatin 40mg/m2 weekly or 100mg/m2 every three weeks is used.
- TPF or TP (Taxane, Platinum and 5 FU) is used for induction therapy and/or sequential therapy.
- TPF: IV Docetaxel 75mg/m2 D1 /IV 5 FU 750mg D1-D5/IV Cisplatin 75mg/m2 D1 for at least 3 cycles or ,
- TP: IV carboplatin AUC 5 or 6 D1/IV Paclitaxel 175mg/m2 D1 for at least three cycles

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 with similar doses as in induction/sequential settings.

- **Combination therapy**
  - IV Carboplatin / IV Paclitaxel
  - IV Cisplatin/ IV 5-FU,
  - IV Cisplatin/ IV gemcitabine,

- **Single agents**
  - Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5-FU, Methotrexate, Gemcitabine, Capecitabine

Supportive care

Nutritional management including assessment, counseling and supplementary feeding (e.g. 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.

5. 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 the following:

- H & P exam (including a complete head and neck exam; mirror and fiberoptic examination)
  - Year 1: every 1-3 months
  - Year 2: every 2-6 months
  - Year 3-5: every 4-8 months
  - > 5 years: every 12 months
- Imaging:
  - Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 month of treatment
  - Chest X-ray or CT scan as clinically indicated for patients with smoking history
  - Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination
  - Routine annual imaging (repeat use of pre-treatment imaging modality) may be indicated in areas difficult to visualize on exam.
- Thyroid -stimulating hormones (TSH) every 6-12 months or as indicated if neck irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intraoral radiation treatment.
- Supportive care and rehabilitation
  - Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated.
  - Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is indicated.
  - Ongoing surveillance for depression
  - Smoking cessation and alcohol counseling as clinically indicated.

C. Hypopharyngeal cancers

1. Introduction

Hypopharyngeal cancer includes tumors arising from the pyriform sinus, posterior pharyngeal wall, post cricoid 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

Clinical Presentation

- Dysphagia
- Odynophagia
- Change in speech (dysarthria)
- Neck mass
- Referred otalgia
- Throat pain
- Weight loss
- Sensation of mass in throat
- Hoarseness

2. Workup

- **History and Physical examination:** A thorough history and physical examination is paramount in diagnosis of hypopharyngeal carcinoma. This includes a complete head and neck exam; EUA with endoscopy; mirror and/or fiberoptic examination as clinically indicated. 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.

3. Staging

Staging is based on the following;

- The clinical presentation and Physical examination
- Imaging reports (Laryngoscopy. Esophagoscopy, CT Scan/MRI etc)

Clinical T Stage

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 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.

Clinical N Stage

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 Metastases 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(+)

NOTE: A designation of «U» or «L» may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

T1, N0, selected T2, N0)

- **Surgery**

When expertise becomes available, partial laryngopharyngectomy + neck dissection, + hemithyroidectomy and pretracheal and ipsilateral paratracheal lymph node dissection. This can be followed by radiotherapy or concurrent chemoradiotherapy if there are adverse features.

T2-3, N0-3:

- **Induction chemotherapy:** This can be followed by definitive RT or consider systemic therapy/RT or Surgery.
- **Surgery:** Partial or total laryngopharyngectomy + neck dissection, + hemithyroidectomy and as indicated pretracheal and ipsilateral paratracheal lymph node dissection. This can be followed by radiotherapy or concurrent chemoradiotherapy if there are adverse features.
- **Concurrent Chemoradiotherapy**

Radiation therapy

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.

CT Simulation

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 simulators can be used.

Radiotherapy Details

Definitive:

RT alone

- Tis, N0: 60.75 Gy (2.25Gy/fraction) to 66Gy (2Gy/fraction)
- T1, N0: 63Gy (2.25/fraction – preferred) to 66Gy (2Gy/fraction)
- T2, N0 "65.25 (2.25Gy/fraction) to 70Gy (2Gy/fraction)
- >T2, N1:
  - PTV
    - High risk: Primary tumor and involved lymph nodes
      - 66Gy (2.2Gy/fraction) to 70-70.2Gy (preferred) (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks
      - 66.96Gy (2.12Gy/fraction) daily Monday- Friday in 6-7 weeks

- Low to intermediate risk: Sites of suspected subclinical spread
  - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Concurrent Chemoradiation

Preferred for patients eligible for chemotherapy

- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66-70.2Gy (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks; typically 70Gy (2Gy/fraction);daily Monday- Friday in 7 weeks.
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Postoperative

RT alone or concurrent Systemic Therapy/RT if adverse features

- Preferred interval between resection and postoperative RT is </= 6 weeks.
- PTV
  - High risk: Adverse features such as positive margins
    - 60-66Gy(2Gy/fraction); daily Monday -Friday in 6-6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Chemotherapy details

- For concurrent chemoradiotherapy IV Cisplatin 40mg/m2 weekly or 100mg/m² every three weeks is used.
- TPF or TP (Taxane, Platinum and 5 FU) is used for induction therapy and/or sequential therapy.
  - TPF: IV Docetaxel 75mg/m² D1 /IV 5 FU 750mg D1-D5/IV Cisplatin 75mg/m² D1 for at least 3 cycles or,
  - TP: IV carboplatin AUC 5 or 6 D1/IV Paclitaxel 175mg/m² D1 for at least three cycles

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 with similar doses as those used in curative intent above.

Combination therapy

- IV Carboplatin / IV Paclitaxel
- IV Cisplatin/ IV 5-FU,
- IV Cisplatin/ IV gemcitabine,

Single agents

- Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5-FU, Methotrexate, Gemcitabine or Capecitabine

5. Follow-Up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow up includes the following:

- H&P exam (including a complete head and neck exam; mirror and fiberoptic examination)
  - Year 1: every 1-3 months
  - Year 2: every 2-6 months
  - Year 3-5: every 4-8 months
  - > 5 years: every 12 months
- Imaging:
  - Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 months of treatment
  - Chest x ray or CT scan as clinically indicated for patients with smoking history
  - Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination
  - Routine annual imaging (great use of pretreatment imaging modality) may be indicated in areas difficult to visualize on exam.
- Thyroid -stimulating hormones (TSH) every 6-12 months or as indicated if the neck irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intraoral radiation treatment.
- Supportive care and rehabilitation
  - Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated.
  - Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is indicated.
  - Ongoing surveillance for depression
  - Smoking cessation and alcohol counseling as clinically indicated.

D. Salivary gland

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 the primary site involved. Mass
- Pain
- Nerve palsies Neck mass

2. Workup

- **History and Physical examination:** A thorough history and physical examination is paramount in diagnosis of salivary gland cancers.
- **Imaging:**
  - Chest X-ray and Abdominal pelvic U/S
  - CT scan and/or MRI of head and neck
- **Pathology:** Definitive diagnosis is confirmed by biopsy of the primary tumor. Fine needle aspiration of a neck mass may also be used.
- **Others:** Nutritional and dental evaluation are also important.

3. Staging

Staging is based on the following;
The clinical presentation and Physical examination Imaging reports (CT Scan/MRI of head and neck)

Major Salivary Gland
Clinical T Stage

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 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 extrapa-renchymal extension*
T3	Tumor larger than 4 cm and/or tumor having extraparenchymal extension*
T4	Moderately advanced and very advanced local 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.

Clinical N Stage

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** Metastases 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(+)

NOTE: A designation of «U» or «L» may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

Major and Minor Salivary Gland (Parotid, submandibular, sublingual)
Surgery with complete resection of tumor +/- neck dissection for high grade and/or T3-4 tumors and cLN+.

- If completely resected and
  - No adverse features then follow up.
  - If adenoid cystic histology then RT
  - If adverse features (intermediate or high grade, close or positive margins, neural/perineural invasion, LN+, LVI or T3-T4) then adjuvant RT (preferred) of systemic therapy/RT.
- If Incompletely resected, gross residual disease
  - Resection if possible and follow as above for complete resection
  - If no further resection possible then definitive RT or systemic therapy/RT

Radiation Details

- VMAT

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

Radiotherapy Details
Definitive:
RT alone or concurrent systemic therapy/RT

- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66Gy (2.2Gy/fraction) to 70-70.2Gy (preferred) (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Concurrent Chemoradiation
Preferred for patients eligible for chemotherapy

- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66-70.2Gy (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks; typically 70Gy (2Gy/fraction); daily Monday- Friday in 7 weeks.
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Postoperative

RT alone or concurrent Systemic Therapy/RT

Preferred interval between resection and postoperative RT is </= 6 weeks.

- PTV
  - High risk: Adverse features such as positive margins
    - 60-66Gy(2Gy/fraction);daily Monday -Friday in 6-6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Recurrent and metastatic disease

Locoregional recurrence without prior RT

- Resectable
  - Completely resected
  - RT
  - If adverse features then adjuvant RT or systemic therapy/RT
- Unresectable
  - RT or systemic therapy/RT

Locoregional recurrence or second primary with prior RT

- Resectable
  - Surgery or reirradiation +/- chemotherapy
- Unresectable
  - Reirradiation+/- chemotherapy
  - Chemotherapy
  - Distant metastases (PS 0-3)
  - Chemotherapy or
  - Expectant management (with slow-growing disease)
  - Selected metastasectomy
  - Best supportive care

Chemotherapy

Chemotherapy is less studied in the salivary gland histologies. Systemic therapy may be used for palliation in advanced disease. Various agents alone or in combination (e.g., cisplatin, cyclophosphamide, doxorubicin, epirubicin, carboplatin and vinorelbine) have been shown in small series to be active for some salivary gland malignant histologies.

5. Follow Up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow up includes the following:

- H & P exam (including a complete head and neck exam; mirror and fiberoptic examination)
  - Year 1: every 1-3 months
  - Year 2: every 2-6 months
  - Year 3-5: every 4-8 months
  - > 5 years: every 12 months
- Imaging:
  - Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 month of treatment
  - Chest x ray or CT scan as clinically indicated for patients with smoking history
  - Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history , and areas inaccessible to clinical examination
  - Routine annual imaging (great use of pretreatment imaging modality) may be indicated in areas difficult to visualize on exam.
- Thyroid -stimulating hormones (TSH) every 6-12 months or as indicated if the neck irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intraoral radiation treatment.
- Supportive care and rehabilitation
  - Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated.
  - Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is indicated.
  - Ongoing surveillance for depression
  - Smoking cessation and alcohol counseling as clinically indicated.

E. Nasal cavity and Paranasal sinus Cancer

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

2. Workup

- **History and Physical exam**: A thorough history and physical examination is very important.
- **Imaging:**
  - Chest X-ray and Abdominopelvic U/S
  - 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.Common histologies are: SCC, Adenocarcinoma, minor salivary gland tumor, esthesioneuroblastoma, undifferentiated carcinoma (SNUC, small cell or SNEC).

3. Staging

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.

Maxillary Sinus

Clinical T Stage

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Tumor *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, sub-cutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4	Moderately advanced and 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 verve (V2), nasopharynx, or clivus.

Nasal cavity and ethmoid sinus

Clinical T Stage

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Tumor *in situ*
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4	Moderately advanced and very advanced local disease
T4a	Moderately advanced local disease. Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, 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 (V2), nasopharynx, or clivus.

Clinical N Stage

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** Metastases 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 (+)

NOTE: A designation of «U» or «L» may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE (–) or ENE(+).

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

T1-2, N0 all histologies except adenoid cystic

- Resection
  - Margin negative -> Follow up
  - Perineural, vascular or lymphatic invasion
    - RT or
    - Systemic therapy/RT
  - Margin positive
    - Re-resection if feasible
      - Margin negative
    - Consider RT
  - Margin positive
    - RT or
    - Systemic therapy/RT

T1-2, N0 Adenoid cystic

- Resection followed by RT or consider observation for margin negative, no perineural spread.

T3-4a, N0

- Complete resection
  - Adverse features
    - RT or systemic therapy/RT to primary and neck
  - No adverse features
    - RT to primary and neck

T1-4a, N+

- Resection + neck dissection
  - Adverse features
    - RT or systemic therapy/RT to primary and neck
  - No adverse features
    - RT to primary and neck

T4b, N0-3

- Definitive RT or systemic therapy/RT

Metastatic Disease

- Systemic chemotherapy

CT Simulation

- Set up the patient in supine position with the head extended.
- Eyes open, straight ahead to keep the posterior pole away from the high dose region.
- The immobilization device should include at least the head and neck (thermoplastic device).
- 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.

Radiotherapy Details
Definitive:
RT alone

- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66Gy (2.2Gy/fraction) to 70-70.2Gy (preferred) (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Concurrent Chemoradiation

Preferred for patients eligible for chemotherapy

- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66-70.2Gy (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks; typically 70Gy (2Gy/fraction); daily Monday- Friday in 7 weeks.
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Postoperative

RT alone or concurrent Systemic Therapy/RT

Preferred interval between resection and postoperative RT is </= 6 weeks.

- PTV
  - High risk: Adverse features such as positive margins
    - 60-66Gy(2Gy/fraction);daily Monday -Friday in 6-6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Chemotherapy Details

- For concurrent chemoradiotherapy IV Cisplatin 40mg/m2 weekly or 100mg/m2 every three weeks is used.
- TPF or TP (Taxane, Platinum and 5 FU) is used for induction therapy and/or sequential therapy.
- TPF: IV Docetaxel 75mg/m2 D1 /IV 5 FU 750mg/m2 D1-D5/IV Cisplatin 75mg/m2 D1 for at least 3 cycles or,
- TP: IV carboplatin AUC 5 or 6 D1/IV Paclitaxel 175mg/m2 D1 for at least three cycles

5. Follow up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow up includes the following:

- H & P exam (including a complete head and neck exam; mirror and fiberoptic examination)
  - Year 1: every 1-3 months
  - Year 2: every 2-6 months
  - Year 3-5: every 4-8 months
  - > 5 years: every 12 months
- Imaging:
  - Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 month of treatment
  - Chest x ray or CT scan as clinically indicated for patients with smoking history
  - Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history , and areas inaccessible to clinical examination
  - Routine annual imaging (great use of preteatment imaging modality) may be indicated in areas difficult to visualize on exam.
- Thyroid -stimulating hormones (TSH) every 6-12 months or as indicated if the neck irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intraoral radiation treatment.
- Supportive care and rehabilitation
  - Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated.
  - Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is indicated.
  - Ongoing surveillance for depression
  - Smoking cessation and alcohol counseling as clinically indicated.

F. Oral cavity Cancer

1. 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

- Non Healing painful ulcer
- Speech difficulty
- Hypersalivation
- Neck mass
- Dysphagia
- Otalgia

2. Workup

- **History and Physical examination:** History and physical examination is necessary in diagnosis of oral cavity carcinoma including complete head and neck examination As clinically indicated:
  - Chest X-ray
  - Abdominal US
  - CT scan and/or MRI of the primary and neck Mirror and fibre-optic endoscopic examination
  - Dental/prosthodontic evaluation
  - Nutrition , speech and swallowing evaluation/therapy
- **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.

3. Staging

Staging is based on the following;
The clinical presentation and Physical examination Imaging reports (Endoscopy, CT Scan/ MRI etc)

Clinical T Stage

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Tumor *in situ*
T1	Tumor ≤2 cm with depth of invasion (DOI)* ≤5 mm

T2	Tumor ≤2 cm, with DOI* >5 mm and ≤10 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 (eg, 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.

* DOI is depth of invasion and not tumor thickness.

Clinical N Stage

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** Metastases 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 (+)

NOTE: A designation of «U» or «L» may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

T1-2 N0

1. Surgery (Preferred)
- Resection of the primary +/- neck dissection
  - No positive LN and no adverse
    - Follow up
  - One positive LN without adverse features
    - Consider RT
  - Adverse features
    - Re-resect for positive margins
    - Systemic therapy/RT (ENE+)
    - RT

2. Definitive RT

T3, N0; T1-3, N1-3; T4a, N0-3

1.Surgery
- Resection of primary, ipsilateral, or bilateral neck dissection
  - RT alone if no adverse features
  - Systemic therapy/RT if adverse features (re-resection for positive margins if feasible)

2. Palliative systemic therapy/RT or palliative RT or best supportive care for very advanced disease.

CT Simulation

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.

Radiotherapy Details
Definitive:
RT alone
- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66Gy (2.2Gy/fraction) to 70-70.2Gy (preferred) (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Concurrent Chemoradiation

Preferred for patients eligible for chemotherapy

- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66-70.2Gy (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks; typically 70Gy (2Gy/fraction); daily Monday- Friday in 7 weeks.
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Postoperative

RT alone or concurrent Systemic Therapy/RT

Preferred interval between resection and postoperative RT is </= 6 weeks.

- PTV
  - High risk: Adverse features such as positive margins
    - 60-66Gy(2Gy/fraction);daily Monday -Friday in 6-6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Chemotherapy details

- For concurrent chemoradiotherapy IV Cisplatin 40mg/m² weekly or 100mg/m² every three weeks is used.
- TPF or TP (Taxane, Platinum and 5 FU) is used for induction therapy and/or sequential therapy.
  - TPF: IV Docetaxel 75mg/m² D1 /IV 5 FU 750mg/m² D1-D5/IV Cisplatin 75mg/m² D1 for at least 3 cycles or,
  - TP: IV Carboplatin AUC 5 or 6 D1/IV Paclitaxel 175mg/m² D1 for at least three cycles

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 a metastatic setting, palliative chemotherapy should be considered for patients with adequate performance status.

5. Follow up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow up includes the following:

- H & P exam (including a complete head and neck exam; mirror and fiberoptic examination)
  - Year 1: every 1-3 months
  - Year 2: every 2-6 months
  - Year 3-5: every 4-8 months
  - > 5 years: every 12 months
- Imaging:
  - Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 months of treatment
  - Chest Xray or CT scan as clinically indicated for patients with smoking history
  - Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination
  - Routine annual imaging (use of pretreatment imaging modality) may be indicated in areas difficult to visualize on exam.
- Thyroid -stimulating hormones (TSH) every 6-12 months or as indicated if the neck irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intraoral radiation treatment.
- Supportive care and rehabilitation
  - Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated.
  - Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is indicated.
  - Ongoing surveillance for depression
  - Smoking cessation and alcohol counseling as clinically indicated.

G. Oropharyngeal Cancer

1. 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 if available.

Clinical Presentation

- Sore throat,
- Non healing oropharyngeal ulcers
- Dysphagia,
- Referred otalgia,
- Hoarseness (with larynx invasion),
- Odynophagia,
- Hot potato voice
- Impaired tongue movement, including protrusion.

2. Workup

- **History and Physical exam:** A thorough history and physical examination including a complete head and neck examination with addition of Indirect mirror examination, fibre-optic 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

3. Staging

Staging is based on the following;

The clinical presentation and Physical examination Imaging reports (Endoscopy, CT Scan/ MRI etc)

Clinical T Stage

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Tumor *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.

* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Clinical N Stage

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** Metastases 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(–)
N2	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 (+)

NOTE: A designation of «U» or «L» may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE (–) or ENE(+).

Clinical M Stage

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

T1-2, N0-1

1. Definitive RT or
2. Resection of primary and ipsilateral or bilateral neck dissection
    - Follow up if no adverse features
    - RT or Systemic therapy/RT if adverse features
3. Concurrent systemic therapy/ RT for T1-2, N1 only

T3-4a, N0-1 or T1-4, N2-3

1. Concurrent systemic therapy/RT or
2. Resection of primary and ipsilateral or bilateral neck dissection
    - RT alone if no adverse features
    - Systemic therapy/RT if adverse features
3. Induction chemotherapy or systemic therapy/RT

CT Simulation

- 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.

Radiotherapy Details
Definitive:
RT alone

- PTV
    - High risk: Primary tumor and involved lymph nodes
        - 66Gy (2.2Gy/fraction) to 70-70.2Gy (preferred) (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks
    - Low to intermediate risk: Sites of suspected subclinical spread
        - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Concurrent Chemoradiation

Preferred for patients eligible for chemotherapy

- PTV
  - High risk: Primary tumor and involved lymph nodes
    - 66-70.2Gy (1.8-2Gy/fraction) daily Monday-Friday in 6-7 weeks; typically, 70Gy (2Gy/fraction); daily Monday- Friday in 7 weeks.
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Postoperative

RT alone or concurrent Systemic Therapy/RT

Preferred interval between resection and postoperative RT is </= 6 weeks.

- PTV
  - High risk: Adverse features such as positive margins
    - 60-66Gy(2Gy/fraction); daily Monday -Friday in 6-6.5 weeks
  - Low to intermediate risk: sites of suspected subclinical spread
    - 44-50Gy (2Gy/fraction) to 54-63Gy (1.6-1.8Gy/fraction)

Chemotherapy details

- For concurrent chemoradiotherapy IV Cisplatin 40mg/m² weekly or 100mg/m² every three weeks is used.
- TPF or TP (Taxane, Platinum and 5 FU) is used for induction therapy and/or sequential therapy.
  - TPF: IV Docetaxel 75mg/m² D1 /IV 5 FU 750mg D1-D5/IV Cisplatin 75mg/m² D1 for at least 3 cycles or,
  - TP: IV carboplatin AUC 5 or 6 D1/IV Paclitaxel 175mg/m² D1 for at least three cycles

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 a metastatic setting, palliative chemotherapy should be considered for patients with adequate performance status.

5. Follow up

Post treatment surveillance is important for early detection of recurrent local or metastatic disease and for monitoring for toxicity. Follow up includes the following:

- H & P exam (including a complete head and neck exam; mirror and fiberoptic examination)
  - Year 1: every 1-3 months
  - Year 2: every 2-6 months
  - Year 3-5: every 4-8 months
  - > 5 years: every 12 months
- Imaging:
  - Post-treatment, consider repeating pre-treatment baseline imaging of primary (and neck, if treated) within 6 months of treatment
  - Chest x ray or CT scan as clinically indicated for patients with smoking history
  - Further reimaging as indicated based on worrisome or equivocal signs/symptoms, smoking history, and areas inaccessible to clinical examination
  - Routine annual imaging (great use of pretreatment imaging modality) may be indicated in areas difficult to visualize on exam.

- Thyroid -stimulating hormones (TSH) every 6-12 months or as indicated if the neck irradiated.
- Dental evaluation for oral cavity and sites exposed to significant intraoral radiation treatment.
- Supportive care and rehabilitation
  - Speech/hearing and swallowing evaluation and rehabilitation as clinically indicated.
  - Nutritional evaluation and rehabilitation as clinically indicated until nutritional status is indicated.
  - Ongoing surveillance for depression
  - Smoking cessation and alcohol counseling as clinically indicated.

THORACIC MALIGNANCIES

A. Lung Cancer

- 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, broncho-alveolar 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.

A.1. Small Cell Lung Cancer (SCLC)

1. Introduction

- Small cell lung cancer is the aggressive form of lung cancer, which most commonly occurs in smokers.
- It usually starts in bronchioles and grows very quickly, resulting into a large mass and eventually spread throughout the body (metastasizing).
- The common risk factors are – smoking cigarettes, pipes or cigars, second hand smoke exposure, exposure to asbestos, arsenic, chromium, beryllium, nickel, any family history of lung cancer, HIV infection, and being exposed to radiation.
- **Symptoms comprise** – bloody phlegm, cough, chest pain and shortness of breath.

2. Workup

- History and Physical Examination
- Pathology review – post biopsy, possibly with bronchoscopy and/or CT-guided biopsy
- Full Blood Count (FBC), Electrolytes, liver function tests, renal function tests
- Chest, abdomen, pelvis CT scan
- Brain MRI.

The following additional workup is made based on the different staging –limited or extensive stage – of the disease, which differs from the Non- Small cell part, which uses the mass size, nodal disease and presence of metastatic disease in its staging. The limited stage class refers to a disease that is only on one side of the chest, and that can be treated with a single radiation field. It 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. The extensive stage class refers to a disease that has spread widely throughout the lung, the contra-lateral lung, and to lymph nodes on the other side of the chest, or to other parts of the body (including bone marrow)

For limited stage, the additional workup (for potential upstaging) is:

- If pleural effusion is present – thoracentesis is recommended
- Pulmonary function tests – during evaluation for surgery or definitive radiation therapy
- Consider unilateral marrow aspiration or biopsy for patients presenting with neutropenia or thrombocytopenia on FBC, and nucleated red blood cells on peripheral blood smear, suggestive of bone marrow infiltration (becomes extensive stage)

3. Staging

TNM staging

Limited stage: stage I-III (any T, any N, M0) that can be safely treated with definitive radiation doses. Excludes T3-4, due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan

Extensive stage: Stage IV (any T, any N, M1a/b/c), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan

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, ≤ 3cm 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 ≤4cm or if the size cannot be determined and T2b if >4cm but ≤5cm
T2a	Tumor >3cm but ≤4cm in greatest dimension
T2b	Tumor >4cm but ≤5cm 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 non-bloody 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 extra-thoracic metastasis in a single organ (including involvement of a single non-regional node)
cM1c	Multiple extra-thoracic metastases in a single organ or in multiple organs

4. Management

The treatment includes surgery (for small tumors) as well as chemotherapy, sometimes in combination with radiation therapy.

4.1. Limited stage SCLC

- **Clinical stage I-IIA (T1-2, N0, M0) – with pathologic mediastinal staging with chest CT negative: Lobectomy (preferred):**
  - N0 – add systemic therapy
  - N1 – systemic therapy +/- mediastinal RT (sequential or concurrent)
  - N2 – systemic therapy + mediastinal RT (sequential or concurrent)

- **For patients who are medically inoperable or decision is made not to pursue surgical resection:**
  - Systemic therapy + concurrent or sequential RT

- **Clinical stage I-IIA – with positive mediastinal staging with chest CT positive:**
  - Good Performance Status (PS) (0-2) – systemic therapy + concurrent or sequential RT
  - Poor performance status (3-4) due to SCLC - systemic therapy +/- concurrent or sequential RT
  - Poor performance status (3-4) not due to SCLC – Individualized treatment including supportive care

- **Clinical stage IIB-IIIC (T3-4, N0, M0; T1-4, N1-3, M0):**
  - Good Performance Status (0-2) – systemic therapy + concurrent or sequential RT
  - Poor performance status (3-4) due to SCLC - systemic therapy +/- concurrent or sequential RT
  - Poor performance status (3-4) not due to SCLC – Individualized treatment including supportive care

4.2. Extensive stage

- **Extensive stage without localized symptomatic sites or brain metastases:**
  - Good PS (0-2) OR Poor PS (3-4) due to SCLC: Combination systemic therapy including supportive care;
  - Poor PS (3-4) not due to SCLC: Individualized therapy including supportive care

- **Extensive stage with localized symptomatic sites**
  - Superior Vena Cava (SVC) syndrome OR lobar obstruction OR bone metastasis – systemic therapy + RT to symptomatic sites; If high risk of fracture due to osseous structural impairment, consider orthopedic stabilization and palliative external beam RT;
  - Spinal Cord compression: RT to symptomatic sites before systemic therapy unless immediate systemic therapy is required

- **Extensive stage with brain metastases:**
  - Asymptomatic patients: May administer systemic therapy before brain RT (WBRT), after completion of induction systemic therapy
  - Symptomatic patients: Brain RT (WBRT) before systemic therapy, unless immediate systemic therapy is indicated

4.3. Principles of Surgery

Indicated in Stage I-IIA SCLC (<5% of patients), after standard staging evaluation. The preferred operation is lobectomy, with mediastinal lymph node dissection. Patients undergoing complete resection should be treated with post-operative systemic therapy. The benefit of Prophylactic Cranial Irradiation (PCI) is unknown in patients who have undergone complete resection for pathologic stage I-IIA (T1-2N0M0) SCLC; need to consider PCI or brain MRI CT surveillance for N0

4.4. Principles of Chemotherapy

Primary or adjuvant chemotherapy for limited stage SCLC:

- 4 cycles of systemic therapy are recommended. Planned cycle length should be every 21-28 days during concurrent RT (with Cisplatin and Etoposide).
- Recommended regimens: Cisplatin IV 75 mg/m² day 1 and Etoposide IV 100 mg/m² on days 1, 2, 3 OR Cisplatin IV 60 mg/ m² on day 1, and Etoposide IV 120 mg/ m² days 1, 2, 3 or Carboplatin AUC 5-6 days 1 and Etoposide 100 mg/m² on days 1, 2, 3.

Chemotherapy as a primary therapy for extensive stage SCLC:

- 4 cycles are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.
- Recommended regimens: Carboplatin IV AUC 5-6 day 1 and Etoposide IV 100 mg/m² on days 1, 2, 3 OR Cisplatin IV 75/ m² on day 1 and Etoposide IV 100 mg/m² on days 1, 2, 3 OR Cisplatin IV 80/m² on day 1 and Etoposide IV 80 mg/m² on days 1, 2, 3 OR Cisplatin IV 25 mg/m² on day 1 and Etoposide IV 100 mg/m² on days 1, 2, 3
- In case of relapse ≤ 6 months (PS 0-2): Topotecan PO or IV OR single agent Paclitaxel, Docetaxel or Irinotecan.
- In case of relapse > 6 months, with a good PS – consider original treatment

4.5. Principles of Radiation Therapy

Limited Stage:

- Post-operative RT is recommended in pathologic N2 disease, and may be considered in pathologic N1 disease, for patients with otherwise clinical stage I-IIA (T1-2, N0, M0).
- Medically inoperable patients – or patients in whom a decision not to pursue surgery is made: Definitive RT.
- RT concurrent with systemic therapy is standard and preferred to sequential chemotherapy and RT
- Planning: Supine, Volume to be based on pre-surgical staging. Clinically uninvolved mediastinal nodes, historically included in RT target volumes – are no longer added as part of elective nodal irradiation (ENI). For sequential treatment (post chemotherapy) – volumes to include post-induction systemic therapy volume to avoid excessive toxicity; initially involved nodal regions should be covered.
- Timing: Radiation needs to start before cycle 2 of chemotherapy (if concurrent).
- Dose: 60-70 Gy, with conventional fractionation, or where possible, 45 Gy in 1.5 Gy twice daily, given in 3 weeks

Extensive Stage:

- Consolidative thoracic RT is beneficial for selected patients with complete or good response to systemic therapy if residual disease and/or low-bulk extra-thoracic metastatic disease are present.
- Usual dose: 30 Gy in 10 fractions or 60 Gy in 30 fractions

Prophylactic Cranial Irradiation (PCI):

- In patients with limited stage SCLC with good response to initial therapy, PCI decreases brain metastases and increases overall survival. In patients with extensive stage SCLC who respond to systemic therapy, PCI decreases brain metastases.
- Dose: 25 Gy in 10 fractions. A shorter course may be appropriate for some patients with extensive-stage disease.
- PCI is not recommended in patients with poor performance status or impaired neuro-cognitive functioning

Brain metastases:

- Typically treated with Whole Brain Radiation Therapy
- Recommended dose: 30 Gy in 10 fractions. If brain metastases are present post PCI, repeat WBRT for a few selected patients, or best supportive care

Palliative radiation for extracranial masses:

- Common radiation dose-fractionation regimens – 30 Gy in 10 fractions, 20 Gy in 5 fractions or 8 Gy in 1 fraction

5. Follow-up

- Chest, abdomen, pelvis CT with contrast, Brain MRI or CT with contrast and routine laboratory workup (FBC, LFTs, RFTs):

Complete or partial response:

- Limited Stage – PCI. After completion of initial therapy – oncology follow-up every 3 months during year 1-2, every 6 months during year 3, then annually;
- Extensive Stage – Consider PCI or MRI brain surveillance; consider thoracic RT. After completion of initial therapy – oncology follow-up every 2 months during year 1, every 3-4 months during year 2-3, then every 6 months during years 4-5, then annually

Stable disease:

- Limited Stage – After completion of initial therapy: oncology follow-up every 3 months during year 1-2, every 6 months in year 3, then annually
- Extensive Stage – After completion of initial or subsequent therapy: oncology follow-up every 2 months during year 1, every 3-4 months during year 2-3, then every 6 months

NOTE: At every visit – history and physical examination, CT chest, abdomen, pelvis; blood work as indicated; Brain MRI/CT scan with contrast every 3-4 months during year 1, then every 6 months during year 2; new pulmonary nodule should initiate workup for potential new primary

Primary progressive disease or relapse:

- PS (0-2) – subsequent systemic therapy OR palliative symptom management, including localized RT to symptomatic sites. Continue until progression or development of unacceptable toxicity, with subsequent systemic therapy provided in case of progression (if performance status allows).
- PS (3-4) – palliative symptom management, including localized RT to symptomatic sites.

A.2. Non-Small Cell Lung Cancer

1. 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.
- Chest CT scan screening for non-small cell lung cancer is usually recommended for 40 pack-year smoking, elsewhere.
- The common clinical presentation features are:
  - Cough
  - Hemoptysis
  - Chest pain
  - Wheezing
  - Dyspnea

2. Workup

- History and Physical Examination – Performance Status
- Chest X/ray
- CT Chest and upper abdomen with contrast + adrenals
- FBC, organ function tests, Chemistry profile
- Pathology review (post-bronchoscopy) + Sputum Cytology.
- PET scan
- Cytologic confirmation is not mandatory

3. Staging

Staging is based on the clinical presentation and Physical examination along with MRI Brain for patients with neurological symptoms to rule out brain metastasis. For TNM staging details, refer to the SCLC staging.

4. Management

4.1. Stage IA (peripheral T1abc, N0):

- Pulmonary function tests, Bronchoscopy, consider CT-guided biopsy for pathologic mediastinal lymph node evaluation; Chest CT
- If negative or unknown mediastinal nodes:
  - Operable patients – surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
  - If margins are negative – Observe
  - If margins are positive – Re-resection (if possible) OR RT
  - If medically inoperable – definitive RT
- If positive mediastinal nodes – upstage: see management of stage IIIA/IIIB

4.2. Stage IB (peripheral T2a, N0), Stage I (Central T1abc-T2a, N0), Stage II (T1abc-2ab, N1; T2b, N0), Stage IIB (T3, N0) and Stage IIIA (T3, N1)

- Pulmonary function tests, Bronchoscopy, consider CT-guided biopsy for pathologic mediastinal lymph node evaluation; Chest CT, Brain MRI or CT with contrast
- If negative or unknown mediastinal nodes:
  - Operable patients – surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
  - If margins are negative – observe (IB) or Chemotherapy for high risk patients (IB, IIA, IIB and IIIA)
  - If margins are positive – re-resection (if possible) OR RT
  - If medically inoperable – N0: Definitive RT; N1: Definitive or sequential chemo-radiation; consider adjuvant chemotherapy for high-risk stages IB-IIB.

4.3. Stage IIB (T3 invasion, N0), Stage IIIA (T4 extension, N0-1; T3, N1; T4, N0-1)

- Pulmonary function tests (if not done previously), bronchoscopy, CT-guided biopsy for pathologic mediastinal lymph node evaluation, Brain MRI or CT-scan with contrast, MRI spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels.
  - Superior Sulcus tumor (T3 invasion, N0-1): Preoperative chemo-radiation OR Preoperative sequential radiation followed by chemotherapy THEN surgery + chemotherapy
  - Superior Sulcus tumor (T4 extension, N0-1):
    - Possibly resectable: Preoperative chemo-radiation OR Preoperative sequential radiation followed by chemotherapy THEN surgical re-evaluation with Contrast chest CT scan. If disease is resectable – surgery + chemotherapy. If disease is not resecta ble – complete definitive RT + Chemotherapy.
    - Unresectable disease: Definitive concurrent chemo-radiation or definitive sequential radiation followed by chemotherapy.
  - Chest wall, proximal airway, or mediastinum (T3 invasion, N0-1 and resectable T4 extension, N0-1):
    - Chemotherapy OR Concurrent chemoradiation THEN surgical re-evaluation including chest CT with contrast followed by surgery. If negative margins are present – observe; if positive margins are present – re-resection.
    - Surgery: Margins negative – follow with chemotherapy; Positive margins – follow with re-resection + chemotherapy OR RT or chemoradiation (concurrent or sequential)
  - Stage IIIA (T4, N0-1), Unresectable – Definitive concurrent chemoradiation OR definitive sequential radiation followed by chemotherapy

4.4. Stage IIIA (T1-2, N2); Stage IIIB (T3, N2); Separate pulmonary nodules (Stage IIB, IIIA, IV):

Stage IIIA, IIIB - Usual workup investigations:

- N2, N3 nodes negative – treat as T1-3, N0-1 (see point 4.2)
- N2 positive, M0 – Definitive chemoradiation OR induction chemotherapy. If no apparent progression post induction chemotherapy – surgery +/- RT; if progression is present – Local: RT +/- chemotherapy; Systemic: Treat as metastatic disease (see 4.7. below)
- N3 positive, M0 – Definitive concurrent chemoradiation OR definitive sequential chemo-radiation - Separate pulmonary nodule (s) – Stage IIB, IIIA, IV – usual workup investigations:

4.5. Multiple lung cancers (N0-1)

Asymptomatic:

- Multiple lesions – Observe OR definitive local therapy – with RT;
- Solitary lesions – Definitive local therapy with RT; if definitive local therapy is not possible – Palliative chemotherapy +/- local palliative therapy OR observe

Symptomatic: Definitive local therapy with RT; if definitive local therapy is not possible – Palliative chemotherapy +/- local palliative therapy OR observe

4.6. Principles of Systemic Therapy

Concurrent chemo-radiation:

- Carboplatin + Docetaxel; Doses are: IV Carboplatin AUC 2 and Docetaxel 45mg/m², weekly for 6 weeks (of radiation therapy)
- Cisplatin + Etoposide; Doses are: IV Cisplatin 25mg/m² and Etoposide 100mg/m² both for 3 consecutive days. Start first cycle with 1st day of radiation therapy; repeat every 3 weeks for 4 cycles.

Adjuvant chemotherapy:

- Carboplatin + Paclitaxel; Doses are: IV Carboplatin AUC 5-6 and Paclitaxel 200mg/m² every 3 weeks for 6 cycles
- Cisplatin + Vinolrebine; Doses are: IV Cisplatin 80mg/m² on day 1 and Vinolrebine 30mg/m² on day 1, 8 and 15, every 3 weeks for 4 cycles.

Advanced/Metastatic Lung Cancer:

- Immunotherapy (if available):
  - EGFR mutation positive – 1st line: Afatinib; Doses are: Oral Afatinib 40mg daily
  - EGFR mutation positive – Maintenance after 1st line with cytotoxic chemotherapy (usually started with stable disease after 4-6 cycles with platinum-based doublet): Erlotinib; Doses are: Oral Erlotinib 150mg daily
  - ALK positive – 1st line: Alectinib; Doses are: Oral Alectinib 600mg twice daily; if not available – Crizotinib; Doses are: Oral Crizotinib 250mg twice daily
  - PD-L1 inhibition: Nivolumab IV 3mg/kg or maximum 240mg every 2 weeks OR Pembrolizumab (usually associated with Paclitaxel and Carboplatin) at dose: 2mg/kg (maximum 200mg) every 3 weeks for 4 cycles. Single agent Pembrolizumab can be used upfront or as maintenance post 4 cycles of combined Pembrolizumab and chemotherapy at same dose, every 3 – 6 weeks (dose reaches 4mg/kg if 6 weeks intervals are used)

- Chemotherapy:
  - Chemotherapy with Carboplatin and Paclitaxel (detailed above)
  - Pemetrexed (Non squamous cell carcinoma histologies); Doses are: 500mg/m² every 3 weeks continuously until high-grade toxicity or evidence of disease progression. Mandatory folic acid 0.4mg daily and Vitamin B12 1000mcg IM every 9 weeks, to start 7 days before 1st cycle of Pemetrexed. Pemetrexed can also be used in combination with Cisplatin at doses of 75mg/m2 (Pemetrexed doses, unchanged).

5. Follow-Up

- Follow-up 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 Chest X-ray every 3–4 months for 2 years, then every 6 months for 3 years, then annually.
- CT-chest to be done on an annual basis.

B. Thymoma and Thymic Carcinomas

1. Introduction

- Thymoma is a rare malignancy with an unknown etiology. The age of predilection is mostly in the middle-aged population, and in the 7th decade, but less so in children and young adults.
- The clinical presentations are – persistent cough, shortness of breath, pain/pressure in the chest, muscle weakness, and double vision.

2. Workup

- History and Physical Examination
- Chest CT with contrast
- Serum b-hCG, AFP if appropriate
- FBC, LFT, RFT
- Pulmonary function tests, as clinically indicated.

3. Staging

MasaokStage	Diagnostic Criteria
Stage I	Macroscopically and microscopically completely encapsulated
Stage II	Microscopic trans-capsular invasion Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
Stage III	Macroscopic invasion into neighboring organs (i.e. Pericardium, great vessels, lung) Without invasion of great vessels With invasion of great vessels
Stage IV	Pleural or pericardial dissemination Lymphogenous or hematogenous metastasis

TNM Staging

T 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 pleural 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, brachio-cephalic vein, superior vena cava, phrenic nerve, chest wall, or extra-pericardial pulmonary artery or veins
T4	Tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intra-pericardial pulmonary artery, myocardium, trachea, esophagus

N Staging

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in anterior (peri-thymic) lymph nodes
N2	Metastasis in deep intra-thoracic or cervical lymph nodes

M Staging

M Category	M Criteria
M0	No pleural, pericardial, or distant metastasis
M1	Pleural, pericardial, or distant metastasis
M1a	Separate pleural or pericardial nodules
M1b	Pulmonary intra-parenchymal nodule or distant organ metastasis

4. Management

a. Surgery Indications

- If tumor is surgically resectable – surgical resection – total thymectomy and complete excision of tumor.
- If tumor is advanced, and unresectable – tissue diagnosis with core needle biopsy; open biopsy, if core biopsy is not feasible or not diagnostic.

In the postoperative setting:

- R0 resection – if thymoma, with no capsular invasion or thymic carcinoma (Masaoka – Koga, stage I) – place patient on follow-up; If thymoma – or thymic carcinoma, with capsular invasion (Masaoka – Koga, stage II-IV) – consider postoperative RT.
- R1 resection – thymoma – consider postoperative RT; add chemotherapy to radiation if tissue study concludes in thymic carcinoma;
- R2 resection – thymoma OR thymic carcinoma – definitive RT _ Chemotherapy

b. Radiation Therapy

- Dose and fractionation schemes of RT depend on the indication of the radiation and completeness of surgical resection in post-operative cases
- Doses – 60-70 Gy given to patients with unresectable disease, and gross residual disease (R2); for adjuvant settings – consider 45-50 Gy for clear/close margins, and 54 Gy for patients with microscopic positive resection margins. Palliative doses – 8 Gy single fraction, 20 Gy in 5 fractions or 30 Gy in 10 fractions
- CTV (Post-operative disease) – entire thymus, surgical clips and potential sites with residual disease; Extensive Nodal Irradiation (ENI) – not recommended.

4.3. Systemic Therapy

- Thymoma, combination chemotherapy regimen – (All on Day 1) Cisplatin IV 50mg/m², Doxorubicin IV 50mg/m², Cyclophosphamide IV 500mg/m², administered every 3 weeks
- Thymic Carcinoma – (All on Day 1) Carboplatin IV AUC 6, Paclitaxel IV 200mg/m², administered every 3 weeks.
- Other regimens: Cisplatin IV 50mg/m² day 1, Doxorubicin IV 40mg/m² day 1, Vincristine 0.6mg/m² day 3, Cyclophosphamide IV 700mg/m² day 4, administered every 3 weeks OR Cisplatin IV 60mg/m² , day 1 and Etoposide IV 120mg/m² on day 1-3.

4.4. Recurrent Disease:

- Locally advanced – unresectable disease – concurrent chemo-radiation
- Potentially resectable – chemotherapy, then assess for resectability. If still not resectable – consider chemo-radiation;
- Solitary metastasis or ipsilateral pleural metastasis – consider chemotherapy then assess for resectability OR upfront surgery – then consider chemotherapy OR RT.
- If evidence of extra-thoracic metastases – chemotherapy.

5. Follow-Up

- Surveillance for recurrence with chest CT contrast every 6-12 months for 2 years, then annually for 5 years for thymic carcinoma, and 10 years for thymoma.

C. Thyroid Carcinoma

1. Introduction

Thyroid is the most common endocrine malignancy. 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.

Females are mostly affected, the male to female ratio being 3:1.

Clinical presentation varies from – anterior neck swelling, obstructive symptoms, stridor and hoarseness. Metastatic disease presents with weight loss, difficulty breathing, bone pain and pathological fractures.

2. Workup

- History and Physical Examination
- Laboratory tests – Thyroid function tests, FBC, Serum Calcium, Vitamin D level – if available
- Imaging – Chest X-Ray (if clinically indicated), Neck Ultrasound
- Nuclear Medicine – with thyroid scan and bone scans have a key role in thyroid malignancies' diagnosis
- Pathology – FNA under ultrasound guidance, wherever possible; Excisional Biopsy after positive FNA

3. Staging

TNM staging for Thyroid- differentiated and Anaplastic Carcinoma

T Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2cm or less in greatest dimension limited to the thyroid
T1a	Tumor ≤1cm in greatest dimension limited to the thyroid
T1b	Tumor >1cm but ≤2cm in greatest dimension limited to the thyroid
T2	Tumor >2cm but ≤4cm in greatest dimension limited to the thyroid
T3	Tumor >4cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor >4cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sterno-hyoid, sterno-thyroid, thyro-hyoid, or omo-hyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension beyond the strap muscle
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 staging

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No evidence of loco-regional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of loco-regional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral, or contra-lateral lateral neck lymph nodes (levels I, II, III, IV, or V) ot retropharyngeal lymph nodes

M Staging

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

4. Management

4.1. 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.

4.2. Radioactive Iodine Therapy (RAI) of differentiated thyroid carcinoma (DTC)

The therapy is defined as the systemic administration of I-131 sodium or potassium Iodide for selective irradiation of thyroid remnants, microscopic DTC, in the adjuvant setting or other non-resectable or incompletely respected DTC or both. There are 2 main forms of procedures:

a. Radio-Iodine Ablation
Given in the adjuvant setting, to increase sensitivity and specificity of using the serum thyroglobulin (Tg) assay as a tumor marker, and of diagnostic whole body scintigraphy, to detect occult metastases. I-131 decreases local recurrence and may have a survival benefit, in the adjuvant setting. Breast-feeding women should at least stop 6-8 weeks prior to RAI

treatment.

b. RAI scan

Usually performed to pick up occult metastases in the postoperative setting, but also for unresectable primary disease.

– Ablation Success Criteria:

On follow-up diagnostic Whole Body Scintigraphy – negative thyroid bed uptake or thyroid bed uptake beneath an arbitrary set, low threshold, eg. 0.1% or absence of suspicious findings on neck ultrasound.

4.3. Recurrence

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 I-131 iodine: Persistent abnormal uptake of 123/131-I after ablation generally requires repeat administration of 131-I with a higher dose.

4.4. Indications of palliative chemotherapy

Patients with visceral metastatic disease not responding to 131-Iodine may be offered palliative chemotherapy.

Regimen: Adriamycin IV 50mg/m2 every 3 weeks for a total of 6 weeks.

4.5. Indications of Radiation Therapy

Adjuvant radiation to the thyroid bed and neck nodes should be considered in the following situations:

- Macroscopic residual disease – consider imaging then resection if possible. If unresectable and RAI uptake is absent – monitoring of residual disease, consider radiation therapy if disease is threatening vital structures
- Microscopic/unresectable and local recurrence disease that does not take up I-131
- pT4 disease and extranodal 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.

5. 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 Thyroxine is indicated – in all patients post-ablation and post-lobectomy. The goal is to keep TSH <0.1 mU/L

D. Medullary Thyroid Cancer

1. Workup

All patients with a personal medical history of primary C cell hyperplasia, MTC, or MEN 2; patients with intestinal ganglio-neuromatosis; family history consistent with MEN 2 or FMTC, and at risk for autosomal dominant inheritance.

Investigations:

- Laboratory tests: FBC, Blood chemistry evaluation, CEA, Thyroid function tests, calcitonin levels, (albumin-corrected calcium or ionized calcium, plasma free metanephrines and normetanephrines, or 24-hour urine metanephrines and normetanephrines,
- Imaging: Neck ultrasound, neck CT, abdominal USS and CT, MRI, Preoperative chest CT, neck CT, and three-phase contrast enhanced multidetector liver CT or contrast-enhanced MRI and somatostatin receptor imaging
- Fine Needle Aspiration and Cytology

2. Management

2.1. Loco-regional disease

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 mI/UL

2.2. Metastatic disease

Surgery, External Beam Radiation Therapy, Percutaneous interventions, and hepatic embolization. Somatostatin analogs and cytotoxic chemotherapy have a limited role.

E. Anaplastic Thyroid Cancer

1. Workup

- History taking and physical examinations
- FBC, 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

2. Management

Loco-regional disease

- 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.
- Radiation Therapy – Following 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.

3. Follow-up

3-month in the first 2 years, then 6 months for 3 years, followed by yearly visits

SARCOMA, SKIN CANCERS AND MELANOMA

A. Soft Tissue Sarcoma

1. Introduction

- The median age 40–60 years with slight male predominance, more frequent among African- Americans.

Risks factors vary between:
- Genetics factors - 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

2. Workup

- History and Physical Examination
- Core biopsy OR incisional/excisional biopsy: place biopsy along future resection axis with minimal dissection and careful attention to hemostasis; immunohistostains are useful in most of soft tissue tumors/sarcomas
- FBC, Liver and Renal function tests
- Molecular tests
- Imaging: primary tumor, chest, abdomen/pelvis to rule out metastasis

3. Management

a. Extremity/Superficial Trunk, Head/Neck

i. Stage IA/IB (low grade)
Surgical wide resection.
- If oncologically appropriate margins – evaluate for rehabilitation; start follow-up visits
- If failure to obtain oncologically appropriate margins – re-resection OR observation (stage IA) OR consider RT (stage IA/IB) then start follow-up visits

ii. Stage II/III, resectable with acceptable functional outcomes
- **Stage II:** Surgery to obtain oncologically appropriate margins OR Surgery to obtain oncologically appropriate margins followed by RT OR Pre-operative RT then Surgery to obtain oncologically appropriate margins

- **Stage IIIA/IIIB:** Surgery to obtain oncologically appropriate margins or Pre-operative RT OR Pre-operative chemoradiation OR Pre-operative chemotherapy – all pre-operative options to be followed by Surgery to obtain oncologically appropriate margins.
  - Pre-operative chemotherapy followed by surgery is to be followed by RT OR RT + adjuvant chemotherapy.

iii. Stage II/III, resectable with adverse functional outcomes OR unresectable primary disease

- RT OR Chemo-radiation OR Chemotherapy OR amputation:
  - If the mass is resectable with acceptable functional outcomes post upfront treatment – treat as specified above (reference – point 1.2)
  - If mass is resectable with adverse functional outcomes – amputation or definitive RT
  - If mass is unresectable:
    - If not previously irradiated – definitive RT
    - Chemotherapy
    - Palliative surgery
    - Observation, if asymptomativ
    - Best supportive care

iv. Stage IV

Single organ and limited tumor bulk that are amenable to local therapy:

- Primary tumor management as above (ref. point 1.2 or 1.3) and considering – metastatectomy +/- pre-operative or post-operative chemotherapy +/- RT, chemotherapy or observation

Disseminated disease:

- Palliative options – chemotherapy, RT, Surgery, observation (if asymptomatic) or best supportive care

v. Recurrent disease

- Local recurrence: Follow workup and appropriate primary treatment pathway
- Metastatic disease:
  - Single organ and limited tumor bulk that are amenable to local therapy:
    - Primary tumor management as above (ref. point 1.2 or 1.3) and considering – metastatectomy +/- pre-operative or post-operative chemotherapy +/- RT, chemotherapy or observation
  - Disseminated disease:
    - Palliative options – chemotherapy, RT, Surgery, observation (if asymptomatic) or best supportive care
  - Isolated regional disease or nodes:
    - Options – regional node dissection for nodal involvement +/- RT +/- chemotherapy OR metastatectomy +/- pre-operative or post-operative chemotherapy +/- RT

b. Retroperitoneal/Intra-abdominal STS

i. Resectable disease

- Biopsy performed:
  - Desmoid tumors (aggressive fibromatosis) – biopsy and assess resectability:
    - If resectable – options are:
      - Observation – if stable: continue observation with appropriate imaging, If progression, see below:
      - Treatment – Surgery (R0 – observe, R1 – observe or consider re-resection or adjuvant RT, R2 – definitive RT/systemic chemotherapy OR radical surgery Or observation) OR RT and/or systemic therapy then observation.
    - If unresectable – options are:
  - Definitive RT OR systemic therapy OR radical surgery to be considered if all other modalities fail OR observation
  - Other sarcoma – Surgery to obtain appropriate margins OR pre-operative therapy with RT or Chemotherapy followed by surgery to obtain appropriate margins

c. Rhabdomyosarcoma (RMS):

- Pleomorphic RMS – treat like soft tissue sarcoma
- Non-pleomorphic RMS (alveolar and embryonal) – see Pediatric Oncology guidelines

d. Principles of Surgery

- A pre-treatment biopsy to diagnose and grade a sarcoma is highly preferred, and can be done by open incisional or needle technique (preferred – core needle biopsy)
- Surgical procedure – aim at resecting tumor with oncologically appropriate margins; close margins may be necessary to preserve critical neuro-vascular structures, bones, and joints;
- The biopsy site should be excised en bloc with the definitive surgical specimen, and dissection should be through grossly normal tissue planes, uncontaminated by tumor; surgical clips should be placed to mark the periphery of the surgical field and other relevant structures to help guide potential future RT;
- If margins are positive on final pathology, re-resection to obtain negative margins should strongly be considered, if it will not have a significant impact upon functionality;
- Adjuvant RT for close soft tissue margin or a microscopically positive margin on bone, major blood vessels, or a major nerve
- Limb Sparing Surgery – goal: functional limb preservation for extremity sarcoma;
- Amputation – consideration made for patient preference or if gross total resection of the tumor is expected to render the limb non-functional

e. Radiation Therapy

- Pre-operative RT: 50 Gy EBRT – surgery with clips to follow; following this, and surgery for positive margins, consider observation OR RT boost;
- RT Boost: 16-18 Gy for microscopic residual disease OR 20-26 Gy for gross residual disease
- Post-operative RT: EBRT (50 Gy) + EBRT boost at doses of 10-16 Gy (negative margins), 16-18 Gy (Microscopically positive margins) and 20-26 Gy (Gross residual disease); Field: Tumor bed, scar, drainage sites + 5-7 cm longitudinal
- For retroperitoneal/intra-abdominal sarcoma: Pre-operative RT: 50 Gy OR post-operative RT: same as pre-operative RT. Boost is discouraged – but if deemed necessary: add 16-18 Gy (microscopically positive margins) and 20-26 Gy (Gross residual disease);
- Alternative dose – post-operative RT: 45-50 Gy in 25-28 fractions to entire CTV with dose-painted Simultaneous Integrated Boost (SIB) to total dose of 57.5 Gy in 25 fractions to high risk retroperitoneal margin defined by surgeon

f. Systemic chemotherapy

Soft tissue sarcoma with non specific histologies:

- Doxorubicin and Dacarbazine; Doses are: IV Doxorubicin 60mg/m² and Dacarbazine 850mg/m² every 3 weeks for 6 cycles
- Doxorubicin, Ifosfamide and Mesna; Doses are: IV Doxorubicin 60mg/m², Mesna at 600mg/m² before Ifosfamide, Ifosfamide at 5000mg/m² and Mesna post Ifosfamide infusion at 1250mg/m², every 3 weeks for 6 cycles. Alternatively, the medications can be given on a 3-consecutive day regimen; Doses are: IV Doxorubicin 25mg/m², Mesna 600mg/m² before Ifosfamide, Ifosfamide at 3000mg/m² (concurrently with Mesna 3000mg/m²), followed by Mesna at 600mg/m²
- Ifosfamide, Epirubicin, Mesna
- Gemcitabine and Docetaxel; Doses are: IV Gemcitabine 900mg/m2 (D1 and D8) and Docetaxel 75mg/m² (D8 only) every 3 weeks for 6 cycles
- Doxorubicin: Single dose at 50mg/m²
- Ifosfamide; Doses are: IV Mesna 600mg/m², Ifosfamide 5000mg/m², followed by Mesna 1250mg/m² with Lasix IV 20mg
- Gemcitabine; Doses are: IV Gemcitabine 1000mg/m² (D1 and D8), every 3 weeks for 6 cycles

Desmoid tumors:

- Tamoxifen oral 20mg OD
- Doxorubicin-based regimens

Non-pleomorphic RMS:

- Vincristine, Dactinomycin, Cyclophosphamide; Doses are: IV Vincristine 1.4mg/m², Dactinomycin 40mcg/kg and Cyclophosphamide 1200mg/m², every 3 weeeks for 6 cycles
- Vincristine,Doxorubicin,Cyclophosphamide;DosesforVincristineandCyclophosphamide same as above; Doxorubicin at 50mg/m²

- Vincristine, Doxorubicin, Cyclophosphamide, alternating with Ifosfamide and Etoposide: Vincristine, Doxorubicin and Cyclophosphamide same as above, alternating after 2-3 weeks with Ifosfamide and Etoposide at doses of: IV Etoposide 100mg/m² (given first), followed by Mesna 360mg/m², and Ifosfamide 1800mg/m², then Mesna 360mg/m², with hydration.
- Doxorubicin IV 50mg/m² every 3 weeks for 6 cycles

Angiosarcoma:
- Paclitaxel; Doses are: IV Paclitaxel 175mg/m², every 3 weeks for 6 cycles
- Docetaxel; Doses are: IV Docetaxel 75mg/m², every 3 weeks for 6 cycles

Alveolar Soft Part Sarcoma:
- Sunitinib oral 50mg once daily for 4 weeks, followed by 2 weeks break
- Conventional chemotherapeutic agents – see single agents as for soft tissue sarcoma subtypes with non-specific histologies

Well-differentiated/Dedifferentiated liposarcoma (WD-DDLS) for retroperitoneal sarcoma:
- Palbociclib

Solitary fibrous tumor/hemangiopericytoma
- Bevacizumab and Temozolomide; Doses are: Oral Temozolomide 150mg/m² on Day 1-7 then Day 15-21, inclusive and IV Bevacizumab 5mg/kg D8 and D22; Repeat every 28 days for 6 cycles
- Sorafenib oral 200mg twice daily

5. 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.

B. Bone Cancers

1. Introduction

Bone cancers are much rare than their soft tissue counterparts. The most common type of bone malignancies is osteosarcoma. Symptoms consist of bone pain, followed by tenderness at the mass site.

2. Workup

- Symptomatic bone lesion with an abnormal radiograph:
  - Patients <40 years of age – refer to oncologist, biopsy to be performed
  - Patients ≥40 years of age – workup for potential bone metastasis as clinically indicated:
    - History and Physical Examination
    - Chest radiograph
    - SPEP/Labs
    - Chest/Abdominal pelvic CT with contrast
    - PSA
    - Mammogram.
- If no other bone lesions – refer to oncologist, biopsy to be performed
- If other lesions are present – refer to appropriate, site-specific treatment guidelines.

3. Staging

Appendicular skeleton, Trunk, Skull, and Facial Bones

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

Spine

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor cannot be confined to one vertebral segment or 2 adjacent vertebral segments
T2	Tumor confined to 3 adjacent vertebral segments
T3	Tumor confined to 4 or more adjacent vertebral segments
T4	Extension into the spinal canal or great vessels
T4a	Extension into the spinal canal
T4b	Evidence of gross vascular invasion or tumor thrombus in the great vessels

Pelvis

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one pelvic segment with no extra-osseous extension
T1a	Tumor ≤8 cm in greatest dimension
T1b	Tumor > 8 cm in greatest dimension
T2	Tumor confined to one pelvic segment with extra-osseous extension or 2 segments without extra-osseous extension
T2a	Tumor ≤8 cm in greatest dimension
T2b	Tumor >8 cm in greatest dimension
T3	Tumor spanning 2 pelvic segments with extra-osseous extension
T3a	Tumor ≤8 cm in greatest dimension
T3b	Tumor > 8 cm in greatest dimension
T4	Tumor spanning 3 pelvic segments or crossing the sacro-iliac joint
T4a	Tumor involves sacro-iliac joint and extends medial to the sacral neuroforamen
T4b	Tumor encasement of external iliac vessels or presence of gross tumor thrombus in major pelvic vessels

Note: There is no AJCC prognostic stage groupings for spine and pelvis

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Note: 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 is clearly evident

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Bone or other distant sites

G Category	G Criteria
GX	Grade cannot be assessed
G1	Well differentiated – low grade
G2	Moderately differentiated – high grade
G3	Poorly differentiated – high grade

4. Histology-specific Management

a. Chondrosarcoma

- Presentation and subsequent management

Low grade and Intra-compartmental:

- Intralesional excision +/- surgical adjuvant OR wide excision if resectable OR consider RT if unresectable OR best supportive care if unresectable.
- Surveillance – Physical exam, Radiographs of primary site +/- cross sectional imaging MRI if available or CT and chest imaging as clinically indicated, every 6-12 months for 2 years, then yearly as appropriate
- If local recurrence – Wide excision if resectable or RT, if unresectable.
  - Positive margins – consider RT OR consider re-resection to achieve negative margins
  - Negative margins – observe

High grade (grade II, grade III) OR clear cell OR extra-compartmental:

- Wide excision if resectable OR consider RT if borderline resectable or unresectable
- Surveillance - Physical exam, Radiographs of primary site +/- cross sectional imaging MRI if available or CT and chest imaging as clinically indicated, every 3-6 months for 5 years, then yearly as appropriate; reassess function at every follow-up visit
- If local recurrence – wide excision if resectable OR RT, if unresectable
  - Positive margins – consider RT OR consider re-resection to achieve negative margins
  - Negative margins - observe
- Systemic recurrence – see guidelines for metastatic disease at presentation

Metastatic disease at presentation:

- Oligometastatic disease – When possible – attempt surgical excision of all sites if possible OR best supportive care
- Widespread disease – consider radiation therapy, and/or surgery for symptomatic sites OR systemic therapy OR best supportive care

Dedifferentiated – see treatment guidelines of Osteosarcoma (below)
Mesenchymal – see treatment guidelines of Ewing Sarcoma (below)

b. Chordoma

- Presentation and subsequent management

Conventional OR chondroid:

- Sacrococcygeal and mobile spine:
  - Wide resection +/- RT if resectable – consider RT for positive surgical margins or for large extra-compartmental tumors
  - Consider RT if unresectable
- Skull base/Clival:
  - Intra-lesional excision +/- RT if resectable – follow-up with MRI of primary site with contrast to assess adequacy of resection; consider RT for positive surgical margins or for large extra-compartmental tumors; consider re-resection if necessary
  - Consider RT if unresectable OR best supportive care
  - Continue with surveillance, with physical exam, imaging of surgical site as clinically indicated – up to 10 years and chest imaging every 6 months, including CT scan for 5 years, then annually thereafter.
- If local recurrence – surgical excision and/or RT and/or systemic therapy
- If metastatic recurrence – systemic therapy and/or surgical excision and/or RT and/or best supportive care

c. Ewing Sarcoma

Workup:

- History and Physical Exam
- MRI +/- CT of primary site, CT chest, Consider bone marrow biopsy and/or screening MRI of spine and pelvis, LDH

Primary treatment:

- Multi-agent chemotherapy (see under principles of chemotherapy) for at least 9 weeks prior to local therapy;
- Restage – CT chest, MRI +/- primary site, radiographs of primary site, repeat other (primary) abnormal studies; Surveillance and further treatment to be based on restaging results

Further treatment:

- Stable/improved disease following primary treatment:
  - Wide excision – if positive margins: continue chemotherapy followed by RT OR RT and chemotherapy. If negative margins – chemotherapy. Continue with surveillance*
  - Definitive RT and chemotherapy then surveillance
  - Amputation in selected cases – followed by post-operative chemotherapy, consider RT depending on margin status. Continue with surveillance*
- Progressive disease following primary treatment – consider RT and/or surgery to primary site for local control OR palliation. Continue with chemotherapy OR best supportive care.

Surveillance:

- History and Physical examination, MRI+/- CT of primary site, Chest imaging every 2-3 months, radiograph of primary site; increase intervals for physical examination, imaging of primary site and chest after 24 months and annually after 5 years. In case of early OR late relapse – chemotherapy +/- RT.

d. Giant Cell Tumor of the bone

Workup:

- History and Physical Examination
- Imaging of primary site as clinically indicated + chest imaging
- Biopsy to confirm diagnosis – and if there is malignant transformation: treat as Osteosarcoma (see below).

Management:

- **If localized disease:**
  - Resectable – excision and surveillance
  - Resectable with unacceptable morbidity and/or unresectable axial lesions – RT or offer best supportive care. Consider Denosumab if available. Continue with imaging to assess response; if stable/improved disease with incomplete healing – consider excision; if not – best supportive care.
- **Metastatic disease at presentation** – resectable – treat as above; if unresectable – treat with RT, observation OR denosubam if available OR best supportive care.

Surveillance

Physical examination, Imaging of surgical site as clinically indicated, chest CT every 6 months for 2 years, then annually thereafter:

- If local recurrence – resectable – consider chest imaging – consider denosumab (if available) prior to surgery; if resectable with unacceptable morbidity OR unresectable axial lesions – see treatment above
- Metastatic recurrence – treat as metastatic disease at presentation

e. Osteosarcoma

Workup:

- History and Physical Examination
- Imaging – MRI +/- CT of primary site, chest imaging, MRI or CT of skeletal metastatic sites, LDH, ALP

Primary presentation and subsequent management

- **Low-grade osteosarcoma: intramedullary + surface:**
  - Wide excision:
    - High grade – proceed to chemotherapy
    - Low grade – Surveillance
- **Periosteal osteosarcoma:**
  - Consider chemotherapy – then wide excision.
    - High grade – proceed to chemotherapy
    - Low grade – Surveillance
- **High grade osteosarcoma: intramedullary + surface:**

- Pre-operative chemotherapy then restage with imaging
  - Unresectable – RT OR chemotherapy
  - Resectable – Wide excision
    - Positive margins with good response – chemotherapy OR consider additional local therapy – surgical resection +/- RT
    - Positive margins with poor response – consider additional local therapy (surgical resection +/- RT) OR continue with pre-operative regimen OR consider changing chemotherapy
    - Negative margins with good response – Chemotherapy
    - Negative margins with poor response – Continue with pre-operative regimen OR consider changing chemotherapy

- **Metastatic disease at presentation:**
  - Resectable (pulmonary, visceral, or skeletal metastases) – refer to management of primary tumor (above)
  - Unresectable – chemotherapy OR RT OR reassessing primary site as appropriate for local control
- **Extra-skeletal osteosarcoma – treat as soft tissue sarcoma (see above)**

Follow-Up:
- Physical examination, imaging of primary site and chest
- Follow-up schedule: Every 3 months x 2 years, every 4 months for year 3, every 6 months in year 4 to 5, then annually.

5. Management Principles

A. Surgery
- Biopsy – core needle OR surgical biopsy; needle biopsy not recommended for skull base tumors
- Surgery – wide excision to achieve histologically negative surgical margins, optimizing local tumor control. Tumor control can be achieved either by limb-sparing resection OR limb amputation

B. Systemic therapy agents
a. Chondrosarcoma
- Conventional chondrosarcoma (grade 1-3) – no known standard chemotherapy options
- For Mesenchymal and Dedifferentiated chondrosarcoma – follow Ewing Sarcoma and Osteosarcoma regimens, respectively.

b. Chordoma
- Cisplatin
- Imatinib
- Sorafenib
- Lapatinib with EGFR-positive chordomas

c. Ewing Sarcoma

- First-line – primary, neo-adjuvant and adjuvant therapy regimens (doses are similar to soft tissue sarcoma chemotherapy regimens):
  - VDC/IE – Vincristine, Doxorubicin and Cyclophosphamide alternating with Ifosfamide and Etoposide
  - VAI – Vincristine, Doxorubicin, and Ifosfamide
  - VIDE – Vincristine, Ifosfamide, Doxorubicin, and Etoposide
- Primary treatment for metastatic disease at initial presentation:
  - VDC - Vincristine, Doxorubicin and Cyclophosphamide
  - VDC/IE
  - VAI
  - VIDE
- Second-line therapy – relapsed/refractory or metastatic disease
  - Irinotecan +/-Temozolomide
  - Ifosfamide and Etoposide
  - Ifosfamide, Carboplatin and Etoposide
  - Docetaxel and Gemcitabine
  - Vincristine + Irinotecan

d. Giant Cell Tumor of Bone

- Denosumab

e. Osteosarcoma

- First-line therapy – primary, neo-adjuvant, adjuvant therapy or metastatic regimens:
  - AP: Cisplatin and Doxorubicin (Adriamycin); Doses are: IV Cisplatin 100 mg/m² and Doxorubicin 75mg/m², every 3 weeks for 6 cycles
  - MAP (high dose Methotrexate, Cisplatin and Adriamycin)
  - Ifosfamide, Cisplatin, and Epirubicin
- Second-line therapy (relapsed/refractory or metastatic disease)
  - Docetaxel and Gemcitabine
  - Cyclophosphamide and Etoposide
  - Gemcitabine
  - Ifosfamide and Etoposide
  - Ifosfamide, Carboplatin and Etoposide; Doses are similar (STS), addition of Carboplatin at AUC

f. High grade Undifferentiated Pleomorphic Sarcoma

- Follow Osteosarcoma regimens

C. Principles of Radiation Therapy

- Doses listed for chondrosarcoma and chordoma are for conventional fractionated regimens (1.8 – 2.0 Gy): Low-grade and intracompartmental AND high-grade, clear cell, or extra-compartmental:
  - Unresectable – Consider RT with 70 Gy
  - Resectable: Pre-operative RT: Consider if positive margins are likely (19.8 – 50.4 Gy), followed by individualized post-operative RT with final target dose of 70 Gy for R1 resection, 72-78 Gy for R2 resection; radiation not needed for R0 resection

Chordoma:

- Extra-cranial (mobile spine/sacrum)
  - Resectable – Pre-operative RT: Consider if positive margins are likely (19.8 – 50.4 Gy) followed by individualized postoperative RT. Consider postoperative RT for R1/R2 resection with final dose target dose of 70 Gy for R1 and 72-78 Gy for R2 resection
  - Unresectable – consider RT >70 Gy
- Cranial (base of skull)
  - Resectable – consider postoperative RT (>70 Gy) after R1/R2 resection
  - Unresectable – consider RT >70 Gy

Ewing Sarcoma

- Definitive RT – start by week 12 of VDC/IE chemotherapy or week 18 of VIDE, given concurrently with chemotherapy, withholding anthracyclines during radiation therapy
- Treatment volumes – 45 Gy to initial GTV-1 + 1-1.5 cm for clinical target volume (CTV-1) + 0.5-1 cm for PTV1. GTV-1 is defined as the pre-treatment extent of bone and soft tissue disease. If the tumor has responded to chemotherapy and normal tissues have returned to their natural position. Excludes pre-chemotherapy soft tissue volume that extended into a cavity; cone down to cover original bony extent + total of 55.8 Gy to post-chemotherapy soft tissue volume (GTV2) + 1-1.5 cm for CTV 2 + 0.5-1cm for PTV2
- Pre-operative RT – consider for marginally resectable tumors and given concurrently with consolidation chemotherapy; 36-45 Gy for initial GTV + 2cm
- Post-operative RT – should begin within 60 days of surgery and given concurrently with consolidation chemotherapy; R0 – consider only for poor histologic response even if margins are adequate (45 Gy to GTV2 equivalent volume + 1-1.5 cm for CTV1 + 0.5-1 cm for PTV1); R1 – 45 Gy to GTV2 equivalent volume + 1-1.5 cm for CTV1 + 0.5-1cm for PTV1; R2 resection – 45 Gy to GTV2 equivalent volume + 1-1.5 cm for CTV2 + 0.5-1 cm for PTV2

Giant Cell Tumor of the bone:

Consider RT (50-60 Gy) for unresectable, progressive, recurrent disease that has not responded to Denosumab. An increased risk of malignant transformation following RT has been noted in some studies;

Osteosarcoma:

- RT for positive margins (R1) or gross residual (R2) or unresectable disease – to be considered only for limb sparing surgery; doses – 55 Gy with 9-13 Gy boost to microscopic or gross disease (total dose to high-risk sites 64-68 Gy)
- Unresectable disease – 60-70 Gy
- Metastatic disease – Palliative RT: 30 – 40 Gy in 10 fractions, 20 Gy in 5 fractions

C. Kaposi Sarcoma

1. Introduction

- Kaposi's sarcoma (KS) is a spindle-cell tumor derived from endothelial cell lineage caused by Human herpesvirus-8 (HHV-8). Kaposi sarcoma can be primarily categorized into 4 types:
  - Epidemic or AIDS-related KS
  - Immunocompromised KS
  - Classic, or sporadic KS
  - Endemic (African) KS
- Lesions may involve skin, oral mucosa, lymph nodes, visceral organs and mucous membrane (palate, gingiva, conjunctiva).

2. Workup

- History and Physical examination: history of additional immunosuppression, glucocorticoids, HIV history, ART history, systemic symptoms
- HIV serology, if HIV+ then HIV viral load, CD4 T cell count
- CBC, Comprehensive metabolic panel
- Stool hemoccult
- Chest imaging – if Chest X-ray is abnormal – TB testing
- Abdominal and pelvic CT scan
- Pregnancy testing in women of child-bearing age – if chemotherapy or radiation therapy is planned
- Bronchoscopy if unexplained pulmonary symptoms, Esophago-gastro-duodenoscopy or colonoscopy can be considered based on symptoms
- Punch biopsy for diagnosis

3. Staging

HIV positive patients (Epidemic KS) staging – AIDS Clinical Trials Group Classification System

	Good risk (all of the following)	Poor risk (any of the following)
Tumor (T)	T0: 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: Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in organs other than lymph nodes
Immune system (I)	I0: CD4+ T cell count ≥ 150/mcL	I1: CD4+ T cell count < 150/mcL
Systemic disease, S	S0: No history of opportunistic infection or thrush No "B" symptoms Karnofsky performance status ≥70	S1: History of opportunistic infection and/or thrush "B" symptoms present Karnofsky performance status <70 Other HIV-related illness (eg. Neurologic disease, 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)

4. Management

4.1. HIV-associated KS

a. Limited Cutaneous Disease (T0 disease)

- Anti-retroviral therapy (ART)
- Radiation Therapy (RT)
- In case of stable disease or clinical response:
  - Continue ART and observe – if limited cutaneous relapse, repeat same as above

b. If Progressive disease post-treatment or patients with advanced cutaneous, oral, visceral or nodal disease:

- Systemic therapy (if eligible) + ART:
  - If clinical response – continue ART and observe. If relapse – ART + RT
  - If stable or progressive disease – ART + RT
- ART + RT if not eligible for systemic therapy and reassess for eligibility for systemic therapy.
  - If not eligible – best supportive care
  - If eligible – treat with systemic therapy

c. Treatment Components

c.1. Systemic therapy

- Paclitaxel 100 mg/m² IV every 2 weeks (premedication with dexamethasone 10 mg at time of administration is acceptable for prevention of hypersensitivity reaction)
- Bleomycin + Vincristine
  - Bleomycin 10-15 U/ m² IV
  - Vincristine 1.4 mg/ m² IV (2mg cap), every 2-3 weeks for 6 cycles
- Doxorubicin + Bleomycin + Vincristine
  - Doxorubicin 25-50 mg/m² IV
  - Bleomycin 10-15 U/ m² IV
  - Vincristine 1.4 mg/ m² IV (2mg cap), every 3 weeks for 6 cycles
- Alternative regimens:
  - Vincristine – 1.4 mg/ m² IV (2mg cap), every 3 weeks for 6 cycles
  - Etoposide – 50mg/d orally for 7 days of each 14- day cycle. After 2 cycles, escalate dose to 100 mg/d orally for 7 days of each 14-day cycle in patients without partial or complete response and no toxicity > Grade 2. Dose can be further escalated to 150 mg/d and then to a maximum dose of 200 mg/d based on tolerance and response.

c.2. Radiation therapy

- For patients with advanced disease a dose of 8Gy in one fraction is preferable. In case of partial response, this dose can be repeated up to 3 times.
- Other recommended options include; 20Gy/5 fractions, 24 Gy/12 fractions or 30Gy/10 fractions

d. Follow-up

Physical examination, CXR, Abdominal Pelvic ultrasound, every 3 months × 2 year, every 4 months in third year, every 6 months in fourth and fifth years, then annually.

4.2. HIV-negative disease

a. Stage I/II:

- Watchful waiting
- Radiation Therapy:

In case of stable response or stable disease: Observe – and if limited cutaneous relapse – treat as stage I/II

- If advanced cutaneous or visceral/nodal disease – treat with systemic therapy and/or RT

b. Stage III/IV

- First line Systemic therapy and/or RT:
  - If response – observe – if relapse or progressive disease – treat with different therapy line
  - If refractory disease – treat with a different therapy line

Note: Treatment and follow-up components are similar to HIV-positive Kaposi Sarcoma patients

D. Skin Cancers

D.1. Non-melanoma skin cancers

1. 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)
- **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

2. Workup

- History and physical examination.
- Biospy
- Laboratory tests: Baseline RFT, LFT and FBC.
- CT or MRI for suspected Nodal and bone involvement.

3. Staging and Risk Stratification

Staging – Skin squamous cell carcinoma, Basal cell carcinoma and Other skin carcinoma

T Category	T Criteria
TX	The primary tumor cannot be evaluated
T0	There is no evidence of primary tumor

Tis	Carcinoma in situ
T1	Tumor is ≤2cm at its largest point; with <2 high risk features
T2	Tumor >2cm but ≤4cm in greatest dimension
T3	Tumor >4cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion
T4	Tumor with gross cortical bone/marrow, skull invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

N Stage: Spread of cancer to the lymph nodes in the neck

N Category	N Criteria
Nx	The neck lymph nodes cannot be assessed
N0	There is no evidence of any spread to the nodes
N1	Single node, ipsilateral lymph nodes, of ≤3cm in greatest size and no Extra-Nodal Extension (ENE)
N2a	Ipsilateral, single node, >3cm but ≤6cm in greatest dimension and ENE (-)
N2b	Multiple ipsilateral nodes none larger than 6cm, and ENE (-)
N2c	Bilateral neck positive lymph nodes, none larger than 6 cm and ENE (-)
N3	Metastasis in a LN larger than 6cm in greatest dimension and ENE (-) OR metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6cm in greatest dimension and ENE (-)
N3b	Metastasis in any node(s) and ENE(+)

M Stage: Spread of cancer outside the head and neck

M Category	M Criteria
M0	No evidence of distant spread
M1	Evidence of spread outside of the head and neck – lungs, bone, brain, etc

Risk Stratification

Risk Group	Low Risk	High Risk	Very High Risk
History and P/E			
Location/Size	Trunk, extremities <2cm	Trunk/Extremities 2-4cm; Head, neck, hands, feet, pre-tibia and ano-genital (any size)	≥4cm, any location
Borders	Well defined	Poorly defined	
Primary v Recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammatory process	(-)	(+)	
Rapidly growing tumor	(-)	(+)	
Neurologic symptoms	(-)	(+)	
PATHOLOGY			

Degree of differentiation	Well or moderately differentiated		Poor differentiation
Histologic features: Acantholytic (adenoid), adenosquamous (with mucin production), or metaplastic (carcinosarcomatous) subtypes	(-)	(+)	Desmoplastic SCC
Depth; Thickness or level of invasion	≤6mm and no invasion beyond subcutaneous fat		>6mm or invasion beyond subcutaneous invasion
Peri-neural involvement	(-)	(+)	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1mm
Lymphatic or vascular involvement	(-)	(-)	(+)

4. Management

Squamous and Basal cell carcinomas are most commonly treated with surgery, radiation therapy or a combination of the two. Selection of treatment is based on outcomes in function preservation, cosmesis and patient's preference.

4.1. Surgery

Surgical excision is indicated mostly for primary curative or palliative intents.

- For local, low-risk disease – standard excision with 4-6m clinical margins, and post-operative margin assessment with second intention healing, linear repair, or skin graft. If positive margins – re-excision if clinically feasible OR RT for non-surgical candidates. If negative margins – Observe
- For local, high risk/very high-risk disease – Standard excision with wider surgical margins and post-operative margin assessment and linear or delayed repair. If positive margins – discuss re-excision OR multi-disciplinary consultation for RT +/- systemic chemotherapy (for non surgical candidates.

4.2. Radiation Therapy

Commonly used in treating lesions on the face of more than 5cm in size, for better cosmetic and functional results

- Definitive Radiation therapy dose is – 60-64 Gy in conventional fractionation (6-7 weeks) or 50 Gy in 15 fractions over 3 weeks 50-55 Gy over 3-4 weeks
- Post-operative RT – 60-64 Gy in conventional fractionation (6-7 weeks)

Regional disease

- Lymph node regions, after lymph node dissection
- Negative margins, no ECE: 50-60 Gy over 5-6 weeks, Positive margins OR ECE: 60-66 Gy over 6-7 weeks
- Lymph node regions, without lymph node dissection
- Clinically negative, at risk: 50 Gy over 5 weeks; Clinically positive: 60-70 Gy over 6-7 weeks

For palliative settings – consider 30 Gy in 10 fractions

4.3. Systemic Therapy

Usually indicated for patients with residual disease, and further surgery is not feasible, in combination with RT. For patients with complicated cases, and where no curative surgery and RT are feasible, recommending multi-disciplinary consultations to consider systemic therapy alone

- Regimens to be used with RT: Cisplatin weekly 40mg/m², or Carboplatin (AUC-2).
- Regimens to be used alone: Immunotherapy indicated but when not available, options include: Cisplatin, 3-weekly 100mg/m², Capecitabine 750-1000 mg/m² BD for 14 days in a 21-day cycle, Carboplatin (AUC-6).

5. Follow Up

- History and Physical Examination – every 3-6 months for 2 years, and 6 monthly for 2-5 years, then yearly
- Investigations – requested on the basis of clinical symptoms

D.2. Melanoma

1. Introduction

Suspicious lesions are characterized by Asymmetry, Border irregularities, Colour heterogeneity, Dynamics, (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.

2. Workup

- History and Physical Examination
- Basic laboratory studies: FBC, RFTs, LFTs, LDH
- Biopsy – Excisional or incisional biopsy
- Imaging studies – CT scan of the primary lesion, CT chest/ abdomen to rule out metastasis

3. Staging

AJCC TNM Staging

T Category	T Criteria	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	≤1.0mm	Unknown or unspecified
T1a	<0.8mm	Without ulceration
T1b	<0.8mm	With ulceration
T1b	0.8-1.0mm	With or without ulceration
T2	>1-2mm	Unknown or unspecified
T2a	>1-2mm	Without ulceration
T2b	>1-2mm	With ulceration
T3	>2-4mm	Unknown or unspecified
T3a	>2-4mm	Without ulceration
T3b	>2-4mm	With ulceration
T4	>4mm	Unknown or unspecified
T4a	>4mm	Without ulceration
T4b	>4mm	With ulceration

Regional Lymph node staging

N Category	N Criteria	Presence of in-transit/satellite, and/or micro-satellite metastases
NX	Regional nodes cannot be assessed (Pathological N category is not required for T1 melanomas)	No
N0	No regional metastases detected	No
N1	One tumor involved node or in-transit satellite, and/or metastases with no tumor-involved nodes	One tumor involved node or in-transit satellite, and/or 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	Yes
N2	2-3 tumor involved node or in-transit, satellite, and/or micro-satellite metastases with 1 tumor involved node	2-3 tumor involved node or in-transit, satellite, and/or micro-satellite metastases with 1 tumor involved node
N2b	2-3, at least one of which was clinically detected	No
N2c	1 clinically occult or clinically detected	Yes
N3	4+ tumor involved node or in-transit satellite, and/or metastases with 2+ tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	4+ clinically occult (i.e. detected by SLN biopsy)	No
N3b	4+, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	2+ 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	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 non-regional LNs	Not recorded/unspecified
cM1a(0)	Distant metastasis to skin, soft tissue including muscle, and/or non-regional LNs	Not elevated

cM1a(1)	Distant metastasis to skin, soft tissue including muscle, and/or non-regional LNs	Elevated
cM1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded/unspecified
cM1b(0)	Distant metastasis to lung with or without M1a sites of disease	Not evelated
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/unspecified
cM1c(0)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not evelated
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/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 non-regional lymph node, microscopically proven	Not recorded/unspecified
pM1a(0)	Distant metastasis to skin, soft tissue including muscle, and/or non-regional lymph node, microscopically proven	Not elevated
pM1a(1)	Distant metastasis to skin, soft tissue including muscle, and/or non-regional lymph node, microscopically proven	Elevated
pM1b	Distant metastasis to lung with or without M1a sites of disease, microscopically proven	Not recorded/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/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(1)	Distant metastasis to CNS with or without M1a, M1b or M1c sites of disease, microscopically proven	Not recorded/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

Satellites = within 2cm of primary tumor
Breslow depth = microscopically measured vertical thickness (mm) of the primary tumor from the epidermal granular layer (or base of the lesion if the tumor is ulcerated) to the deepest identifiable contiguous melanoma cell.

Breslow's Depth

Stage	Depth
I	0.75mm or less
II	0.76mm – 1.50mm
III	1.51mm – 4.00mm
IV	>4mm

Clark's staging:

Level	Criteria
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

4. Management

4.1. Principles of Surgery

- Wide Local Excision: Stage 0 in situ, Stage IA (T1a, <0.8mm thick, no ulceration)
- Wide Local Excision + Sentinel node biopsy: Stage IB (T1b, <0.8mm thick, with ulceration or 0.8-1mm thick +/- ulceration), Stage IB (T2a) or Stage II (T2b or higher), Stage IIIA/B (with microscopic satellites in biopsy specimen from primary lesion)
- Wide Local Excision + Delayed Sentinel node biopsy: Stage IIIA/B (with microscopic satellites in wide excision specimen, if no sentinel node biopsy was performed, or negative if performed during wide local excision)
- Wide Local Excision of primary + Therapeutic lymph node dissection: Stage III (with clinically positive nodes)
- Wide Local Excision with clear margins: Stage III (with clinical satellite/in-transit metastasis)
  - If Sentinel node biopsy is negative – Observe
  - If Sentinel node biopsy is positive, Any stage – Generally: Consider imaging for baseline staging with nodal basin ultrasound surveillance OR Completion of lymph node dissection. Offer systemic therapy after (Nivolumab, Pembrolizumab) or Observe
  - Clinically positive nodes, post therapeutic lymph node dissection – offer adjuvant treatment with systemic treatment (details below) AND/OR Local regional therapy with RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, gross and/or histologic extra-capsular extension OR observation
  - Unresectable disease – offer systemic therapy (details below), local therapy options (intra-lesional injections), Total imiquimod for superficial dermal lesions, consider RT

4.2. Principles of Systemic therapy

Given for adjuvant treatment and as a first line for metastatic or unresectable disease.

- Young fit, patients: Dacarbazine IV 1,100mg/m² every 3 weeks for 4 cycles
- Poor performance status – single agent Dacarbazine
- If molecular tests can be done:
  - Anti PD-1 monotherapy: Pembrolizumab OR Nivolumab; Doses are: IV Nivolumab 3mg/kg (maximum 240mg) every 2 weeks or 6mg/kg (maximum 480mg) every 4 weeks; IV Pembrolizumab 2mg/kg (maximum 200mg) every 3 weeks
  - BRAF V600 activating mutation is present: Dabrafenib and Trametinib

Switch therapies in case of disease progression

4.3. Principles of Radiation Therapy

- **Definitive Radiation Therapy** – considered for medically inoperable patients or those with surgical morbidity, for whom complete resection would be prohibitive.
- Dosing regimens – 64-70 Gy in 32-35 fractions over 6-7 weeks; 50-57.5 Gy in 20-23 fractions over 4-5 weeks; 35 Gy in 5 fractions over 1 week for fields <3cm²
- **Adjuvant Therapy** – considered for select cases of high-risk desmoplastic melanoma based on a combination of risk factors for local recurrence
- Dosing regimens – 60-66 Gy in 30-33 fractions over 6-7 weeks; 48 Gy in 20 fractions over 4 weeks
- Adjuvant Therapy for High-Risk Resected Regional Disease
- Consider if presence of gross and/or histologic extra-capsular extension of melanoma in clinically involved node(s); ≥1 parotid node, ≥2 cervical or axillary nodes, ≥3 inguino-femoral nodes, ≥3cm cervical or axillary node, and/or ≥4cm inguino-femoral nodes. Dosing regimens are: 50-66 Gy in 25-33 daily fractions or 48 Gy in 20 daily fractions or 30 Gy in 5 fractions.

Metastatic Disease:

- Soft tissue (Dermal, subcutaneous and lymph nodes): 44 Gys fractions given 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 Gy/10 fractions, 45 Gys/18 fractions.

4.4. Treatment of recurrent disease

- True scar recurrence (persistent disease): Biopsy to confirm + workup appropriate to primary tumor characteristics then re-excise tumor site to appropriate margins; consider lymphatic mapping/Sentinel node biopsy according to recurrence characteristics
- Local satellite/in-transit recurrence: Biopsy to confirm, imaging to assess disease extent, BRAF mutation testing if available and not previously tested. If limited and resectable disease – complete excision to clear margins; If unresectable disease – Consider systemic therapy

- Nodal recurrence: Biopsy to confirm, imaging to assess disease extent, BRAF mutation testing if available and not previously tested. If disease is limited to nodal recurrence – Offer therapeutic lymph node dissection (IF no previous lymph node dissection); If systemic disease – treat as distant metastatic disease

5. Follow-up

- Educate patients on self-skin examination, ABCD changes.
- Schedule 3-4 months first 2 years, then 6 monthly for 5 years then yearly to 10 years.

PEDIATRIC CANCERS

A. Brain tumors in children

1. Introduction

Infratentorial tumors: Cerebellar astrocytoma-30% Medulloblastoma- 30% Ependymoma-10% Brainstem glioma –15%, Other-15%
Supratentorial tumors: include sellar and suprasellar tumors which comprise about 20% of all childhood brain tumors eg: Craniopharyngioma. Other supratentorial tumors include Astrocytoma- low grade, high grade, mixed Oligodedroglioma PNET
Others include:

- Diencephalic tumors i.e., tumors of chiasm, thalamus/hypothalamus Germ cell tumors
- Ependymoma meningioma (rare in children), Choroid plexus tumors, Pineal gland tumors - pineoblastoma, pineocytoma, mixed tumor, germ cell tumor, Neuronal and mixed neuronal/glial tumors- gangioglioma
- Desmoplastic gangioglioma -DNET
- Metastases
- Spinal cord tumours are rare: 1-2% of all childhood CNS tumors 70%= low grade astrocytomas &/or gangiogliomas

2. Workup

- History and Physical Examination
- Blood tests – FBC, RFT, LFT, BUN
- Imaging tests – Brain MRI (+/- Spinal MRI, when clinically indicated and depending on pathology)
- Pathology – tissue biopsy needed from the mass excision. Perform immunostains where available
- CSF cytology – if clinically indicated, and depending on pathology

1. Infratentorial tumors

1.1. Cerebellar astrocytomas
Peak incidence in children between the ages 5-10 years; more than 80%= Juvenile Pilocytic Astrocytoma (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 the standard of care but can be used in younger children with recurrent disease to delay RT.
RT – Dose: 1.8 Gy x 28 fractions (50.4 Gy)
1.2. Medulloblastoma
Generally the most common malignant CNS tumor of childhood; Arises in midline of cerebellum growing into and compressing 4th ventricle (V4)

May cause hydrocephalus and associated raised ICP. i.e. headache, nausea, vomiting, papilloedema, 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; Lumbar puncture best done not less than 10-14 days after surgery, to allow post-surgical contamination to be clear.

3. Staging

Modified Chang Criteria

T Category	T Criteria
T1	Tumor < 3cm in diameter
T2	Tumor ≥3cm in diameter
T3a	Tumor > 3 cm and with extension into Aqueduct of Sylvius or foramen of Luscka
T3b	Tumor > 3cm and with unequivocal extension into brainstem
T4	Tumor >3cm with extension past Aqueduct of Sylvius or down past the foramen magnum

M Stage

M Category	M Criteria
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in CSF
M2	Gross nodular seeding intra-cranially 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 cm2 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)

4. Treatment

Surgery – Resection of the tumor +/- shunt
Radiation therapy and chemotherapy - Craniospinal irradiation (CSI) to 36 Gy with a boost to the posterior fossa (Total Dose = 50-55 Gy).

Average Risk:

- 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 concurrent weekly Vincristine at 1.5mg/m² Maintenance (6 weeks post chemo-radiation): IV Cyclophosphamide 1000mg/m² on Days 1 and 2, and Vincristine 1.5mg/m² on Days 1 and 7, every 4 weeks for 6 cycles.

High Risk patients

- Craniospinal RT + daily carboplatin and weekly vincristine, followed by Vincristine and Cyclophosphamide, monthly for 6 months, one month post-concurrent chemo-radiation.
- Doses are: Concurrent chemotherapy: IV Carboplatin daily at 35mg/m² and weekly vincristine at 1.5mg/m². Maintenance (6 weeks post chemo-radiation): IV Cyclophosphamide 1000mg/m² on Days 1 and 2, and Vincristine 1.5mg/m² on Days 1 and 7, every 4 weeks for 6 cycles.
- 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 receive chemotherapy to delay RT until either aged 3yrs, or 6 cycles to be given.

Follow-up: Brain and Spinal MRI, and CSF analysis if M1 and above at presentation

1.3. Ependymoma

Classification:

- Subendymoma – WHO grade I
- Ependymoma – WHO grade II, cellular papillary epithelial clear cell mixed
- Malignant (anaplastic) ependymoma – WHO grade III
- Ependymoblastoma – PNET

Staging – same as medulloblastoma

Management:

- Surgery – Complete Resection
- Radiation Therapy - 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 tumors – Re-resection and/or radiosurgery

1.4. Childhood Brainstem Glioma

Classification:

- Diffuse Astrocytomas: located in the pons, also called diffuse intrinsic pontine glioma (DIPG)
- Pilocytic astrocytomas: occur throughout the brainstem

Investigations – mostly diagnosed on the basis of clinical findings and on neuro-imaging studies using MRI; For DIPG – biopsy is recommended for pontine tumors when the diagnosis is uncertain based on imaging findings. Non-DIPG, biopsy or resection is generally indicated.
Management – Usually not amenable to surgery, RT is mainstay of treatment
Radiation Therapy – Total dose: 56 Gy in conventional fractionation

2. Supratentorial Tumors

2.1. Pineal Tumors
Germ cell tumors and PNET (Pinealoblastoma) – see adult protocol; treat as Medulloblastoma.

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
Radiation Therapy - Dose= 1.80Gy X 25 Fractions = 45.00 Gy to large volume (Mass + edema 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)
(Total dose = 59.4 Gy) - reduce for OAR if required.
Adjuvant chemotherapy – Vincristine, CCNU, Prednisolone
Recurrence – Re-resection +/- chemotherapy (Temozolomide) if good performance status

2.3. Childhood Visual Pathway Glioma/Hypothalamic

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

2.3.2. Craniopharyngiomas

Introduction:
These are histologically benign tumours that may be disabling/ life-threatening because of their position
Presentation is insidious- usually decreasing visual acuity or visual function, and/or endocrine abnormalities

Management
Radiation therapy: 1.8 Gy x 30 fractions – 54 Gy
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:
Combines neuro-paediatric /endocrine clinic if possible. Growth monitoring, pituitary function testing, visual assessment and many psychosocial issues are addressed.

2.3.3. Spinal Cord Tumors

Very rare in children (<2% of CNS malignancy) Approximately half are malignant
Investigations – Standard: Biopsy; Cerebrospinal Fluid Analysis, Imaging (MRI spine)

B. Retinoblastoma

1. 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.
Retinoblastoma occurs in heritable and non-heritable 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.

2. Workup

- 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

Staging

Stage Category	Stage Criteria
0	Eye has not been enucleated and no dissemination of disease
I	Eye enucleated, completely resected histologically
II	Eye enucleated, microscopic residual tumor
III	Regional extension (a) over orbital disease, (b) pre-auricular 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: pre-chiasmatic lesion, CNS mass, Leptomeningeal disease and cerebral spinal disease

4. Management

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). Tumor 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 tumor 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 tumor
B	Tumor >3mm and close to the optic disc or fovea. 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 juxta-papillary areas. If focal therapy is indicated chemotherapy should be given within 6hours of focal therapy.
C	Well-defined tumors with small amounts of sub-retinal or vitreous seeding	Standard dose Chemo-reduction is indicated. Chemotherapy should be given within 6hr of focal therapy (cryotherapy or TTT or sub-tenon 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 sub-retinal seeding. There is retinal detachment of up to 50% of the globe	Enucleate all unilateral retinoblastoma to prevent spread of the tumor; if bilateral, start 3 cycles of chemo-reduction. 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 weeks intervals. Needs to be given within 6 hours of focal therapy, as it acts synergistically to increase the medicine penetration to the tumor (cryotherapy or TTT or sub-tenon, carboplatin 2ml of 20mg), given under aseptic precaution. Local radiation is indicated, for persistent vitreous seeds, use a plaque placed on the sclera over the tumor, staying 36-72 hours

E	The tumor is very large with 1 or more of the following features – No visual potential; tumor in the anterior segment; tumor in OR on the ciliary body; Neuro-vascular glaucoma; Vitreous hemorrhage obscuring the tumor OR significant hyphema; Phthisical or pre-phytisical eye; orbital cellulitis-like presentation; total RD >50%	Enucleation with minimal manipulation is indicated for All group E with no visual potential, tumor invasion to anterior chamber; When direct visualization of an active tumor is obstructed by cataract or vitreous hemorrhage. Note: Optic nerve length should not <17mm to minimize risk of leaving tumor at surgical site; During enucleation, take care not to perforate the globe. For cosmetic appearance – use primary orbital implant. Chemo-reduction indicated if histopathological results are positive for high risk features. High risk features are: 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 High Risk features – no need of chemotherapy; protective glasses needed for all children who have been enucleated
Extra-Orbital Extension	Orbital retinoblastoma	3-6 cycles of high dose chemo-reduction followed by enucleation/exenteration if disease is shown to be responsive External beam radiation therapy and adjuvant chemotherapy for a total of up to 8-12 cycles
	CNS involvement retinoblastoma	Palliative care according to the national palliative care guidelines
	Metastatic retinoblastoma	Palliative care according to the national palliative care guidelines

- **Chemotherapy Agents:** Carboplatin, Vincristine and Etoposide; Doses are: IV Carboplatin 600mg/m², Vincristine 1.5mg/m² and Etoposide IV 300mg/m² every 3 weeks.

- **Radiation Therapy:** Dose ranges: 40-45 Gy

C. Neuroblastoma

1. Introduction

Neuroblastoma, is also known as ganglioneuroblastoma and ganglioneuroma, and is mostly found in the adrenal glands, but also the GI tract, chest, neck, pelvis and bones. The ages of 5 and younger are the most commonly affected.

2. Workup

- History and Physical Examination
- Basic laboratory tests – FBC, RFT, LFT, electrolytes, LDH, Ferritin, IgG, TSH, T4, Coagulation profile
- Urine VMA/HVA
- Imaging – CT/MRI of primary tumor
- Biopsy
- Bone marrow aspirates

3. Staging

The commonly used system is by the INRGSS (International Neuroblastoma Risk Group Staging System).
L1 – Localized tumor not involving the vital structures, as defined by the list of image-defined risk factors and confined to one body compartment
L2 – Loco-regional tumor with presence of one or more Image-Defined Risk Factors (IDRFs)
M – Distant metastatic disease
MS – Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow.
Note: IDRFs are site-specific, and are detailed below:

General:
- Ipsilateral tumor extension within two body compartments: Neck-chest, chest-abdomen, abdomen-pelvis

Neck:
- Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
- Tumor extending to base of skull
- Tumor compressing the trachea

Cervico-thoracic junction:
- Tumor encasing brachial plexus roots
- Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
- Tumor compressing the trachea

Thorax:
- Tumor encasing the aorta and/or major branches
- Tumor compressing the trachea and/or principal bronchi
- Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12

Thoraco-abdominal:
- Tumor encasing the aorta and/or vena cava
- Abdomen/Pelvis:
- Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
- Tumor encasing branches of the superior mesenteric artery at the mesenteric root
- Tumor encasing the origin of the coeliax axis, and/or of the superior mesenteric artery
- Tumor invading one or both renal pedicles
- Tumor encasing the aorta and/or vena cava
- Tumor encasing the iliac vessels
- Pelvic tumor crossing the sciatic notch

Intra-spinal tumor extension whatever the location provided that:
- More than 1/3 of the spinal canal in the axial plane is invaded and/or the peri-medullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal

Infiltration of adjacent organs/strtuctures
- Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery

Conditions to be recorded, but NOT considered IDRFs
- Multifocal primary tumors
- Pleural effusion, with or without malignant cells
- Ascites, with or without malignant cells

4. Management

Decision is made after risk stratification.
- Low Risk Disease: Age < 18 months, localized disease, MYCN negative tumor (if available), Infantile Neuroblastoma (widely metastatic – stage 4S)
- Intermediate Risk Disease: Age >18 months, localized disease without MYCN amplification, complete tumor resection with MYCN amplification, Age <12 months, with widely metastatic disease without MYCN amplification.
- High Risk Disease: Not falling in the above category; best supportive care

4.1. Surgery
Complete tumor excision for resectable tumors; un-resectable tumors are to be treated with pre-operative chemotherapy

4.2. Chemotherapy

Diagnosis confirmed by histology or urine VMA/HVA:

- Infants <12 months with metastatic disease:
  - Clinically stable – Observation
  - Life threatening condition/critically ill – Chemotherapy:
    - 4 cycles of VP-Carbo regimen (Etoposide and Carboplatin). If symptoms persist:
    - 2 more cycles of VP-Carbo then 2 cycles of CADO (Cyclophosphamide, Doxorubicin, Vincristine)
    - Then Surgical resection
- Low Risk and intermediate risk > 12 months
  - Chemotherapy as neo-adjuvant for un-resectable tumor with 2 cycles of VP-Carbo then 2 cycles of CADO
    - Un-resectable – give 1x VP (Etoposide) + 1 -2 cycles of CADO followed by surgery
    - Resectable – surgery then 1 x VP-Carbo + 1-2 cycles of CADO followed by local radiation therapy

Note: For infants <5kg, need of dose reduction by 33%

Doses Solutions are:

- VP-Carboplatin: IV Etoposide 150mg/m² and Carboplatin 200mg/m², given at 3-weeks interval, if more than 1 cycle is required;
- CADO: IV Cyclophosphamide 300 mg/m², Doxorubicin 30mg/m² and Vincristine 1.5mg/m², given at 3-weeks interval, if more than 1 cycle is required;

4.3. Radiation Therapy

Usual Doses: 30-36 Gy

D. Wilm's Tumor

1. Introduction

Wilms tumor, also known as Nephroblastoma, is a relatively common and treatable kidney tumor. The disease is primarily a sporadic condition, and 1-2% of individual have a relative with the disease. 10% of cases, Wilms tumors occur as part of a multiple malformation syndrome, including WAGR (Wilm's Tumor, Aniridia, Genito-urinary malformations and mental Retardation) and Beckwith-Wiedemann syndrome.

2. Workup

- History and Physical Examination; most patients present with an asymptomatic abdominal mass, some with abdominal pain, fever, or severe general malaise, hypertension and haematuria.
- Basic laboratory tests: CBC, RFTs, LFTs, Serum electrolytes, calcium, Urinalysis, Coagulation profile, and if available, 1p and 16q deletion
- Imaging: Abdominal CT scan, Chest
- Biopsy

3. Staging

There are 2 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 2mm	The vessels of the renal sinus are not involved
	There is no residual tumor apparent beyond the margins of excision	Intra-renal 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 peri-aortic 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 intra-operatively (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 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

4. Management

The current guidelines are consistent with the SIOP guidelines for Wilm's tumor management.

I. Pre-operative chemotherapy:
Given to reduce surgical complications, especially tumor rupture, and to downstage the tumor at surgery, allowing for less intense post-operative chemotherapy without radiotherapy.

a. Localized disease – 4-week regimen:
- Vincristine 1.5 mg/m² IV push (2mg is the maximum)
- Actinomycin D 0.045 mg/m² IV Push (2mg is the maximum)
- If no significant shrinkage of tumor by clinical measures, consider additional pre-operative chemotherapy

b. Metastatic disease – 6-week regimen
- Vincristine 1.5 mg/m² IV push (2mg is the maximum)
- Actinomycin D 0.045 mg/m² IV push (2mg is the maximum)
- Doxorubicin 50 mg/m² IV push

Chest and abdominal imaging can be done at week 6 to reassess; 3 additional weeks of chemotherapy should be considered if there is insufficient shrinkage of tumor by clinical measures, or if lung metastases persist. At week 9, referral to surgeon for eligibility assessment; if no improvement, transition to palliative care or best supportive care.

II. Post-operative chemotherapy
Chemotherapy may be administered as soon as gut peristalsis resumes following surger, within 21 days of the last pre-operative chemotherapy dose, unless presence of surgical complications.

a. Surgical stage I intermediate risk:
- 1 post-op cycle
- Vincristine 1.5mg/m² IV push (2mg is the maximum)
- Actinomycin D 0.045 mg/m² IV push (2mg is the maximum)

b. Surgical stage I or II (Complete and easy tumor resection)
- 5 post-operative cycles
- Vincristine 1.5mg/m² IV push (2mg is the maximum)
- Actinomycin D 0.045 mg/m² IV push (2mg is the maximum)

c. Surgical stage III – V (incomplete, difficult resection or rupture/spill)
- 5 post-operative cycles
- Vincristine 1.5 mg/m² IV push (2mg is the maximum)
- Actinomycin D 0.045 mg/m² IV push (2mg is the maximum)
- Doxorubicin 50 mg/m2 IV push

When there is inadequate surgical data to stage – patients will be upstaged and treated with Doxorubicin-containing regimen

III. Radiation Therapy

Ideally, radiation therapy is to occur within 10 days after surgery. If delays occur, it can be offered up to 2 months after surgery with significant benefit. Indications are based on histology, surgical abdominal stage, and presence of metastatic sites despite pre-operative chemotherapy.

- Stage I, low risk: No Radiation Therapy
- Stage I-II, intermediate risk: No Radiation Therapy
- Stage III, intermediate risk: Flank RT + boost to tumor bed
- Stage I, high risk: No Radiation Therapy
- Stage II – III, high risk: Flank RT + boost to tumor bed
- Presence of spillage, regardless of stage and risk stratification: Whole Abdomen + boost to flank and tumor bed

5. Follow up

Follow-up includes screening for tumor recurrence and screening for chemotherapy side effects.

5.1. Screening for tumor recurrence

- Imaging – alternating chest x-ray and abdominal ultrasound with CT scan – chest, abdomen and pelvis. Ideally, imaging should be performed as follows:
  - Every 6-8 weeks during treatment
  - Every 3 months for the first two years
  - Every 6 months for an additional two years
- Focus on chest imaging as lung is the most frequent site of disease recurrence; no modality of choice, alternating is advised.
- Abdominal ultrasound is advised to detect early recurrences or residual disease – stages II and III

5.2. Screening for chemotherapy side effects

The frequency of screening depends on the agents and intensity used during treatment. It consists of early and late complications that both need to be screened.

- Early Complications: Limited to direct side effects of chemotherapy and radiation therapy and complications of surgery
- Late Complications:
  - Renal impairment – resulting from direct surgical loss of the renal parenchyma, and/or injury caused by radiation therapy and chemotherapy
  - Cardiotoxicity – from anthracyclines use, and from lung irradiation if it was used;
  - Hepatotoxity – as a long term side effect of Vincristine and Dacarbazine and hepatic irradiation
  - Fertility – generally not an issue for patients with Wilms tumor, but could be present in females treated with high dose abdominal irradiation
  - Second malignancies – occurring along areas where high dose of irradiation were used (abdomen or chest).

E. Hepatoblastoma

1. Introduction

The condition is the most common primary hepatic malignancy in early childhood. Majority of the disease occurs in the first 2 years of life, and rarely above 5 years of age. The incidence in males is twice that in girls, and roughly 20 times increased risk in children with very low birth weight (<1,500g) and a double risk among those with moderately low birth (1,500-2,500g).
Children usually present with abdominal distension, discomfort or abdominal mass in the right upper quadrant. Vomiting and severe anemia are signs of a ruptured tumor.

2. Workup

- History and Physical Examination
- Basic laboratory tests: FBC, LFTs, RFTs, and AFP
- Imaging: Abdominal CT scan, Chest CT scan
- Tissue Biopsy

3. Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2cm, or >2cm without vascular invasion
T1a	Solitary tumor ≤2cm
T1b	Solitary tumor >2cm without vascular invasion
T2	Solitary tumor >2cm with vascular invasion, or multiple tumors, none >5cm
T3	Multiple tumors, at least one of which is >5cm
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 gall-bladder 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

PRETEXT Staging

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

4. Management

4.1. Surgery
Complete resection of tumor for stage I and II

4.2. Chemotherapy
Single Agent: Cisplatin
Combination: Doxorubicin, Vincristine, Cyclophosphamide, 5-FU OR
Cisplatin, Vincristine, 5-FU, OR Gemcitabine and Bevacizumab

4.3. Radiation Therapy
Dose: 12-20 Gy

5. Follow-Up
- Physical Examination: Every 2-3 months in the 1st and 2nd year, every 6 months in the 3rd year, every 6 months in the 4th and 5th year
- Alpha-Fetoprotein: Every month in the 1st year, every 3 months in the 2nd year, every 6 months in the 3rd, 4th and 5th year
- Chest Xray: Every 3 months in the 1st and 2nd years, every 6 months in the 3rd year, and yearly in the 4th and 5th year
- Abdominal ultrasound: Every 2-3 months in the 1st and 2nd year, every 6 months in the 3rd year, and yearly in the 4th and 5th year
- Serum Magnesium: Yearly from year 1-5
- GFR: 51Cr EDTA Clearance – 1 year off treatment – to be repeated yearly from year 1 to 5 if <80ml/min/1.73m²
- Audiometry: Yearly until reliable result obtained with pure tone audiometry (age ≥3.5 years)

F. Rhabdomyosarcoma

1. 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.

2. 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:

a. Pathology
Favorable = all embryonal, spindle cells, botryoid RMS
Unfavorable = all alveolar tumors (including the solid-alveolar variant)

b. Post-surgical stage (IRS grouping)
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).

c. Site
Favorable = orbit, GU non bladder prostate (i.e. para-testicular and vagina/ uterus) and head & neck non PM
Unfavorable = all other sites (para-meningeal, extremities, GU bladder-prostate and "other site")

d. Node Stage (According to the TNM classification)
N0 = no clinical or pathological node involvement
N1 = clinical or pathological nodal involvement

e. Size & Age
Favorable = Tumor size (maximum dimension) <5 cm and Age < 10 years Unfavorable = all others (i.e. Size >5 cm or Age ≥ 10 years)

Note: Patients with malignant effusion (i.e. tumor 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 non metastatic RMS

Risk Group	Sub-Groups	Pathology	Post-Surgical stage (IRS Group)	Site	Node Stage	Size &Age
Low Risk	A	Favorable	I	Any	N0	Favorable
Standard Risk	B	Favorable	I	Any	N0	Unfavorable
Standard Risk	C	Favorable	II, III	Favorable	N0	Any
Standard Risk	D	Favorable	II, III	Unfavorable	N0	Favorable
High Risk	E	Favorable	II, III	Unfavorable	N0	Unfavorable
High Risk	F	Favorable	II, III	Any	N1	Any
High Risk	G	Unfavorable	I, II, III	Any	N0	Any
Very High Risk	H	Unfavorable	I, II, III	Any	N1	Any

Confirming the Diagnosis

The diagnosis must be established pathologically. Open surgical biopsy is the preferred approach as this maximizes 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 are sufficient to confirm tumor infiltration.

3. Workup

- History and Physical Examination
- Basic laboratory tests: FBC, RFTs, LFTs, Serum electrolytes, LDH, Alkaline Phosphatase, Urinalysis, CSF examination
- Bone Marrow Aspiration/Biopsy
- Cardiac Ultrasound
- Imaging – CT scan – site + metastatic workup, MRI

4. Staging

IRS Group	Definition	pTNM
I	Tumor macroscopically and microscopically removed	
I(A)	Tumor confined to organ or tissue of origin	pT1
I(B)	Tumor 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	
	Macroscopic residuals after resection or biopsy with malignant effusion	pT3b, pT3c
IV	Metastatic present or non-regional lymph nodes involved	pT4

5. Management

5.1. Surgery – Tumor resection

5.2. Chemotherapy

VAC: Vincristine, Actinomycin-D, and Cyclophosphamide:
Doses: Day 1: IV Vincristine 1.5mg/m², Actinomycin-D 0.045mg/kg, Cyclophosphamide 1200mg/m²; D8 and D15: Vincristine 1.5mg/m² only. Repeat for a total of 14 cycles.

5.3. Radiation Therapy

Radiation doses for the primary tumor according to histology and IRS group for children aged 3 years or older:

IRS Group	Emrbyonal RMS	Alveolar RMS
I	No RT	41.4 Gy/23 fractions
IIa, b and c	41.4 Gy/23 fractions	41.4 Gy/23 fractions
III with:		
- Secondary complete resection	36 Gy/20 fractions (partial response) 41.4 Gy/23 fractions (minor partial response) Subgroup C: option A (no RT) or B (36 Gy)	41.4 Gy/23 fractions
- Second look surgery but incomplete secondary resection		
- Clinical complete remission, no 2nd look surgery	41.4 Gy/23 fractions	50.4 Gy/28 fractions
- Partial remission, minor PR, SD, Progressive disease, no 2nd look surgery	50.4 GY/28 fractions (+boost of 5.4 Gy/3 fractions); orbit and PR (>2/3): 45 Gy/25 fractions	50.4 GY/28 fractions (+boost of 5.4 Gy/3 fractions)

Radiation Dose for regional lymph node areas

Situation	Embryonal/Alveolar RMS
No clinical/pathological involvement of regional LNs	No RT
Clinically or pathologically positive LNs, excised or in complete remission before RT	41.4 Gy/23 fractions
Positive LNs, macroscopic residual disease before RT	41.4 Gy/23 fractions + 9Gy boost/5 fractions

6. Follow-up

- 1st year: Clinical Examination, Imaging (ultrasound, CT scan or MRI of primary tumor site, Chest X-ray) – every 3 months
- 2nd and 3rd years: Same, every 4 months
- 4th and 5th years: Same, every 4 months

G. Malignant Bone Tumors in Children

G.1. Osteosarcoma

1. Introduction

Osteosarcoma is the most common malignant bone tumor in children, along with Ewing Sarcoma. It presents as:

- Painful mass on the extremities,
- History of injury
- Pathological fractures
- Constitutional symptoms such as fever, weight loss and malaise are generally rare.

2. Workup

- History and Physical Examination
- Basic laboratory tests: FBC, RFTs, LFTs, Serum electrolytes, Coagulation profile, LDH
- Imaging: Plain X-ray, affected bone, MRI, Metastatic workup – Chest and Abdomen CT scan
- Tissue biopsy
- Cardiac Ultrasound

3. Staging

AJCC/TNM Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤8cm in greatest dimension
T2	Tumor >8cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

N Staging

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed. Because of rarity of LN involvement in bone sarcomas, the designation NX may not be appropriate, and cases should be considered N0 unless clinical node involvement is clearly evident
N0	No regional LNs metastasis
N1	Regional lymph node metastasis

M Staging

M Category	M Criteria
cM0	No distant metastasis
cM1	Distant metastasis
cM1a	Lung
cM1b	Bone or other distant sites

4. Treatment

4.1. Surgery

- Tumor resection with histological evaluation

4.2. Chemotherapy:

- AP: Doxorubicin, Cisplatin – Day 1: IV Doxorubicin 37.5mg/m² and Cisplatin 100mg/m², Day 2: IV Doxorubicin 37.5mg/m²
- Repeat every 3 weeks for 6 cycles

4.3. Radiation therapy:

- Median dose – 60 Gy (Range: 40-68 Gy)

G.2. Ewing Sarcoma

1. Introduction

Ewing's sarcoma (ES) 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 sarcomas most often arise in the long bones of the extremities or soft tissue. Compared to undifferentiated ES of bone, patients with extra-osseous ES (EES) are more frequently older, more likely to be female, and arise more often within the axial, rather than the appendicular, skeleton. The usual presentation consists in:

- Localized pain or swelling
- Trauma history which may be the initiating event calling attention to the lesion
- Constitutional symptoms or signs, such as fever, fatigue, weight loss or anemia

2. Workup

- History and Physical Examination
- Basic laboratory tests: FBC/RFT/LFT/ Serum electrolytes and Calcium, ESR, CRP, LDH, blood cultures
- Imaging: Plain Chest X-Ray, X-ray of affected bones (with onion peel's sign pattern from reactive periosteum)
- CT scan/MRI
- Cardiac Ultrasound
- Bone Marrow Aspiration/Biopsy
- Cytogenetics/Molecular testing

3. Treatment

3.1. Surgery

Tumor resection with histological evaluation

3.2. Chemotherapy:

- **VAC** – Vincristine, Doxorubicin, Cyclophosphamide

Cycles 1-6: Day 1- Vincristine 1.5mg/m2, Doxorubicin 37.5mg/m2, Cyclophosphamide 1200mg/m2; Day 2: Doxorubicin 37.5mg/m2;
From cycles 7-12: Switch Doxorubicin to Actinomycin-D at dose of 0.045mg/kg

3.3. Radiation Therapy

The dose ranges fro 40-60 Gy

4. Follow-up

- Year 1: 3 monthly visits, with physical examination; imaging, twice annually
- Year 2: 6 monthly visits, with physical examination; imaging, once annually
- Year 3 – 5: Every year, plus imaging, once annually.

H. Germ Cell Tumor

1. 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: Ovary, Testis
  - Extra-gonadal: Brain, Neck, Mediastinum, Retroperitoneum, Sacro-coccygeal region
- Most childhood extra-gonadal GCTs arise in midline sites, representing aberrant embryonic migration of the primordial germ cells.
- Extra-cranial GCTs are broadly classified as follows:
  - 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).

GCTs produce tumor markers, on base of which are divided secretory and non-secretory GCTs.

2. Workup

- History and Physical Examination
- Basic laboratory tests – FBC, RFTs, LFTs, Serum electrolytes, LDH, AFP, Ca-125, β-HCG
- Imaging – CT scan (Chest, Abdomen), Abdominal Ultrasound
- Biopsy for histopathology
- Lung Function Tests

3. Staging

TNM Classification

T Category	Clinical/Radiological staging (no initial surgery)	Post-surgical staging (post biopsy/initial surgery)
T0	No primary tumor	No tumor on histology
T1	Localized <5cm	Complete resection of local tumor

T2	Localized >5cm and <10cm	Complete resection of T4 tumor
T3	Localized >10cm	Residual tumor pT3a – microscopic (+ascites for ovarian tumor), pT3b macroscopic, pT3c – biopsy alone
T4	T of any size with loco-regional extension	
T5	Bilateral	
Tx	Unknown	Unknown
N Category		
N0	No lymph node involved	No regional nodes
N1	Clinical or imaging node involvement	Involvement of regional nodes pN1a – Complete removed pN1b – Incompletely removed
Nx	Unknown	Unknown
M Category		
M0	No metastasis	No metastasis
M1	Distant nodes (lumbar-aortic – loco-regional for testicular tumors)	Present including distant nodes
Mx	Unknown	Unkown

Risk groups for extra-cranial malignant GCTs

a. Low Risk

Gonadal Stage 1 tumors (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.

b. 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 tumors. Pure germinoma/seminoma, any site, Stage 2, 3 + 4
- Pure HCG secreting tumors, any HCG, Stage 2 + 3

c. High Risk

- All Stage 4 tumors except testis < 5yrs and germinoma/seminoma
- AFP > 10,000 kU/L except all Stage 1 tumors and testis < 5yrs Stage 2,3+ 4. All thoracic tumors, Stage 2,3 + 4

4. Management

4.1. Overview of management of GCTs

- Imaging of primary tumor + Serum AFP + hCG:
  - Resectable – resection, preserving major organs:
    - Mature/Immature teratoma only – Complete staging.
  - Stage I – observe, monitor AFP (except gonadal mature teratoma with normal pre-operative AFP)
  - Stage II/III – AFP normal: Further surgery if feasible, observe and monitor AFP
  - Rising AFP – Restage then risk group classification, followed by chemotherapy.
    - If no residual tumor – observe/monitor AFP/hCG
    - If residual tumor – further surgery if feasible then observe/monitor AFP/hCG
  - Malignant GCTs – Complete staging.
    - Stage I, AFP/hCG fall to normal – observe/monitor AFP/hCG.
    - Stage 2-4 or stage I with raising AFP/hCG – restage then risk group classification followed by chemotherapy.
      - If no residual tumor – observe/monitor AFP/hCG
      - If residual tumor – further surgery if feasible then observe/monitor AFP/hCG
- Tumor unresectable – biopsy unless AFP/hCG raised and biopsy would be hazardous, followed by complete staging
  - Mature/Immature teratoma only – further surgery if feasible, monitor AFP/hCG
    - Malignant GCTs – restage then risk group classification followed by chemotherapy.
    - If no residual tumor – observe/monitor AFP/hCG
    - If residual tumor – further surgery if feasible then observe/monitor AFP/hCG

4.2. Principles of surgery

Gross total resection of the tumor is the main objective; if a residual mass is present at the end of chemotherapy, second look surgery should be considered if non-mutilating resection is deemed feasible

4.3. Principles of Chemotherapy

Bleomycin, Etoposide and Cisplatin/Carboplatin (BEP):
IV Bleomycin 15mg/m2, Etoposide 100mg/m² and Cisplatin 20mg/m², every 3 weeks for 4 cycles.
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

4.4. Principles of Radiation Therapy

Radiotherapy is not an integral part of the management of extra-cranial germ cell tumors of childhood. It may however be useful for the occasional patient with relapsed tumor. Dysgerminoma of the ovary and seminoma of the testis are exquisitely radio-sensitive and large tumors would be expected to regress with only modest doses of radiation (20 - 40 Gy). Those tumors with secreting or teratomatous elements are more radio-resistant (40-45Gy)

5. 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.

I. Acute Lymphoblastic Leukemia

1. Introduction

No routine screening is recommended.
Common Findings at Presentation

Symptoms

- Anorexia, fatigue, irritability
- Bone or, less often, joint pain
- Signs and symptoms of bone marrow failure: pallor, fatigue, bruising, epistaxis, and fever, which may be caused by infection

Findings on Examination

- Pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage reflect bone marrow failure
- Lymphadenopathy, splenomegaly, or hepatomegaly
- Tenderness over the bone or objective evidence of joint swelling and effusion
- Signs of increased intracranial pressure, such as papilledema, retinal hemorrhages, and cranial nerve palsies, indicate leukemic involvement of the central nervous system (CNS)
- Respiratory distress related to anemia or a large anterior mediastinal mass.
- Testicular swelling - palpation should be done in all boys; if abnormal, do U/S to delineate mass

2. Workup

Pathologic Work-Up

- Peripheral blood smear
- Bone marrow aspirate and biopsy specimen using standard morphology and immune-histochemical stain will help identify leukemia and differentiate ALL from AML
- Flow cytometry: To improve diagnostic accuracy and distinguish among subtypes of ALL: B-precursor from T-cell ALL
- Cytogenetic studies: To determine t(9;22) and other abnormalities
- LP for CNS involvement analysis

Laboratory Work-Up

- Full blood count with differential, creatinine, urea, urinalysis, SGOT/SGPT, bilirubin, uric acid, LDH, alkaline phosphatase, electrolytes (K, Na, Ca, Mg, Phosphates), HIV testing, Malaria smear: to diagnose and treat, pregnancy test in women with childbearing potential.
- Hepatitis viral studies for HCV and HBV and CMV are also recommended where available.

Radiological work-up

- Chest x-ray
- CT head/chest/abdomen/pelvis as indicated for symptoms
- Testicular US
- Cardiac ultrasound prior to doxorubicin administration

Risk Stratification Post-Induction

Definitions of Risk Stratification Criteria:

CNS Involvement

- CNS1: negative cytology (no blasts)
- CNS2: positive cytology, <5WBC/ul
- CNS3: positive cytology, ≥ 5WBC/ul or any CNS lesion

Prednisone Response (based on peripheral smear)

- Prednisone good responder (PGR): <1000 leukemic blasts/microliter on day 8
- Prednisone poor responder (PPR): 1000 or more leukemic blasts/microliter on day 8

Bone Marrow Response

Perform a bone marrow aspirate on Day 29 of induction therapy

Risk Stratification:

NCI Standard risk group: WBC <50,000/microL and age 1 -10 years

Lower Risk

ALL of the following:

1. NCI standard risk group*
2. Lesser risk cytogenetics:
   Trisomies 4 and 10
   or
   ETV-RUNX1 (United States)
   or
   Hyperdiploid (Europe)
3. Rapid response to therapy

Higher Risk

ANY of the following:

1. NCI high risk group◊
   and
   Rapid response to therapy
2. NCI standard risk group*
   and
   Slow response to therapy
3. CNS-positive leukemia
4. Testicular leukemia

Very High Risk
ANY of the following:

1. MRD+ at day 29§
2. Induction failures
3. MLL rearrangements
   or
   iAMP21 amplification
4. Age <1 year (or >13 years if treated on a COG protocol)

3. Treatment

Use of allopurinol and aggressive hydration before starting steroids or chemo to prevent tumor lysis .
The following is the management for Ph- ALL or unknown status

2 mg is the maximum Vincristine dosing in all regimens

Induction (4 weeks)

D 1	Cytarabine intrathecal
D 1-28	Prednisone prophase (60mg/m²/day) PO
D 1, 8, 15, 22	Vincristine (1.5mg/m²) IV Push
D 1, 8, 15, 22	Daunorubicin IV
D 8, 29	Intrathecal (IT) Methotrexate (MTX)
D 4, 5, 6	Pegaspargase (IM)
D 15, 22	Extra IT MTX if CNS3

Consolidation (4 weeks)

D 1 and 29	Cyclophosphamide
D 2-5, 9-12, 30-33 , AND 37-40	Cytarabine IV
D 1-14, 29-42	6-Mercaptopurine (75mg/m²) PO
D 15,22,43,50	Vincristine
D 15 and 43	Pegaspargase (IM)
D 1, 8, 15 ,22	Intrathecal (IT) Methotrexate (MTX)

Interim Maintenance (8 weeks)

D 1, 11, 21, 31, and 41.	Vincristine IV
D 1, 11, 21, 31, and 41	MTX IV
D 2 and 22.	Pegaspargase IM
D 1 and 21	IT MTX on days

Delayed Intensification (8 weeks)

D 1-21	Dexamethasone (10mg/m²/day) PO
D 1,8,15, 43 and 50	Vincristine (1.5mg/m²) IV Push
D 1,8,15	Doxorubicin (25mg/m²) IV Push
D 4,5 and 43	Pegaspargase IM
D 29	Cyclophosphamide (1000mg/m²) IV
D 30-33, 37-40	Cytarabine (75mg/m²) IV
D 29-42	6-Mercaptopurine (60mg/m²) PO
D 1, 29, 36	IT MTX

Maintenance

D 1-5, 29-33, 57-61	Dexamethasone (6mg/m²/day) PO
D 1, 29, 57	Vincristine (1.5mg/m²) IV Push
D 1-84	6-Mercaptopurine (75mg/m²) PO
D1 and then weekly to D78	Oral MTX (20mg/m2) PO, omit oral MTX when IT MTX given
D 1	IT MTX (no oral given)

Maintenance therapy repeats every 12 weeks until total duration of therapy is 2 years from the start of interim maintenance I for female patients and 3 years from the start of interim maintenance I for male patients.
Patients with testicular disease may receive testicular radiotherapy for 8 days during one of the first 3 courses of maintenance therapy.
Patients are followed every 2 months for 2 years, every 3 months for 1 year, every 6 months for 1 year, and then annually thereafter.

Special Consideration for IT Methotrexate

IT MTX is diluted in 6mL of preservative free sterile water or preservative free normal saline. The volume of CSF removed should be equal to the volume delivered. IT MTX is dosed via the age-based dosing table below and administered in a single syringe along with 15mg of hydrocortisone for pediatric patients (increase hydrocortisone to 50mg for adult patients).

IT MTX Doses			
Age (yr)	1-1.99	2-2.99	≥ 3
Dose (mg)	8	10	12

4. Follow-up Care

Every 3 months for the first year or more frequently, as needed.

- Physical Exam
- Full blood count

J. Non-Hodgkin's Lymphoma

J.1. Burkitts Lymphoma (BL)

1. Introduction

No routine screening is recommended.
Common Findings at Presentation

– **Findings on examination**

- Rapidly growing mass, peak age 4 – 7 years, boys more often affected than girls.
- Common sites of presentation:
  - Abdomen (lymph nodes, spleen, kidneys, liver, ovaries)
  - Face (orbit, mandible, maxilla)
  - Paraspinal (can cause paraplegia, urinary incontinence),
  - Bone marrow or central nervous system.
  - Lymph nodes, bone, the breast, and testes may be involved
- The tumor may double in size within 48 hours and requires urgent treatment, especially when children present with neurological symptoms or orbital disease to try to prevent irreversible damage.

– **Differential Diagnosis**

BL usually grows faster than the other tumors in the differential diagnosis.

- *Wilm's Tumor: children usually more malnourished, renal tumor(s), usually without acute pain or severe general malaise; hematuria, hypertension*
- *Other lymphomas, acute leukemias, neuroblastoma*
- *Face/jaw: abscess, dental cyst*
- *Eye: retinoblastoma, rhabdomyosarcoma*
- *Extremity (arm/leg): osteosarcoma*

2. Workup

Pathological work up:

- Biopsy
- Ideally incisional biopsy, but core biopsy if unable
- Bone marrow biopsy for staging when feasible but should not delay treatment
- Burkitt's Lymphoma is a ***medical emergency***; in some instances, it may be unsafe to obtain a proper biopsy. Consult with a specialist for guidance on starting treatment and timing of safely attempting for a biopsy

Radiological work up:

- Minimal requirements
  - Chest x-ray: AP and lateral
  - Abdominal ultrasound
- Recommended
  - CT scans of neck, chest, abdomen, and pelvis

Laboratory Work-Up

- Full blood count with differential, creatinine, urea, urinalysis, SGOT/SGPT, bilirubin, uric acid, LDH, alkaline phosphatase, HIV testing, Malaria smear: to diagnose and treat, pregnancy test in women with childbearing potential
- Hepatitis viral studies for HCV and HBV are also recommended where available.
- CSF examination is part of staging, but should not delay starting treatment if unavailable

3. Staging

St. Jude Non-Hodgkin Lymphoma (Murphy) Staging System:
Staging: If unable to stage, treat at Stage 4

Stage	Criteria
I	A single tumor or nodal area involved, excluding the abdomen and mediastinum
II	Tumor is limited to a single tumor with regional node involvement, two or more tumors or nodal areas involved on one side of the diaphragm, or a primary gastrointestinal tract tumor (completely resected) with or without regional node involvement
III	Tumors or involved lymph node areas on both sides of the diaphragm. It includes any primary intrathoracic (mediastinal, pleural or thymic) disease, extensive primary intra-abdominal disease, or any paraspinal or epidural tumors
IV	Tumors involve bone marrow and/or central nervous system, regardless of other sites of involvement

*Bone marrow involvement is defined as 5% malignant cells in an otherwise normal bone marrow with normal peripheral blood counts and smears.

4. Treatment

Use of allopurinol, aggressive hydration before starting steroids or chemo and close monitoring of electrolytes and renal function to prevent tumor lysis syndrome.

Dosing of intrathecal drugs

Age	Methotrexate	Hydrocortisone
<2 years	10mg	10mg
2-3 years	12mg	12mg
>3 years	15mg	15mg

Stage I & II: COPI, followed by COMPI & COMPII over 35 days

Day 1	**COPI** Vincristine 1mg/m² IV Push Cyclophosphamide 150 mg/m² IV Methotrexate intrathecal (IT) +hydrocortisone Prednisone 60mg/m² PO divided in two doses
Day 2	Cyclophosphamide 150 mg/m² IV Prednisone 60mg/m² PO divided in two doses
Days 3-7	Prednisone 60mg/m² PO divided in two doses
Day 15	**COMPI** Vincristine 2mg/m² IV Push Methotrexate 2,000mg/m² IV Prednisone 60mg/m² PO divided in two doses
Day 16	Cyclophosphamide 250 mg/m² IV Leucovorin 15mg PO every 6 hours x4 doses (start strictly 24 hours after start of MTX IV administration) Prednisone 60mg/m2PO divided in two doses
Day 17	Cyclophosphamide 250 mg/m² IV Leucovorin 15mg PO every 6 hours x4 doses Prednisone 60mg/m²PO divided in two doses
Day 18	Leucovorin 15mg PO every 6 hours x 4 doses Prednisone 60mg/m²PO divided in two doses
Day 19-23	Prednisone 60mg/m²PO divided in two doses
Day 29	**COMPII** Vincristine 2mg/m²IV Push Methotrexate 2,000mg/m²IV Prednisone 60mg/m2PO divided in two doses
Day 30	Cyclophosphamide 250 mg/m² IV Leucovorin 15mg PO every 6 hours x4 doses (start strictly 24 hours after start of MTX IV administration) Prednisone 60mg/m² PO divided in two doses
Day 31	Cyclophosphamide 250 mg/m² IV Leucovorin 15mg PO every 6 hours x4 doses Prednisone 60mg/m² PO divided in two doses

Day 32 Leucovorin 15mg PO every 6 hours x 4 doses
Prednisone 60mg/m² PO divided in two doses

Day 33-35 Prednisone 60mg/m² PO divided in two doses

Stage III & IV: COPI, COPII, COMPI and COMPII over 42 days

Day 1 **COPI**
Vincristine 1mg/m² IV Push
Cyclophosphamide 150 mg/m² IV
Methotrexate intrathecal (IT) +hydrocortisone
Prednisone 60mg/m² PO divided in two doses

Day 2 Cyclophosphamide 150 mg/m² IV
Prednisone 60mg/m² PO divided in two doses

Days 3-7 Prednisone 60mg/m² PO divided in two doses

Day 8 **COPII**
Vincristine 2mg/m² IV Push
Cyclophosphamide 250 mg/m² IV
Methotrexate intrathecal (IT) +hydrocortisone
Prednisone 60mg/m² PO divided in two doses

Day 9 Cyclophosphamide 250 mg/m² IV
Prednisone 60mg/m² PO divided in two doses

Days 10-15 Prednisone 60mg/m² PO divided in two doses

Day 22 **COMPI**
Vincristine 2mg/m² IV Push
Methotrexate 2,000mg/m² IV
Prednisone 60mg/m² PO divided in two doses

Day 23 Cyclophosphamide 250 mg/m² IV
Leucovorin 15mg PO every 6 hours x4 doses (start strictly 24 hours after start of MTX IV administration)
Prednisone 60mg/m² PO divided in two doses

Day 24 Cyclophosphamide 250 mg/m² IV
Leucovorin 15mg PO every 6 hours x 4 doses
Prednisone 60mg/m² PO divided in two doses

Day 25 Leucovorin 15mg PO every 6 hours x 4 doses
Prednisone 60mg/m² PO divided in two doses

Day 26-28	Prednisone 60mg/m² PO divided in two doses
Day 36	**COMP II** Vincristine 2mg/m² IV Push Methotrexate 2,000mg/m² IV Prednisone 60mg/m² PO divided in two doses
Day 37	Cyclophosphamide 250 mg/m² IV Leucovorin 15mg PO every 6 hours x4 doses (start strictly 24 hours after start of MTX IV administration) Prednisone 60mg/m² PO divided in two doses
Day 38	Cyclophosphamide 250 mg/m² IV Leucovorin 15mg PO every 6 hours xPrednisone 60mg/m² PO divided in two dose
Day 39	Leucovorin 15mg PO every 6 hours x 4 doses Prednisone 60mg/m² PO divided in two doses
Day 40-42	Prednisone 60mg/m² PO divided in two doses

2 mg is the maximum VCR dosing in all regimens
2000mg is the maximum Cyclophosphamide dosing in all regimens
When administering IV MTX:
5% Dextrose in water (D5W) with 30 mL of 4% NaHCO3, added per liter of D5W, should be administered at a rate of 3L/m2/24 hours and must be started 4 hours before IV Methotrexate administration and continued for the next 48 hours.
Check urine pH with each micturition (goal > or = 7.5). Administer PO Sodium Bicarbonate 500mg q 6 hool dose if urine pH > or = 7.5, check with specialist to clarify instructions.

5. Gaps and Future Directions

Comprehensive supportive care services crucial to care (ICU level care and intensive nursing) are not available in all settings

6. Follow-up Care

Physical Exam and Blood Work

- First 6 months: every month
- 6 months – 2 years post treatment: every 3 months
- 2 years post treatment: once per year

7. References

1. Hesseling P, Broadhead R, Mansvelt E, et al. The 2000 Burkitt Lymphoma trail in Malawi. Pediatr Blood Cancer. 2005; 44:245-50.
2. .Hesseling PB, Trijin I, Harif M, et al. Practical Recommendations for the Management of Children with Endemic Burkitt Lymphoma (BL) in a Resource Limited Setting. Pediatr Blood Cancer 2013; 60: 357–362

J.2. Diffuse Large B Cell Lymphoma

1. Introduction

- Genetic: Male predominance, Caucasians have higher rates familial aggregation of patients with DLBCL observed
- Other: HIV, Richter's transformation from CLL (or transformation from other indolent non-Hodgkin lymphomas)

– **Prevention & Screening**

Assess patients with established CLL for Richter's transformation

– **Common Symptoms:**

- Rapidly enlarging symptomatic mass, commonly nodal enlargement in neck or abdomen. Systemic B symptoms (fever, weight loss, drenching night sweats)
- **Common Signs:** Lymph node enlargement on lymphoid survey (examination of Waldeyer's ring, head and neck, axillary and chest, abdomen, inguinal regions). Signs related to mass and compression of nearby structures (ie) SVC syndrome if mediastinal mass.
- **Common Presentations:** Extranodal involvement in up to 40%. Extranodal sites include GI tract, bone, testis, spleen, Waldeyer's ring, and salivary gland. Bone marrow involvement in 11-27% or cases and can be discordant low-grade B-cell lymphoma.

2. Workup

- **Laboratory:** Lymph node pathology (excisional preferred), CBC and differential, creatinine, electrolytes, liver enzymes, LDH, calcium, viral screen (Hepatitis B surface antibody, Hepatitis B surface antigen, Hepatitis C antibody, HIV serology)
- **Diagnostic Imaging:** PET/CT of neck/chest/abdomen/pelvis. Echo or MUGA for baseline cardiac function prior to anthracycline.
- **Diagnostic Procedures:** Bone marrow biopsy and aspirate. Lumbar puncture (CSF for flow cytometry) and MRI Brain with gadolinium if suspect CNS involvement.
- **Common Histology:** Large B lymphoid cell morphology. Immunohistochemistry CD20+, CD19+, CD10+/-, bcl6+ (60-90%), MUM1+ (35- 65%).
- **Common Extranodal Sites:** CNS (leptomeningeal), testicular, skin

3. Staging

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 ileo-cecal 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 intra-thoracic 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

4. Treatment

i. NON-BULKY LIMITED STAGE DLBCL

- Bottom Line General Approach: Nonbulky (<10cm), limited stage (Stage I or II) DLBCL are treated with combined modality therapy consisting of R-CHOP chemoimmunotherapy (Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Prednisone) and involved field radiation therapy (IFRT).
- Also acceptable R-CHOP x 3-4 cycles + IFRT if no stage adjusted IPI factors; R-CHOP x 6 cycles (with or without IFRT for local control) if >=1 stage adjusted IPI factors

ii. ADVANCED STAGE DLBCL

- Bottom Line General Approach: Advanced stage (Stage III or IV) or bulky disease (>10cm) DLBCL are treated with combined modality therapy consisting of R-CHOP × 6 cycles +/- IFRT.

iii. RELAPSED DLBCL

- Bottom Line General Approach: If transplant eligible, refer where this can be done.

K. Hodgkin's Lymphoma

1. Introduction

- **Common Risk factors are:**
  - Environmental/Chemical/Infections: History of EBV infection, Immunosuppression (ie) HIV, Autoimmune disorders (ie) RA, SLE, sarcoidosis
  - Genetic: possible genetic susceptibility
- **Common Symptoms:** Asymptomatic lymphadenopathy, alcohol induced pain of lymph nodes, B symptoms (fever, weight loss, night sweats), pruritus, skin lesions, respiratory symptoms due to mediastinal masses (ie) cough, chest pain, SOB
- **Common Signs:** Cervical lymphadenopathy, SVC syndrome (rare)
- **Common Presentations:** Painless asymptomatic cervical/supraclavicular lymphadenopathy

2. Workup

- **Laboratory:** CBC, differential, ESR, liver function tests, ALP, electrolytes, Creatinine, Calcium, Albumin, LDH, HIV serology, pregnancy test (in women of childbearing age)
- **Diagnostic Imaging:** CT scan (neck, chest, abdomen, pelvis), PET
- **Diagnostic Procedures:** Bone marrow biopsy and aspiration can be omitted from staging
- **Other Pretreatment Evaluation Considerations:**
  - Cardiac Function: assessment of ejection fraction through Echo or MUGA if patient to receive anthracycline
  - Pulmonary Function: consider baseline pulmonary function studies (for DLCO) if patient to receive bleomycin. Although baseline results do not predict subsequent development of pulmonary bleomycin toxicity
  - Fertility Counseling: patients of childbearing age should receive counseling on effect of treatment and options for fertility preserving measure
- **Essential to obtain excisional lymph node biopsy to confirm diagnosis of HL**
- **WHO Classification of Histologic Subtypes of HL**
  - **Classical (~95%)**
    - Nodular Sclerosis (70%)
    - Mixed Cellularity (20%)
    - Lymphocyte Rich (5%)
    - Lymphocyte Depleted (1%)
  - **Nodular Lymphocyte Predominant**
- **Common Histology:** Reed Sternberg Cells
- **Relevant Immunohistochemistry:** CD30+, CD15+, CD20+ (20%), PAX-5+

3. Staging

Ann Arbor Staging:

Stage	Description
I	Involvement of a single lymph node region or a single extranodal site
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Diffused/disseminated involvement of one or more extra lymphatic organs or tissues with or without associated lymph node involvement
Other	B Symptoms: absence (A) or presence (B) or fever >38.5°C, drenching night sweats, and/or unexplained weight loss of >10% body weight in past 6 months E: Extranodal disease X: Bulky disease. Defined as mediastinal mass >1/3 thoracic diameter or any nodal mass >10cm in maximal diameter

Limited Stage (Stage III) Definition of Unfavorable Disease

- EORTC (European Organization for the Research and Treatment of Cancer) Definition:
  - Age >50
  - Bulky mediastinal disease
  - ESR >50 without B symptoms
  - ESR >30 with B symptoms
  - >3 lymph node regions
- GHSG (German Hodgkin Study Group) Definition:
  - Bulky mediastinal disease
  - ESR >50 without B symptoms
  - ESR >30 with B symptoms
  - Extranodal disease
  - ≥3 Lymph node groups

Advanced Stage (Stage IIIIV) International Prognostic Score (Hasencleaver Index):

- Hb <105. Age >45, Male, Stage IV, Lymphopenia <600 (and/or 8% total WBC), Albumin <40, WBC >15

Score	5 Yr FFP (%)	5 Yr OS (%)
0	88	98
1	84	97
2	80	91
3	74	88
4	67	85
5 or more	62	67

I.6. PROGNOSIS

- Majority of patients with HL will be alive in 10 years post treatment (>80%)
- Younger patients with limited disease have very good prognosis (ie) 5-year OS <45yo >90%
- Although most have excellent long-term prognosis, approximately 20-25% will relapse with majority in first 3 years following treatment.

General Follow-up considerations

Secondary Cancers post radiotherapy

- Risk continues beyond 30 years
- Chest/Axillary RXT: annual mammogram 8-10years post treatment or at 40yo (whichever comes first)
- Age-appropriate preventative health care and cancer screening

Cardiovascular disease

- At risk if received mediastinal radiation or anthracycline
- Assess and reduce cardiovascular risk factors (HTN, smoking, Diabetes, lipids)

Hypothyroidism

- At risk if received neck/upper mediastinal RXT: annual thyroid function tests

MDS/Leukemia

- Low risk with ABVD (increased if RT), at higher risk if received BEACOPP or BEACOPPescalated
- Annual CBC, evaluate if symptoms

Fertility

- At risk especially if received BEACOPP or older age. Lower risk with ABVD
- Consider referral for reproductive endocrinology, fertility counseling, and options for fertility preserving measure (ie) sperm banking

Radiation pneumonitis/Lung Fibrosis

- Rare, evaluate if symptoms

4. Treatment

EARLY STAGE (STAGE I-II) CLASSICAL HL

Bottom Line General Approach:

- Combined modality therapy for localized disease to improve disease free survival and limit late toxicities.
- ABVD chemotherapy = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
- IFRT = involved field radiation therapy

Clinical Stage	Treatment Regimen
Stage I-II Favorable, Nonbulky	Favorable disease defined by either EORTC or GHSG criteria Classical HL Stage I-II (all histologies): ABVD X2 cycles, plus IFRT 20Gy For pts who prefer to avoid IFRT: ABVDX2 then PET-CT. If Pet negative then further ABVDX2, if PET positive then IFRT Stage IA Nodular Lymphocyte predominant in peripheral nodal sites: IFRT alone Stage IA Nodular Sclerosis with high neck or epitrochlear nodes <3cm: IFRT alone Assessment of response to therapy evaluated with PET-CT (or CT)
Stage I-II Unfavorable, Nonbulky	Unfavorable disease defined by either EORTC or GHSG criteria Classical HL Stage I-II (all histologies): ABVD X4 cycles, plus IFRT 30Gy Assessment of response to therapy evaluated with PET-CT (or CT)
Stage I-II Bulky	Bulky: mediastinal mass >1/3 thoracic diameter or any nodal mass >10cm ABVD X6 cycles plus IFRT 30Gy to prior bulk site

ADVANCED STAGE (III + IV) CLASSICAL HL

Bottom Line General Approach:

- Stage III or IV HL (Some trials also include Stage IIB)
- IPS score for prognostication
- 6 cycles ABVD or escalated BEACOPP (especially if 4-7 risk factors by IPS) +/- IFRT if PET positive residual mass or bulky disease

RELAPSED /REFRACTORY CLASSICAL HL

Bottom Line General Approach:

- Refractory Disease: Failure to achieve remission or relapse at <3months after completing therapy
- Relapsed Disease: Early 3-12 months versus Late >12months (better prognosis)
- Confirm relapse with tissue biopsy and complete restaging. False positive PET-CT causes include local inflammation post therapy, sarcoidosis, deposition of brown fat, infection.
- Identify sites of relapse, initial presenting stage and stage at relapse, previous therapy received (radiation alone, or combined modality), time to relapse, comorbidities
- If initial therapy radiation alone: ABVD ×6 +/- IFRT if localized relapse outside original radiotherapy field
- If initial therapy included chemotherapy: Re-induction with salvage chemotherapy followed by autologous stem cell transplant +/- IFRT to prior bulk site at relapse. Salvage chemotherapy options include:
  - GDP (Gemcitabine, Dexamethasone, Cisplatin)
  - DICEP (Dose Intensive Cyclophosphamide, Etoposide, Cisplatin)
  - DHAP (Dexamethasone, Cytarabine, Cisplatin)
- For Second/Subsequent relapse
  - Palliative chemotherapy for those with symptoms (GDP, vinblastine, CHVVP, MOPP, gemcitabine single agent)
  - Allogeneic stem cell transplant (if eligible, with chemosensitive disease, time to relapse >1year following auto-HSCT)
  - Brentuximab vedotin if failed initial chemotherapy and failed auto-HSCT

- **Prognosis:** Relapse rates 20-25% depending on stage. Salvage therapy can achieve responses in approximately 50%, however long term disease free survival following relapse therapy less common.

Nodular Lymphocyte Predominant HL

Background:

- Uncommon subtype (5% of all cases), indolent course, good survival
- Slight male predominance, median age 37yo. Typically present with peripheral adenopathy, not continguous.
- Immunohistochemistry: negativity for CD30, CD15
- Associated with progressive transformation of germinal centers, T-cell rich B cell lymphoma, diffuse large B cell lymphoma

Bottom Line General Approach:

- No standard therapy
- Early Stage: IFRT, combined modality ie ABVD, or observation
- Advanced stage: Combined modality ie ABVD +/- rituximab if CD20+
- Escalated BEACOPP Risks:
  - Infection, Infertility, Increased risk MDS/AML (0.9%)

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