The Kingdom of Eswatini

ESWATINI NATIONAL CANCER GUIDELINES

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Preface

Eswatini has been making progress to formalize its response to the burgeoning cancer epidemic in the country. Primarily, the Ministry of Health has established the National Cancer Control Unit, demonstrating its commitment to tackling cancer with a formalized program similar to the established responses to HIV and Tuberculosis. The first National Cancer Control Plan was commissioned in 2019, followed by the inaugural Cancer Technical Working Group to provide a coordinating body of technical advisors to enact the control plan.

While the programmatic structures for a robust approach to cancer control are taking shape, it is critical that the country simultaneously dedicates energy and resources to strengthening delivery of clinical services for cancer. To this end, a multi-disciplinary team comprised of oncology specialists, surgeons, gynecologists, radiologists, pathologists, oncology nurses, paediatricians, internists, palliative care specialists, and pharmacists have tirelessly dedicated their time to develop the first Standardized Cancer Treatment Protocols presented here. The protocols emphasize the need for a multi-disciplinary, holistic approach to management of cancer patients with increased focus on palliative care throughout the cancer journey.

While this document is critical to our fight against cancer, we must be reminded that it is only one weapon in the arsenal we require to meaningfully progress towards cancer control. The Ministry of Health and its partners must continue to advocate for and bring to fruition the resources necessary to provide the holistic services outlined within these protocols to the people of Eswatini.

Dr. Vusi Magagula
Director of Health Services
Ministry of Health

Acknowledgements

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Acronyms

ART	Antiretroviral Therapy
BMAT	Bone Marrow Aspiration & Trephine
bPFS	Biochemical Progression Free Survival
CBE	Clinical Breast Exam
CEA	Carcinoembryonic Antigen A
CMP	Comprehensive Metabolic Panel
CRPC	Castrate Resistant Prostate Cancer
CSS	Cancer Specific Survival
CT	Computerized Tomography
DWI	Diffusion Weighted Imaging
ECE	Extracapsular extension
ER	Estrogen Receptor
FBC	Full Blood Count
FDA	Food and Drug Administration
FNA	Fine Needle Aspirate
GS	Gleason Score
HER2	Human Epidermal Growth Factor 2
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSPC	Hormone Sensitive Prostate Cancer
IHC	Immunohistochemistry
KFT	Kidney Function Test
KS	Kaposi's Sarcoma
LDH	Lactate Dehydrogenase
LEEP	Loop Electrosurgical Excision Procedure
LFT	Liver Function Test
MDT	Multi-disciplinary Team
MRI	Magnetic Resonance Imaging
NHL	Non-Hodgkin's Lymphoma
PET	Positron Emission Tomography
PR	Progesterone Receptor
PS	Performance Status
PSA	Prostate Specific Antigen
RCC	Red cell concentrate
SIRS	Systemic Inflammatory Response Syndrome
TB	Tuberculosis
TLS	Tumour Lysis Syndrome
TRUS	Transrectal Ultrasound
VIA	Visual Inspection with Acetic Acid
VTE	Venous thromboembolism

1 Introduction

1.1 Overview of Cancer Care in Eswatini

Currently, Eswatini does not have a comprehensive cancer treatment center. The guidelines aim to optimize care with available limited resources and make use of the existing referral system only for patients assessed to derive the maximal outcome benefits.

The current expertise of specialists, a majority of whom are stationed at Mbabane Government Hospital (MGH), have immense potential to provide optimal care to patients diagnosed with cancer. The treatment intentions, cost of care, the type of cancer, and patient's co-morbidities do direct the line of care. The system is currently undergoing transformative improvement to provide care in the globally recommended settings of a multi-disciplinary team (MDT) approach.

Many cancers in Eswatini are diagnosed and treated at MGH, with exception of Kaposi Sarcoma which is currently decentralized to regional hospital HIV clinics. The referral system is yet to be streamlined, which creates challenges in the early diagnosis and referral of patients to MGH.

The important services of pathology and radiology, which aid in confirming the diagnosis and staging of cancers, are insufficient. This has caused delays in the delivery of care to cancer patients, in some instances going beyond 3 months. It is our hope that cooperating partners and Government's Ministry of Health will work together to improve cancer services through the provision of timely comprehensive pathology and radiology services.

1.1.1 Importance of Engaging Eswatini National Cancer Registry (ENCR)

The ENCR is a population-based cancer registry established in 2015. It is an established member of the African Cancer Registry Network (AFCRN), using an International Agency for Research on Cancer (IARC)-customized CanReg5 software for data capture and analysis.

ENCR collects information on the incidence of cancer, the types of cancers diagnosed and their location (site) within the body, the extent of cancer at the time of diagnoses (disease stage), and the types of treatment that patients receive. All possible sources of cancer information for the registry

are actively identified and abstracted.

The main sources of information are hospitals, pathology laboratory reports, radiology reports, oncology reports, death certificates, and chemotherapy units. It is therefore imperative that clinicians and healthcare workers alike enter patient information as accurately as possible to ensure ENCR provides the Ministry of Health with data that is useful for health planning.

1.2 Development of the Standard Treatment Protocols

The development of the guidelines relied on the existing expertise of medical specialists from MGH. The discussions held agreed to tailor the treatment and care guidelines to the existing resources against what can be offered to the cancer patients, with an emphasis on the optimization of care.

The guidelines were derived from treatment protocols from other countries and cancer treatment centers such as the European Society for Medical Oncology and Groote Schuur Hospital in South Africa. The protocols were adapted for the context of Eswatini where required; for example, metronomic chemotherapy was included as a treatment option for a select group of advanced cancer patients.

2 How to Approach Care for a Cancer Patient

A cancer patient has complex needs that include medical (e.g. pain), surgical (e.g. bowel obstruction), psychological (e.g. support structure), nutritional, and spiritual factors. Patients may present to their primary healthcare provider (oncology team, local hospital, casualty or general practitioner) with symptoms due to their cancer, secondary complications, or side effects from their treatment. These guidelines provide practical ways on how to manage the most commonly occurring problems experienced by oncology patients.

2.1 Basics of Cancer Treatment

2.1.1 Types of Treatment

Oncology treatment can be local or systemic.

- Local treatment: surgery, radiotherapy.
- Systemic treatment: chemotherapy, endocrine treatment, immunotherapy and targeted therapies (e.g. monoclonal antibodies or small molecules which target specific receptors or cell signaling pathways).

2.1.2 Treatment Aims

1. Curative: treatment given as the definitive treatment of choice depending on the cancer type
2. Radical: usually refers to chemotherapy or radiotherapy or chemo-radiotherapy given with a curative intent
3. Neo-adjuvant: treatment given before a definitive treatment to enable or facilitate a procedure that will improve the chance of cure
4. Adjuvant: treatment given after definitive treatment, usually post an oncologic surgery, aimed at reducing the chance of recurrence, targeting micrometastatic disease or R_1 operations
5. Palliative: aimed at improving a patient's quality of life through alleviating or relieving symptoms caused by the presence of cancer, physically or physiologically

2.1.3 Immediate Needs of an Oncology Patient

A cancer patient has special needs and requirements in order to achieve

optimal care and outcomes. A cancer diagnosis affects not only the index patient, but the family and community at large. A diagnosis of cancer elicits psychological distress and is a very traumatic event. The nature of the disease requires patients to learn about the illness, make difficult decisions regarding the ensuing treatment, and cope with the consequences of the illness and its associated treatment side effects. Given the complex nature of the disease and the treatment modalities as well as the psychosocial impact associated with the disease, those diagnosed with cancer and their family members will encounter information and emotional support needs throughout the course of the disease and treatment. A cancer diagnosis is a catastrophic event and affects all aspects of life for patients. Cancer treatment has also become more complex and aggressive. It is, therefore, crucial to identify and address the information needs of cancer patients in order to inform their decision making and cope with their diagnosis. This will potentially improve their satisfaction with the services received and health outcomes.

- Clear and concise information on the diagnosis, or suspicion thereof
- Adequate and timely pain control
- Prompt reversal or correction of deranged physiology; FBC, renal functions
- Tissue diagnosis of solid tumour. Kindly arrange for an expedited biopsy and call pathologist for prioritization of results
- Contact treating oncology unit prior to referral for guidance on completion of pre-treatment investigation (differs by cancer type). This is to avoid the delay in the initiation of appropriate care and treatment (refer to the Eswatini Oncology Treatment Guidelines)
- Early referral to the following:
    - Psychologist, for the important psychosocial needs of the patient and family
    - Dietician
    - Palliative care team, irrespective of disease stage (refer to Chapter 12)
    - Social worker
- Treat the presenting oncology related emergencies promptly (see guidelines for common emergencies below)

2.1.4 Performance Status[1]

Performance status (PS) is used to try to quantify patients' suitability to withstand an intervention or treatment. Every cancer patient requires an extensive PS assessment prior to referral or intervention. Most patients

1 Ma et al., 2010

with an ECOG/WHO >2 will not withstand pharmacologic tumour interventions.

Score (%)	Karnofsky Performance Status	Score	WHO/ECOG Performance Status
100	Normal, no signs of disease	0	Asymptomatic, fully active and able to carry out all pre-disease activities without restriction
90	Capable of normal activity, a few symptoms or signs of disease	1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out light or sedentary work
80	Normal activity with some difficulty. Some symptoms or signs		
70	Self-caring, not capable of normal activity or work	2	Capable of all self-care but unable to carry out any work activities; < 50% in bed during the day
60	Needs some help with care; can take care of most personal requirements		
50	Help required often; frequent medical care needed	3	Capable of only limited self-care; > 50% in bed during the day
40	Disabled, requires special care and help		
30	Severely disabled, hospital admission needed but no risk of death	4	Completely disabled and cannot do any self-care; totally confined to bed or chair
20	Very ill; needs urgent admission and requires supportive care		
10	Moribund, rapidly progressive fatal disease		
0	Death	5	Death

3 Common Oncologic Emergencies

An oncologic emergency is defined as any acute potentially morbid or life-threatening event directly or indirectly related to a patient's tumour or its treatment. The differential diagnosis for a patient with cancer who presents with acute conditions includes medical emergencies not related to the patient's diagnosis of cancer. Occasionally, these emergent conditions may be the presenting symptom of a previously undiagnosed neoplasm.
Oncologic emergencies may be categorized by their system of origin as metabolic or hematologic. The signs and symptoms of oncologic emergencies are often common problems experienced by individuals with cancer such as nausea, pain, headache, and fever. For prevention and early detection of oncologic emergencies, physicians must maintain a high degree of suspicion and must adequately educate patients about preventative measures and reporting of symptoms.

3.1 Bleeding and Anaemia in Cancer

3.1.1 Overview

Bleeding can occur in up to 10% of patients with advanced cancer. This may increase to up to 30% in those with a haematological malignancy. The most common solid tumour that presents with bleeding is cervical cancer.

Anaemia is a reduction in haemoglobin (Hb), RCC, or packed cell volume.

- Hb <13.5g/Dl in male
- Hb <11.5g/Dl in female

Maybe attributed to underlying comorbidities including:

- Bleeding/Haemolysis
- Hereditary disease
- Renal insufficiency
- Nutritional deficiency
- Anaemia of chronic disease or combinations of the above

Maybe due to tumour/cancer:

- Bone marrow infiltration
- Cytokine production which leads to iron sequestration
- Chronic blood loss at tumour sites
- Nutritional deficiency (appetite suppression)

- Haemolysis (immune mediated antibodies)
- Changes in coagulation capability

Maybe due to cancer therapy:

- Myelosuppressive chemotherapy (platinum)
- Haemolytic anaemia (Fludarabine)
- Microangiopathy (Gemcitabine)
- Renal toxicity (platinum) leads to decreased erythropoietin production
- Pelvic/Skeletal irradiation

3.1.2 Causes Based on Classifications

Macrocytic	Normocytic Normochromic	Microcytic
>100FL	80-100FL	<80FL
High reticulocyte count Haemorrhage Haemolysis DIC Vasculitis Auto-immune	Haemorrhage haemolysis Chronic diseases Liver Malignancy Renal failure HIV Bone marrow infiltration Chronic inflammation	Fe deficiency (low transferrin) Thalassaemia Lead poisoning Sideroblastic
Megaloblastic Vit B12 (+ folic acid) deficiency		
Non-megaloblastic Liver disease Hypothyroidism Alcoholism/Medications		

3.1.3 Management

- **Stop causative factor**
- Blood transfusion with low Hb when indicated and patient is symptomatic or has a comorbidity which could necessitate transfusion (e.g. cardiac disease).
- Erythropoietin Therapy
    - Erythropoiesis-stimulating agent (EPO/ESA)
    - Reduces transfusion requirements
    - Important side effects

        - Increased VTE; can lead to increased mortality and tumour progression (FDA does not recommend use in radical patients), especially if used to Hb >12g/Dl. Only give if Hb <10
        - Fatigue
        - Seizures shown in patients with renal failure
    - Need at least 2 weeks of treatment before effect is seen
- Haematinics ($FeSO_4$, folate, Vit C)

3.2 Hypercalcaemia of Malignancy

3.2.1 Introduction

- Hypercalcaemia occurs in approximately 20-30% of cancer patients.
- The estimated yearly prevalence of hypercalcaemia for all cancers is 1.46% - 2.74%.
- Cancer-related hypercalcaemia has a poor prognosis, as it is most often associated with disseminated disease.
- 80% of patients will die within a year, and there is a median survival of 3 to 4 months.
- The most common cancers are lung cancer, multiple myeloma, and renal cell carcinoma.

3.2.2 Causes of Hypercalcaemia

Primary hyperparathyroidism and malignancy are the most common causes of hypercalcaemia, accounting for more than 90% of cases. Imperatively, hypercalcaemia of malignancy accounts for the majority of hospital admissions.

Parathyroid-related

- Primary hyperparathyroidism
    - Solitary parathyroid adenoma
    - Primary parathyroid hyperplasia
    - Parathyroid carcinoma
    - Multiple endocrine neoplasia (MEN)
    - Familial isolated hyperparathyroidism
- Lithium use

Malignancy-related

- Humoral hypercalcaemia of malignancy (PTHrP) (80% of cases)
- Osteolytic metastases (20% cases)

- Vitamin D mediated (1,25-dihydroxyvitamin D) (1% of cases)
- Ectopic PTH secretion (1% of cases)

Humoral (PTHrP)	Osteolytic Metastases	1,25-dihydroxyvitamin D	Ectopic PTH secretion
Squamous cell carcinoma	Breast Cancer	Lymphoma (NHL, HL)	Ovarian Cancer
Renal Cancer	Multiple Myeloma	Ovarian dysgerminomas	Lung Cancer
Bladder Cancer	Lymphoma		Thyroid papillary Cancer
Breast Cancer	Leukemia		Neuroectodermal tumour
Ovarian Cancer			Rhabdomyosarcoma
NHL			Pancreatic Cancer

Vitamin D-related

- Hyper vitaminosis D (vitamin D intoxication)
- Elevated 1,25(OH)2D levels e.g. sarcoidosis, tuberculosis
- Rebound hypercalcaemia after rhabdomyolysis

High Bone-Turnover Rates

- Hyperthyroidism
- Multiple myeloma
- Prolonged immobilization
- Paget's disease
- Thiazide use
- Vitamin A intoxication

Renal Failure

- Severe secondary hyperparathyroidism
- Tertiary hyperparathyroidism
- Aluminum intoxication
- Milk-alkali syndrome

3.2.3 Initial Assessment and Investigations

History and Examination

Symptoms are usually dictated by the level of serum calcium and the rate of change of serum calcium. “Stones, bones, abdominal moans and psychic groans” is a phrase used to memorize the major clinical manifestations of hypercalcaemia.

- Neurocognitive: anxiety, mood changes, decrease in cognitive function, malaise, lethargy, confusion, and coma
- GIT: constipation, anorexia, nausea, and vomiting
- Renal: nephrogenic diabetes insipidus with resultant polyuria, renal vasoconstriction, distal renal tubular acidosis, nephrolithiasis, and chronic renal failure
- Musculoskeletal: profound muscle weakness, bone pain
- Cardiovascular: shortening of the QT interval and dysrhythmias

Laboratory Evaluation

Confirm hypercalcemia:
• Serum total calcium (recheck if only one measurement) • Serum corrected calcium equation: Ca (mmol/L) + 0.02 (40 – albumin (g/L)
After hypercalcemia is established:
• Serum phosphorous • Creatinine with estimated GFR • PTHrP • 25(OH)D • 1,25(OH)2D
Additional laboratory evaluations to consider if diagnosis is still uncertain:
• SPEP, UPEP serum-free light chains, serum and urine IFE • Skeletal survey • Vitamin A levels

Assess Severity of Hypercalcaemia

- Mild hypercalcaemia 2.6-3 mmol/L.
- Moderate hypercalcaemia 3-3.5 mmol/L.
- Severe hypercalcaemia > 3.5 mmol/L.

3.2.4 Treatment According to Severity[2]

Mild hypercalcaemia < 3 mmol/L	• Does not require immediate treatment. • Avoid factors that can aggravate hyperCa2+ (thiazide diuretics, volume depletion, inactivity, high calcium diet). • Adequate hydration (6-8 glasses of water/ day).
Moderate Hypercalcaemia 3-3.5 mmol/L	• Patients are asymptomatic or mildly symptomatic (often chronic). • Same precautions as for mild hypercalcaemia. • An acute rise may result in symptoms which requires treatment as described for severe hypercalcaemia.
Severe hypercalcaemia > 3.5 mmol/L	• Aim is to promote calcium renal excretion and inhibit bone resorption. • Aggressive treatment is required. • Volume expansion with normal saline: 1-2L as initial bolus and then maintenance fluids at 200-300 ml/h for next 2-3 days or until volume replete. • Fluids to be adjusted to maintain urine output 100-150mls/h. • Caution in patients with CCF or anuric renal failure as there is a risk of fluid overload. Use smaller volumes of isotonic saline in these patients. • Loop diuretics are not recommended for routine use. • Furosemide should be reserved only for patients with heart failure and those who need diuresis. Its overall efficacy has been shown to be limited, and it often exacerbates dehydration and fluid loss. • Bisphosphonates (Zoledronic acid 4mg IV over 15mins) • Glucocorticoids: Hydrocortisone 200 -400mg/d for 3-4 days and then change to prednisone 10-20mg/day for 7 days or Prednisone 40-60 mg/day for 10 days. • +/- Calcitonin (4 IU/kg IM/SC).

2 Zagzag, Hu, Fisher, & Perrier, 2018

Zoledronic Acid

- The maximum recommended dose in hypercalcaemia of malignancy is 4 mg every 7 days. Monitor serum calcium and wait at least 7 days before considering retreatment; Zometa has a delayed onset of action, 4-7 days.
- The 4mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes.
- Patients who receive Zoledronic acid should have serum creatinine assessed prior to each treatment.
- Patients should be adequately rehydrated prior to administration of Zoledronic Acid.
- It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.

Reduced Doses for Patients with Baseline CrCl Less than or Equal to 60 mL/min

Baseline Creatinine Clearance (mL/min)	Zoledronic Acid Recommended Dose
>60	4 mg
50-60	3.5 mg
40-49	3.3 mg
30-39	3 mg

Side Effects of Bisphosphonates

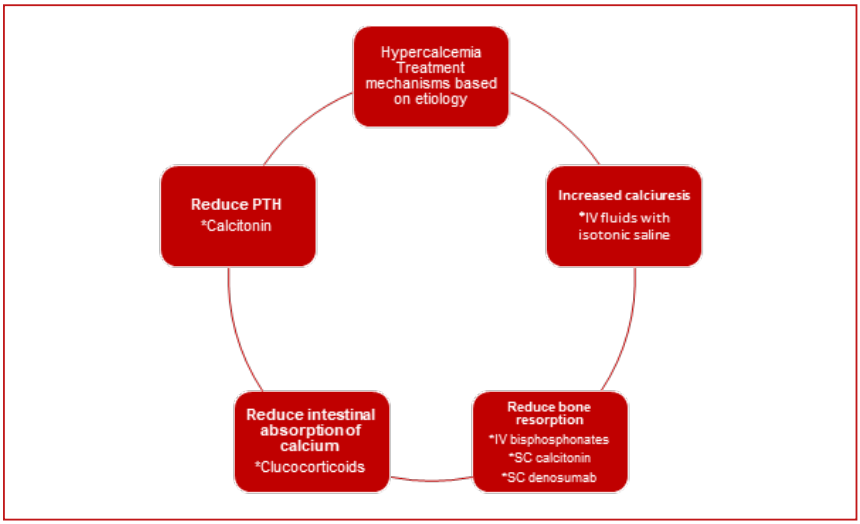
- Flu-like symptoms (fever, arthralgia, myalgia, fatigue, bone pain)
- Ocular inflammation (uveitis)
- Hypocalcaemia
- Hypophosphatemia
- Impaired renal function
- Osteonecrosis of jaw
- Nephrotic syndrome

Denosumab

Denosumab is a human monoclonal antibody to RANKL, which reduces osteoclast activity and bone resorption by preventing RANKL interaction with RANK receptors. Denosumab is an option for patients with hypercalcaemia refractory to Zoledronic acid or in whom bisphosphonates are contraindicated due to severe renal impairment. Denosumab is not cleared by the kidney and therefore there are no restrictions of its use in patients with CKD.

Recent studies have shown that denosumab is more efficacious than zoledronic acid in delaying or preventing hypercalcaemia of malignancy in patients with advanced cancer including breast cancer, other solid tumors, and multiple myeloma. Studies have also shown that denosumab is superior to Zoledronic acid in preventing skeletal related events (SRE), irrespective of age, history of SRE or baseline pain status. Denosumab is not readily available.

Management Summary



Summary of Treatment Options for Management of Hypercalcaemia

Agent	Regimen	Onset	Duration
0.9% Sodium chloride	2-4 L IV/day	Immediate	2-3 days
Calcitonin	4-8 units/kg SQ q 6-12 hours	4-6 hours	Up to 3 days
Bisphosphonates			
Pamidronate	60-90 mg IV over 2-6 hours	48 hours	3-4 weeks
Zoledronic Acid	3-4 mg IV over 15-30 minutes	48 hours	3-4 weeks

Corticosteroids	200-400 mg hydrocortisone IV/day for 3-5 days	7 days	Unclear, perhaps 1 week
Gallium nitrate	200 mg/m^2 daily for 5 days	4 days	2 weeks
Denosumab	120 mg SQ weekly for 4 weeks, then monthly thereafter	7-10 days	3-4 months

3.3 Tumour Lysis Syndrome

3.3.1 Introduction

- Tumour Lysis Syndrome (TLS) is a metabolic syndrome caused by massive tumour cell lysis leading to the release of intracellular contents.
- TLS is characterized by hyperuricemia, hyperphosphatemia, hyperkalemia and hypocalcaemia.
- Morbidity and mortality are high without prompt recognition and early therapeutic intervention.
- Prevention of TLS may be more effective than treatment.

3.3.2 Definition

Cairo-Bishop Classification

Element	Laboratory TLS	Clinical TLS
	Abnormality in two or more of the following, occurring 3 days before or 7 days after chemotherapy	Laboratory TLS plus one or more of the following:
Uric acid	≥ 8mg/dl (≥ 476 umol/L) or 25% increase from baseline	Increased serum creatinine (1.5 x upper limit of normal)
Potassium	≥ 6.0 mmol/L or 25% increase from baseline	Cardiac arrhythmia or sudden death

Phosphorous	≥ 2.1 mmol/L (children) or ≥1.45 mmol/L (adults) or 25% increase from baseline	Seizure
Calcium	≤ 1.75 mmol/L (7mg/dl) or 25% decrease from baseline	

3.3.3 Causes of TLS

- The incidence of TLS varies greatly depending on the underlying malignancy.
- TLS is most commonly described in NHL, particularly Burkitt-type lymphoma.
- In one study (433 adults, 322 children), the reported incidence of TLS in NHL was 6.1%.
- TLS has also been described in solid tumours (large tumour burden, metastatic disease, short doubling time, increased chemo sensitivity, and elevated LDH).
- Among solid tumours, small-cell carcinoma of the lung, germ cell tumours, neuroblastoma, and breast carcinoma have all been linked to development of TLS.
- Males and females of any age or ethnic group can be affected.
- Advanced age may increase the risk of developing TLS due to reduced GFR.

Mortality

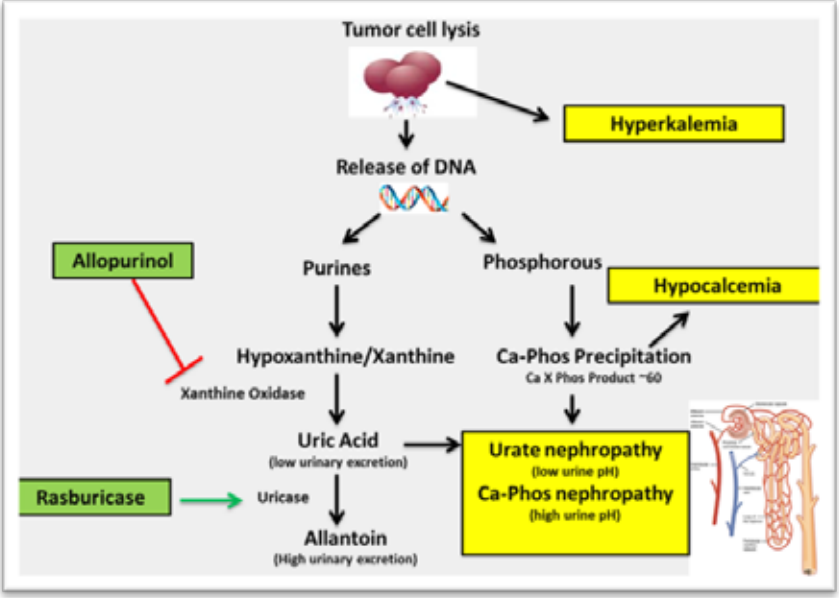
- No randomized trials of TLS therapy have examined mortality as a primary outcome, but the development of AKI associated with TLS is a strong predictor of death.
- Among 63 patients with heamatologic malignancies and TLS, the 6-month mortality was 21% among those without AKI and 66% among those with AKI.
- Given the association between AKI and mortality in this condition, prevention of AKI may be the single best target for therapy.

TLS Occurs in the Following Settings

- After the initiation of cytotoxic chemotherapy (24-72hrs)
- Spontaneously
- Monoclonal antibody therapy
- Ionizing radiation (TBI in transplant setting)
- Embolization
- Radio frequency ablation
- Glucocorticoids

- Haemopoietic stem cell transplant.

Pathogenesis



Risk Stratification

- Assess whether there is evidence of laboratory or clinical TLS at diagnosis
- Assess tumour related factors (type of malignancy and burden of disease)
- Assess patient related factors

Tumour-related Factors

Intrinsic Tumour Related Factors

- High tumour cell proliferation rate.
- Chemo-sensitivity of the malignancy.
- Large tumour burden:
    - Bulky disease > 10cm in diameter and/or
    - WCC > 50000/umol (pretreatment)
    - Pretreatment LDH > 2 x ULN
    - Organ infiltration (hepatomegaly, splenomegaly, kidney infiltration)
    - Bone marrow involvement

Type of Malignancy

High Risk (>5% risk)	Intermediate Risk (1-5% risk)	Low Risk (<1% risk)
Burkitt's Lymphoma	Highly chemotherapy-sensitive solid tumors (neuroblastoma, germ cell tumor, small-cell lung cancer) with bulky or advanced stage disease	Most solid tumors
DLDCL, transformed, and mantle cell lymphomas		Multiple myeloma
Lymphoblastic lymphoma		Indolent NHL
Intermediate risk disease with renal dysfunction and/or renal involvement		Hodgkin's Lymphoma
Intermediate risk disease with uric acid, potassium, and/or phosphate > ULN		

Patient-related Factors

- Increased age (reduction in GFR, reduced renal reserve, complicate volume replacement due to higher rates of cardiac dysfunction)
- Volume depletion (decreased oral intake, nausea, vomiting, diarrhea)
- Pre-existing nephropathy or exposure to nephrotoxins (NSAIDs, ACE-I, ARBs)
- Pre-existing hyperuricemia or hyperphosphatemia
- Concomitant use of drugs that increase uric acid levels (alcohol, ascorbic acid, aspirin, cisplatin, thiazide diuretics, ethambutol, pyrazinamide)

3.3.4 TLS Prophylaxis

- The key to the management of TLS is recognizing patients at risk and using prophylactic measures to prevent its occurrence.

- Prophylaxis is only useful during the first course of treatment and at future points where re-induction or salvage chemotherapy is used.
- There is no rationale for using prophylaxis in the setting of consolidation therapy, including bone marrow transplant, if patient is in or near to a remission.

Low Risk	Intermediate Risk	High Risk
Monitoring	Monitoring	Monitoring
Hydration	Hydration	Hydration
+/- Allopurinol	Allopurinol	Rasburicase *Not available
		Allopurinol

Hydration

- Aim: Improve renal perfusion and maintain high urine output
- 3L/24h in adults before the initiation of chemotherapy
- Normal saline or 5% dextrose saline (Avoid Ringer's lactate because it contains K+ and Ca2+)
- Urine output: 2mls/kg per hour for both children and adults
- Caution in patients with pre-existing kidney disease or cardiac dysfunction: careful monitoring of vital signs and urine output, loop diuretics (Furosemide) may be used to maintain urine output

Urinary Alkalization

- Urinary alkalization is not recommended in TLS prophylaxis
- Urinary alkalization increases uric acid solubility but decreases calcium phosphate solubility (it is more difficult to correct hyperphosphatemia than hyperuricemia)

Hypouricemic Agents

Allopurinol

- Hypoxanthine analog that competitively inhibits xanthine oxidase
- Decreases the formation of new uric acid
- Does not reduce the preexisting serum UA
- Administered orally
- May lead xanthinuria (deposition of xanthine crystals in renal tubules) and Acute Kidney Injury
- Allopurinol should be initiated 24 to 48 hours before start of induction chemotherapy and continued for 3 to 7 days

•Estimate of GFR by the Cockcroft and Gault equation

Man

$$\frac{1.23 \times (140 - \text{Age}) \times \text{BW}}{\text{Sr Cr (umol/l)}}$$

Woman

$$\frac{1.04 \times (140 - \text{Age}) \times \text{BW}}{\text{Sr Cr (umol/l)}}$$

* where BW is body weight in kilograms and Sr Cr is Serum creatinine

The eGFR is the calculated creatinine clearance that will be for allopurinol dose (see below).

Creatinine Clearance	Allopurinol Dose
≥ 20 mL/min	300 mg/d
10 – 20 mL/min	200 mg/d
3 – 10 mL/min	100 mg/d
< 3 mL/min	100 mg/36 – 48 h

Rasburicase

- Recommended for initial management of high risk paediatric and adult patients TLS
- Not readily available
- Degradation of UA by administration of urate oxidase
- Catalyzes oxidation of UA to the much more water-soluble compound allantoin
- FDA and EMA recommend dose 0.2mg/kg once daily for up to 5-7 days
- Trials demonstrating the efficacy in paediatrics and adults
- Contraindicated in patients with G6PD deficiency

Monitoring

- Urine output hourly
- Fluid balance assessment every 6 hours
- UA, K+, CMP, creatinine and LDH 6 hours after initiation of chemotherapy and every 6-12 hours thereafter
- For high risk patients test at 6 hours
- Intermediate risk test at 12 hours
- If no evidence of TLS after 36 hours, patients can be discharged.

3.3.5 Management of Established TLS

Principles

- Multidisciplinary approach (hematologists, nephrologists & ICU)
- Frequent monitoring (continuous cardiac monitoring and measurement of electrolytes and renal function every 4-6hours)
- Correct specific electrolyte abnormalities
- Indications for dialysis

Fluid Balance

- Maintain high urine output with vigorous hydration
- 3l every 24hrs in adults with urine output > 100ml/m2/hr
- Isotonic fluid with no K+ added
- Fluid balance assessment 6 hourly
- Document all fluid losses including vomiting and/or diarrhea)
- Chart body weight daily
- Reduction in urine output should prompt reassessment: physical obstruction to urine flow by tumour
- Alkalization of urine is not recommended

Indications for Dialysis

- Severe oliguria or anuria
- Intractable fluid overload
- Persistent hyperkalemia
- Symptomatic hypocalcaemia (cardiac arrhythmia, seizure or tetany) should be treated with calcium gluconate at lowest standard doses
- Calcium-phosphate product > 70mg/m^2/dL

3.4 Correction of Other Electrolyte Abnormalities in Cancer Patients

Complication	Manifestations	Management
Hyperkalemia	• ECG abnormalities • Muscle cramps, weakness, paresthesia's • Nausea, vomiting, and diarrhea	• Aggressive hydration • Kayexalate (15 – 30 mg in 50 – 100ml water, 6hrly orally) • Calcium gluconate (10mls of 10% solution IV over 2 – 5mins) • Hypertonic dextrose + insulin (Glucose 50 – 100ml of 50% solution with 10U Actrapid IV over 15 – 30mins) • Nebulized Salbutamol 10 – 20mg over 15mins • Loop diuretics: Furosemide 40 – 80mg IV (0,5 – 1mg/kg) over 1 – 2min • Frequent measurement of K+ levels (every 4 – 6 hours) and continuous cardiac monitoring
Hyperphosphatemia	• Acute renal failure • Secondary hypocalcemia	• Aggressive hydration • Hypertonic dextrose + insulin • Oral phosphate binders
Hypocalcemia	• Muscle twitches, cramps, tetany, paresthesia • Mental status changes, confusion, delirium, seizures	• Manage hyperphosphatemia • Asymptomatic hypocalcemia should not be treated • Symptomatic hypocalcemia should be treated with calcium gluconate at lowest standard doses

Hyperuricemia	• Acute renal failure	• Aggressive hydration • Allopurinol: has no effect on preexisting uric acid levels, UA usually don't fall until 48 to 72 hours of treatment • Urate oxidase (not available) • Hemodialysis
Lactic acidosis	• Acidemia	• Volume replacement • Correct acidosis

3.5 Pain in a Cancer Patient

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Another proposed definition of pain is "pain is what the experiencing person says it is, existing whenever (s)he says it does."

More than half of all cancer patients will experience pain, which may be associated with both the disease and its treatment. Generally, pain is moderate to severe and will significantly impact the patient's emotional wellbeing, disability, and quality of life. In long-term cancer survivors, pain can be persistent and chronic.

3.5.1 Types of Pain

ACUTE	• Definite onset, limited duration • Identifiable cause • Associated with anxiety and sympathetic drive • Treatment directed at the cause • Includes breakthrough on a background of controlled chronic pain

Chronic	• Prolonged fluctuating, ill-defined onset • Persists beyond stimulus • Driven by central sensitization • Associated with acute episodes of breakthrough pain • Treatment directed at underlying disease if possible, psychological and supportive care
Incident/ procedural	• Associated with specific movement/following a procedure • NB children – NB manage
Breakthrough	• Transient exacerbation • Background of controlled chronic pain

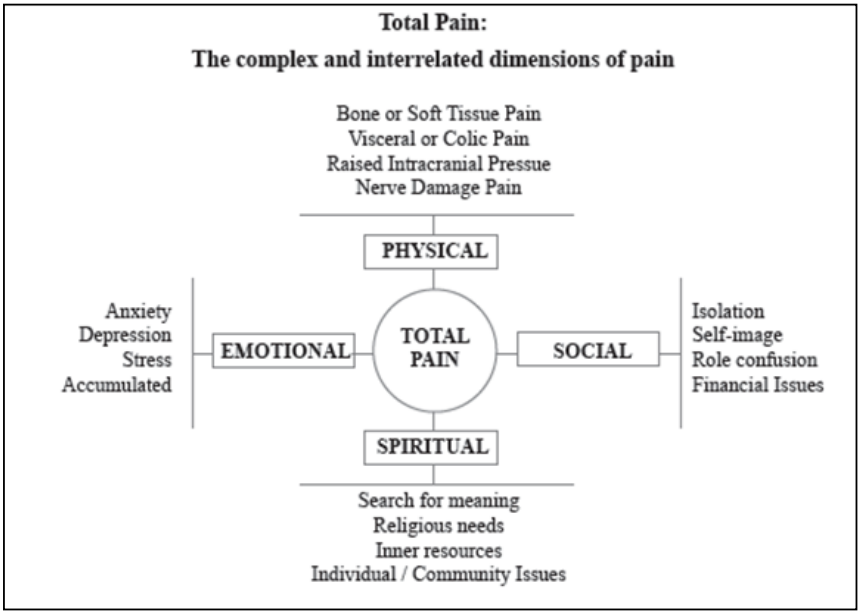


Figure 1. TOTAL PAIN: THE COMPLEX AND INTERRELATED DIMENSIONS OF PAIN
(Teno, Casey, Welch, & Edgman-Levitan, 2001).

Pain can generally be **classified** as nociceptive, neuropathic, or mixed.

Nociceptive Pain

Nociceptive pain is caused by the activation of nociceptive nerve fibres due to physical tissue destruction or chemical, pressure, or thermal

processes. Nociceptive somatic pain can result from injury to skin, muscle, soft tissue, or bone and can have a strong incident- or movement-related component. It is usually well localized, can be constant or intermittent, and is often described as gnawing or aching pain that may become sharp with movement. Nociceptive visceral pain is typically less well localized, is usually constant, and may be referred (e.g., diaphragmatic pain may manifest as shoulder pain). It is often described by a variety of terms such as aching, squeezing, and cramping. Pain arising from liver metastases is an example of nociceptive visceral pain.

Neuropathic Pain

Neuropathic pain is caused by injury to nerve tissue, including the central or peripheral nervous system and even the autonomic system. Neuropathic pain is frequently described as burning and often radiates along nerves or nerve roots. It can also be associated with dysesthesia (numbness and tingling), hyperalgesia (exaggerated response to a painful stimulus), lancinating pain, and allodynia (pain experienced from a stimulus that does not normally produce pain).

Mixed Pain

Mixed nociceptive and neuropathic pain is common in illnesses like cancer. As knowledge about pain has advanced, health care professionals have become increasingly aware of the need to develop a more mechanism-based approach to pain control. Pain is often a combination of physical and inflammatory processes. Cancer pain is an example of pain that may result from tissue damage and the destruction and stimulation of nerves by inflammatory mediators that are produced by the tumour, and by the body in response to tumours. The clinical usefulness of pain classification relates to the use of certain adjuvant medications for specific pains, particularly for neuropathic pain.

Type of Pain and Analgesics (refer to WHO pain ladder)

Type	Typical Analgesics	Adjuvant Analgesics
Nociceptive pain: mild	Non-opioids +/– weak opioids	NSAIDs (brief trial)
Nociceptive pain: moderate to severe	Strong opioids	NSAIDs Radiotherapy Surgery

Neuropathic pain: mild	May not be indicated	Tricyclic antidepressants Typical and atypical anticonvulsants
Neuropathic pain: moderate to severe	Strong opioids Pregabalin Gabapentin SNRIs (for DPN) TCAs Topical lidocaine	Tricyclic antidepressants Typical and atypical anticonvulsants Radiation Surgery

3.5.2 Assessment of Pain

1. The most reliable indicator of pain is the patient's self-report.
2. For effective pain control, the physical, functional, psychosocial, and spiritual dimensions should be assessed.
3. Validated assessment tools need to be used and need to be age and population appropriate (refer to palliative care guidelines).

Assessors of Pain

1. Patient self-report
2. Proxy report from the family or caregiver
3. Health care professional for in-depth assessment of patient's pain
4. A specialized pain team for complex pain assessment

Timing and Frequency of Assessment

1. All patients with cancer-related pain need to be screened at each encounter with a health care professional and at least once per shift for inpatients in acute care settings. Patients with cancer-related pain in long-term care settings should be screened for pain in the same way. Pain should be monitored before, during, and after procedures which might induce discomfort or pain.
2. When a change occurs in the patient's pain or when a new pain occurs, the comprehensive pain assessment and diagnostic evaluation should be repeated.
3. Sudden onset of severe pain in patients with cancer should be recognized by all health professionals as a medical emergency, and patients should be seen and assessed immediately.

Components of Pain Assessment

1. The preferred pain screening tool is the Edmonton Symptom

Assessment System (ESAS), but assessment tools should be age and population appropriate.

2. A comprehensive pain assessment should assess the intensity, distress, and meaning of pain and should include:

Pain Information

- Location of the pain (diffuse or localized, point to location[s])
- Characteristics of the pain (descriptive words, e.g., burning, throbbing, sharp, aching)
- Temporal component of the pain (e.g., onset, duration, variation, pattern)
- Pain intensity – use a patient appropriate measurement tool
- Exacerbating and alleviating factors (what makes it better or worse)
- History of the pain, including response to medications (and adverse effects)

Patient Information

- Current pain medications, past pain medications (effectiveness)
- Current and past treatments for pain (physiotherapy, occupational therapy, chiropractic therapy, acupuncture, heat, cold)
- Associated symptoms (nausea, vomiting, constipation, sweating, tiredness)
- Cognitive impairment and memory deficits
- Presence of psychosocial distress, and other factors that affect the pain experience
- Cultural, family, and religious beliefs and practices that affect pain
- Social history (psychosocial impact of the pain on family, work, social life)
- Family history (mental illnesses, alcoholism)
- Results of physical exam, lab investigations, and diagnostic imaging
- Level of function; how does the pain impact upon the patient (Activities of Daily Living Scale, performance status, mood, sleep patterns, mental concentration)
- Fears or concerns about pain and medications, financial concerns, patient and family educational needs

Pearls

- Pain is a complex bio-psychosocial event that requires a comprehensive, interdisciplinary assessment for management to have the most chance of success
- Pain, particularly cancer pain, is often multifactorial in causation
- Attention to basic principles of pain management leads to consistent

results in pain management
- Opioids are the mainstay of treatment of pain
- Every patient should be offered appropriate multiple modes of adjuvant therapy
- Adverse effects of opioids, particularly constipation, which is the most common adverse effect, can mostly be prevented

Pitfalls

- Although the World Health Organization ladder can be very helpful, remember to begin with the analgesic whose potency best matches the severity of the pain
- Failure to deal with the fears of patients and families about opioids may impede good pain control
- Failure to prevent or minimize adverse effects of opioids will also inhibit the achievement of good pain control
- Failure to monitor pain and the patient's response to treatment adequately may lead to delays in achieving good pain control

3.6 Nausea and Vomiting[3]

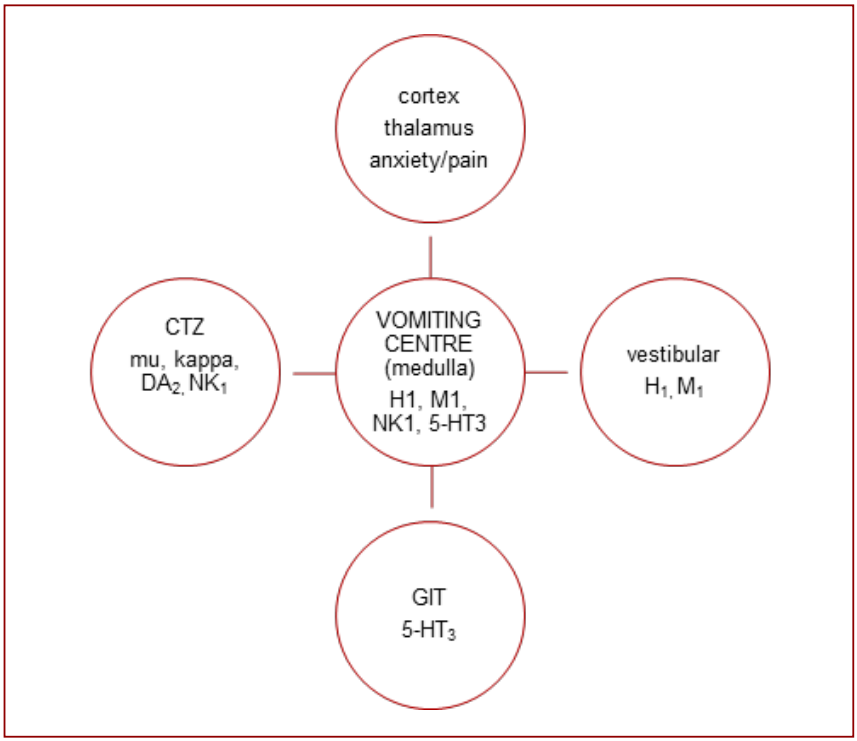
Vomiting results from a multistep pathway controlled by the brain. Vomiting is triggered by afferent impulses to the vomiting centre (located in the medulla) from:

1. Chemoreceptor trigger zone
2. Pharynx
3. GI tract

Via vagal afferent fibers and cerebral cortex. Efferent impulses are sent from the vomiting center to the:

- Salivation center
- Abdominal muscles
- Respiratory center
- Cranial nerves

3 Basch et al., 2012; Gilmore, D'Amato, Griffith, & Schwartzberg, 2018; Thompson & O'Bryant, 2013



GIT

5-HT[3] released by enterochromaffin cells of GIT

Efferent impulses travel along CN IX (glossopharyngeal) + X (vagal)

constipation
fecal impaction
gastritis
RT

VESTIBULAR SYSTEM

body movement

CTZ

chemotherapy
analgesics
CNS pathology
metabolic abnormalities:
fluid, e- abnormalities, uraemia, infection/sepsis
inflammation, ischaemia, toxins

HIGHER CENTRES IN CORTEX + THALAMUS

anxiety + pain
smell + taste

Principal Neuroreceptors:

- Serotonin (5HT3) receptors
- Dopamine receptors

Receptor Name	Drug	Area	Side-effects
5HT3	Ondansetron	Postrema and peripheral and vagal nerve terminals	Not for delayed nausea; headache, constipation, fatigue, dry mouth
Dopamine	Metoclopramide (Maxalon) Prochlorperazine (Stemetil) Haloperidol (D2)	Postrema (medulla)	Extra-pyramidal side-effects e.g. akathisia & dystonia
Acetylcholine	Cyclizine (Valoid)	Peripheral- and increased gastric emptying	
Corticosteroid	Dexamethasone	Crosses blood brain barrier	Gastric ulceration, insomnia, euphoria, hyperglycemia, proximal muscle weakness, AVN femoral head, adrenal suppression
Histamine	Cyclizine (Valoid)	Gastrointestinal tract and vestibular area	
Cannabinoid	Tetrahydrocannabinol (THC) Dronabinol Nabilone	Medulla	
Neurokinin-1	Aprepitant	Medulla (binds substance p)	
Anticholinergic	Valoid		

Additional neuroreceptors:

- Acetylcholine receptors
- Corticosteroid receptors
- Histamine receptors
- Cannabinoid receptors
- Opioid receptors
- Neurokinin-1 receptors

3.6.1 Different Types of Nausea and Vomiting

Chemotherapy induced (CINV)

- Acute (minutes to hours; resolves in 24 hours)
- Delayed (>24hours after chemo; can last 6-7days)
- Anticipatory (before chemo; anxiety)
- Breakthrough (despite treatment; requires rescue treatment)
- Refractory (failure of all treatment)

Presentation

Acute: Young, female, non-drinker, motion sickness
Delayed: Cisplatin, carboplatin, cyclophosphamide, Adriamycin

Emetic Risk	Drug categories
High (>90% of patients will experience N&V with these drugs)	Doxorubicin, Epirubicin, Cyclophosphamide, Cisplat, Dacarbazine, Ifosphamide (high dose), Carmustine, Crizotinib, Olaparib
Moderate (30-90%)	Carboplatin, Actinomycin D, Cytarabine, Oxaliplatin, Irinotecan, Methotrexate, Temozolamide, Interferon-A
Low (10-30%)	5FU, Etoposide, Docetaxel, Paclitaxel, Gemcitabine, Mitomycin C, Pemetrexate, Topotecan, Nibs
Minimal (<10%)	Bleomycin, Vinca Alkaloids, Temsirolimus, Mabs,

Radiation Induced Nausea and Vomiting

Radiation induced nausea and motivation is higher in with whole body- and upper abdominal radiotherapy (due to rapidly dividing GI tract cells). Larger fractional dose, larger amount of tissue involved, and larger total

dose will increase nausea and vomiting.

Treatment Regimens

HIGH EMETIC RISK:	• Aprepitant (125mg po stat) • Granisetron (1-3mg IV stat) (Or Ondansetron 8mg IV) • Dexamethasone (12-20mg stat IV)
MODERATE EMETIC RISK:	• Granisetron (1-3mg IV) • (Or Ondansetron 8mg IV) • Dexamethasone (12-20mg IV)
LOW EMETIC RISK:	• Dexamethasone 8mg IV or • Metoclopramide 10mg IV or • Prochlorperazine 10mg IV or • Ondansetron 8mg
PRESCRIPTION TO TAKE HOME:	
HIGH RISK (D2-4):	• Aprepitant 80mg daily
MODERATE (D2-3):	• Dexamethasone 8mg daily • Ondansetron 8mg 12 hrly or • Dexamethasone 8mg daily

3.7 Neutropenia and Neutropenic Sepsis

Definition of Severe Neutropenia

- ANC<1.0 x 10^9/L and expected to fall over the next 48hours
- ANC <0.5 x 10^9/L

Febrile Neutropenia

- One temperature >38.5° or two readings of >38° 1 hour apart

Cause

- Reduction in bone marrow stem cells secondary to chemo or tumour infiltration
- Increased destruction in circulation (immune mediated)
- Shift from marginal pool to tissue

Systemic Inflammatory Response Syndrome (SIRS) Symptoms

- Fever or hypothermia
- Shaking and chills
- Tachycardia
- Tachypnoea

- Hypotension

Patients at Risk for Neutropenia/Sepsis

- Patients receiving myelosuppressive chemotherapy
- Patients receiving pelvic radiotherapy
- Patients with bone marrow infiltration by malignancy
- Patients receiving dose dense chemotherapy
- Patients who developed neutropenia with previous chemo cycles
- Patients with poor nutritional status (low Albumin) and poor PS
- Patients with comorbidities (HIV, Diabetes Mellitus)
- Patients at extremes of age
- Female patients

Investigations

- Clinical examination

- FBC & diff, U&E, LFT, Clotting profile (D-dimers), Blood culture (and lines)
- Urine MC& S, Stool MC&S, Throat/skin lesion swabs

- CXR
- O_2 saturation and blood gases
- Discuss with Microbiologist and Infectious diseases.

3.8 Management of Neutropenia[4]

Asymptomatic Neutropenia

- Adequate counselling regarding fever and risks
- Prophylactic antibiotic
- Ciprofloxacin 750mg BD + Augmentin 1g BD
- Penicillin allergy: Cipro 750mg + Clarithromycin 500mg BD
- Ofloxacin

Neutropenic Sepsis

- Admit and isolate the patient
- Barrier nursing
- IV antibiotics
    - **Piptaz 4.5g 8 hourly + Amikacin 7.5mg/kg bolus then 1g daily**
- Monitor peak and trough levels
- Modify antibiotics as appropriate according to any culture results

4 Maheshwari, 2016; Rivas, Ruiz, Villasis-Keever, Miranda, Novales, Castelán, Martínez, & Rivas-Contreras, 2019

- Discuss with microbiologist
- **Herpes infection**
    - Acyclovir 10g/kg 8 hourly IV or 250mg 8 hourly 1/52
- Fluid resuscitation (monitor input/output)
- **Anti-fungal**
    - Amphotericin B
    - Initial test dose with solumedrol (methylprednisolone) and Phenergan cover 1 hour before
    - 1mg in 200ml 5% DW over 4 hours – if no reaction
    - 0.25mg/kg IV in 5% DW over 6 hours via CVP/Hickman line
    - Escalate to 0.5mg/kg on D2
    - Further increase to 1mg/kg possibly if aspergillus suspected or isolated
    - Highly nephrotoxic – U+E, Creatinine daily (hypokalaemia*)
    - Allergic reactions (Pethidine may be required)
    - Liposomal Amphotericin
    - If neutrophil count >0.5 or no CVP: Itraconazole 200mg BD
    - Fluconazole only effective against candida and not aspergillus; Itraconazole is effective against both
- Remove central lines
- Infectious diseases/microbiology consult
- Repeat all cultures at day 5
- Full work up as described above
- Daily FBC & diff to monitor neutrophil count
- G-CSF (Filgrastim 30MIU/d s/c OR Lenograstim 5-10mcg/d s/c) until neutrophils >0.5 on 2 consecutive days

Once a patient has recovered, Pegfilgastrim (Neulasta, Long acting) can be administered prophylactically. It is important to note that once a patient develops neutropenia despite Pegfilgastrim administration, Filgrastim **SHOULD NOT** be administered.

3.9 G-CSF Prophylaxis

- Reduce duration and severity of neutropenia
- Increase production, increase mobilization & increase function of neutrophils (survival, adhesion, phagocytosis)

1° PROPHYLAXIS:	• Consider if neutropenic risk ≥20% and/ or where dose delay should compromise outcome
	• Prophylactic use from cycle 1
	• Examples of regimens:
	  ○ Breast: Anthracycline/Taxane
	  ○ NHL: CHOP, IGEV, DHAP
	  ○ Head & Neck, Gastric: Taxane, Platinum and 5-FU (TPF)
	  ○ Germ cell tumours: Ifosfamide, platinum and Etoposide (ICE)
	  ○ GTN: EMA-CO
	• Recombinant human G-CSF- Filgrastim: acts on haematopoietic cells to stimulate production, maturation & activation of neutrophils
	  ○ Increases migration and cytotoxicity of neutrophils
	  ○ Dose: 300mcg SC (5 mcg/kg/day SC) daily start at 24 hours after last dose of chemotherapy: 5-11 days
	  ○ Do not administer within 24 hours period prior to chemotherapy
	• Pegfilgastrim (Neulastim):
	  ○ 6mg s/c 24 hours post chemo
	• Recombinant PEG-conjugated human G-CSF: Filgrastim with polyethylene glycol

2° PROPHYLAXIS:	In patient with previous febrile neutropenia or any dose/cycle delays

3.10 Spinal Cord Compression

The spinal cord is compressed most commonly by a metastatic tumour involving the vertebrae, or less commonly by a benign cause such as a vertebral fracture, abscess, or ruptured intervertebral disc. The spinal cord ends at approximately L1 and compression below this level causes the cauda equina syndrome.

Common Causes

Age Group	Cause
Adults	Metastatic cancer: • Breast • Lung • Prostate Others: • Lymphoma • Melanoma • Renal cancer • Sarcoma • Myeloma
Children	Metastatic or primary: • Neuroblastoma • Ewing's sarcoma • Osteogenic sarcoma • Rhabdomyosarcoma • Lymphoma

In patients without histological diagnosis or an obvious primary, every effort should be made to obtain this. TB frequently mimics metastatic disease in the spine.

The most important determinant of outcome is the severity of neurological damage at the time treatment is initiated. Of patients without significant neurological deficit, 80% remain ambulant or regain the ability to walk, whereas only 50% of those with even a mild transverse myelopathy and 5% of those with paraplegia do so. The prognosis is dependent on the type and extent of the primary malignancy. Untreated patients with SCC often die within a month. With treatment, median overall survival ranges from 3 to 16 months.

3.10.1 Clinical and Radiological Anatomy

A full neurological examination should include search for motor impairment, sensory levels, and local pain and tenderness. These symptoms and signs should be correlated with MRI appearances in consultation with a radiologist.

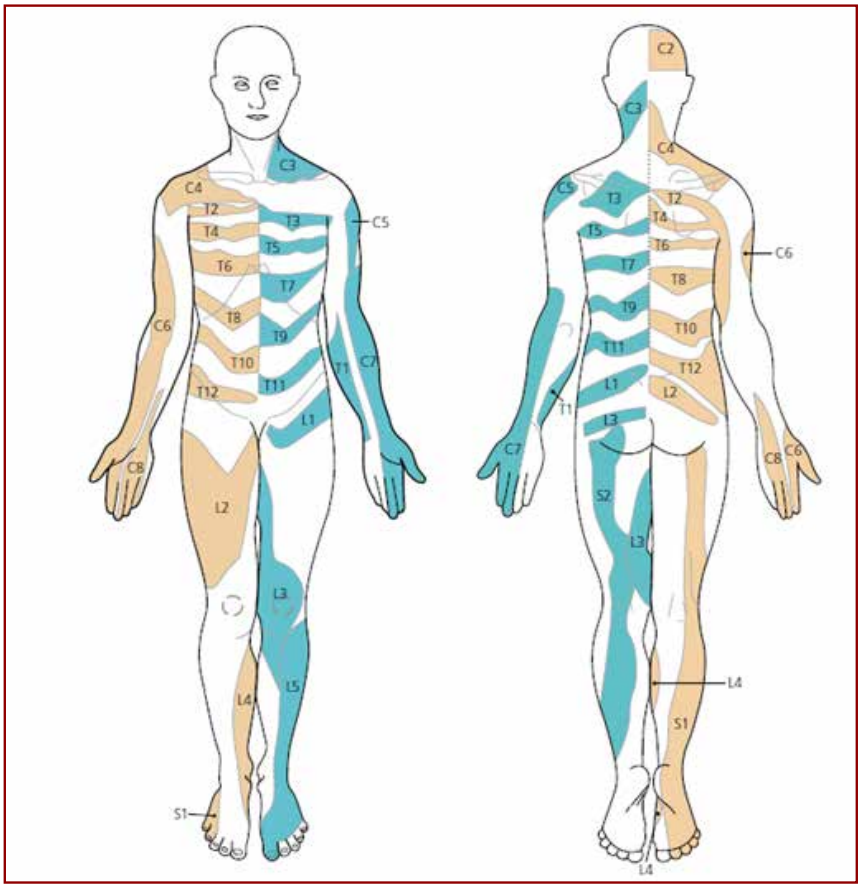


Figure 2. Likely distribution of dermatomes. Source: Lee MWL. et al Clinical Anatomy. 2008. 21(5): 363–73.

Dermatomal distributions

There is individual variation in the distribution of dermatomes. The figure above illustrates the likely distribution of dermatomes, but there is overlap between dermatomes areas of increased individual variability. Blank areas illustrate areas of greatest variability and overlap. The sensory level detected in a skin dermatome arises from compression of the corresponding cord segment, which lies at a higher level than the vertebral body of the same number, e.g. a sensory level at T10 on the skin arises from compression of its cord segment at the level of the T8 vertebra.

Immediate therapy involves the use of corticosteroids. Dexamethasone is

the most commonly used steroid. At presentation:

- All patients suspected to have SCC should be given high dose steroids (e.g. dexamethasone 16 mg daily).
- Steroids are then slowly tapered throughout definitive therapy.
- Always assess and treat pain in these patients.

Surgery

In all suspected SCC seek urgent consultation with a Neurosurgeon and/or orthopaediac surgeon. A neurosurgeon should urgently assess all patients who are fit for surgery, reviewing clinical features and MRI to assess whether there is a place for multimodality treatment.[5] Surgery for SCC involves an anterior decompression and stabilization of the spine. The indications for surgery are:

- Unknown primary tumour
- Unstable spine or vertebral displacement
- Relapse following spinal radiotherapy
- Neurological symptoms which progress during radiotherapy
- Relatively radio-resistant tumour
- Paralysis of rapid onset

There is evidence that some patients have a better functional outcome if treated with emergency spinal decompressive surgery followed by postoperative radiotherapy.[6]

Chemotherapy

Some patients have very chemo-sensitive tumours, such as lymphoma or small cell carcinoma of the lung, and chemotherapy can be started urgently before radiotherapy. The chemotherapy is directed by the histology of the cancer.

Radiotherapy

Radiation therapy alone is the definitive treatment for most patients. If surgery or chemotherapy are not appropriate, EBRT is given immediately to prevent further neurological damage, to improve function, and for pain relief. The recommended radiation field is one normal vertebral body above and below the margins of the epidural tumor, accounting for soft tissue involvement. There is no established optimal dose and fraction schedule. Urgent radiotherapy is indicated (even at the weekends) for patients not suitable for surgery (outcome is thought to be similar).[7]

5 Patchell et al., 2005
6 Loblaw, Perry, Chambers, & Laperriere, 2005
7 Hoskin, Grover, & Bhana, 2003prostate (28%

- Recommended **Dose; 4.0 Gy X 5 fractions, total dose 20 Gy at cord depth** is the most commonly used dose schedule.
- Consider 30 Gy in 10 fractions in young pts and/or in patients with a better prognosis, e.g. breast cancer, prostate cancer with good PS, multiple myeloma.
- Consider 8Gy single fraction in very poor PS pts (retrospective studies have shown effectiveness of this regime, and in several studies, this has been shown to be equivalent to 20Gy/5#).
- Patients should be put on strict bed rest during treatment. They should be on Decadron/ Betamethasone 6 mg twice daily initially, tailing down slowly.
- A corset should be considered depending on site and instability of the Spinal cord compression.
- After treatment, the patient should be referred to physio- and occupational therapy for appropriate rehabilitation.

4 Cervical Cancer

4.1 Prevention

Human papillomavirus (HPV) infection is the leading cause of most cervical cancers. Therefore, HPV vaccination is highly recommended for primary prevention of cervical cancer.[8] Eswatini is currently planning to introduce HPV vaccination for young girls. Caregivers should be encouraged to access HPV vaccination for their young girls and boys age 9-14 years through private sector pharmacies if feasible.

4.2 Screening Education and Services

4.2.1 Health Education and Awareness Building

The first step in cervical cancer screening is to build awareness among patients and health care workers about the screening availability, need for screening, and frequency of screening. Patients must also be educated on the need for completing referrals when required to ensure access to required services in a timely manner.

4.2.2 Cervical Cancer Screening Recommendations

Screening Types

The available screening tests include the following:

- Cytology: conventional (Pap smear)
- Visual inspection with acetic acid (VIA)
- Colposcopy by Gynaecologist

All screening methods are available in Eswatini, but VIA is the widely used screening option for pre-cancerous lesions. If the screening result is negative, a follow-up screening schedule will be provided by the health care worker and will depend on the patient's HIV status.

Screening Age & Frequency

Screening is tailored to HIV status, to avoid leaving out any woman who would benefit.

- HIV positive: Screening starts as soon as one is sexually active
- HIV negative and sexually exposed woman

8 WHO, 2017

The recommended frequency of cervical cancer screening is based on the HIV status and HPV infection status of patients (if known):

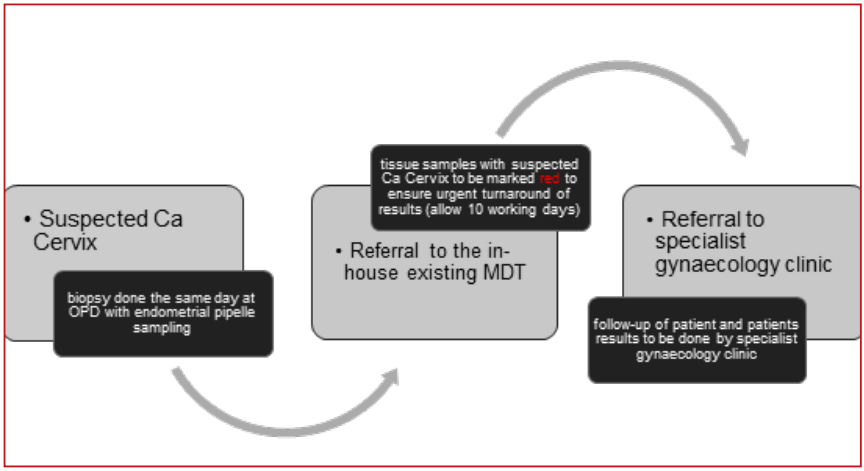
- **HIV-positive:** annual
- **HIV-negative:** every 2 years
- **HIV-negative and known HPV-negative:** every 3 years

- NB: When there are signs of infection on the cervix (cervicitis), treat and repeat VIA after two weeks.

    - **IF THE PATIENT HAS BEEN PREVIOUSLY TREATED FOR CERVICAL CANCER/ PRE-CANCER AND CURED, SHOULD BE SCREENED ANNUALLY BY TRAINED PERSONNEL/ DOCTOR**

Early Referrals

All suspected or confirmed cervical cancer patients should be treated with the utmost urgency.



4.3 Diagnosis

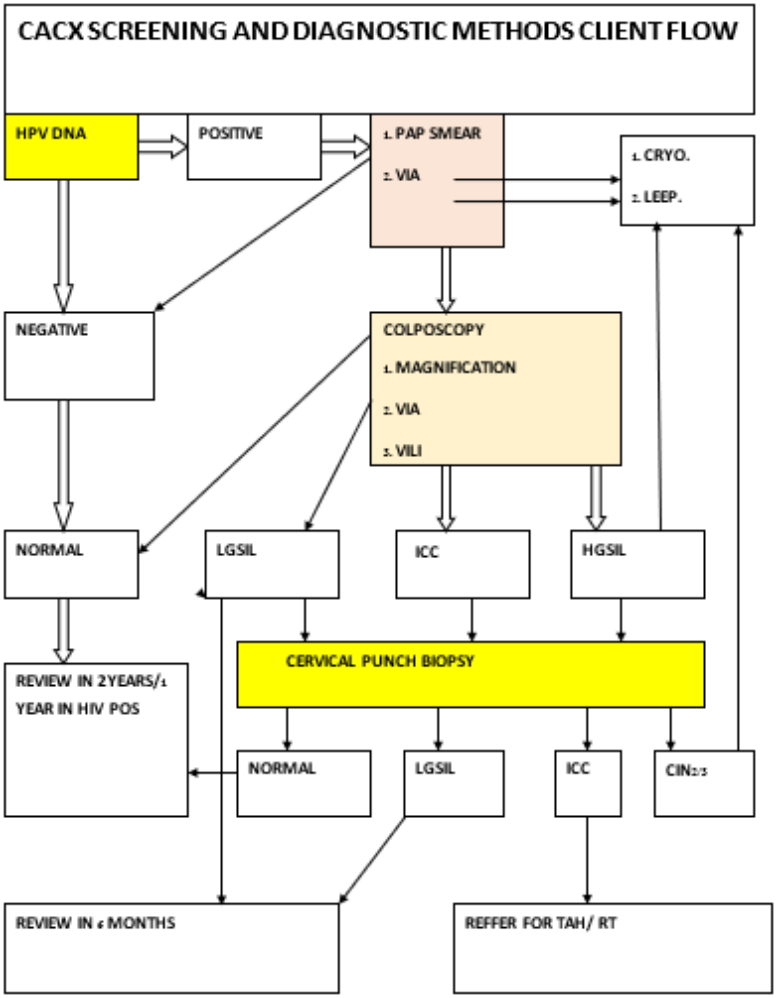
4.3.1 Diagnosis of Cervical Pre-cancer

The definitive diagnosis of cervical cancer is confirmed by histopathological examination of tissue specimens taken from the lesion.

- HPV test: a screening test for cervical cancer, that detects the presence of HPV, the virus that causes cervical cancer, in your system. Certain types of HPV — including types 16 and 18 —

increase your cervical cancer risk.

- **VIA positive:** acetowhite areas apparent after application of acetic acid. This is cervical pre-cancer and must be treated immediately. If an obvious abnormal/fungating lesion is noted, do not apply acetic acid but conduct a biopsy to confirm if cancerous. This diagnosis is a priority screening method for premenopausal women.
- **Pap smear:** if cytology of smear shows abnormal cells, conduct a biopsy of abnormal area with colposcopy.
- If a patient has a negative Pap smear but is VIA positive, they should be referred to a gynecologist.



The following table summarizes the recommended diagnostics for cervical cancer:

Diagnostic Category	Investigation
Pathology	• Biopsy performed with the aid of colposcopy (colposcopy directed biopsy) is the standard method for diagnosis of cervical pre-cancer lesions and pre-clinical invasive cancer • A full pathology report including cell type and differentiation

Laboratory Tests	• A full biochemistry report, including:
	  ○ KFT
	  ○ LFT
	• FBC and differential count

Radiology	• Baseline CT chest/abdomen/pelvis with contrast recommended if available and no renal impairment • MRI is recommended and to be requested by the gynaecologist • Note: an MRI is recommended over a CT scan due to better soft tissue visualization, prior to surgery for early stage cervical cancer (Early stages – IA and IB (maximum IIA)) • Nephrostomy to be performed by a urologist if available and proper infection controls are in place • PET/CT scan recommended for advanced disease and recurrence, when available
Breast Cancer Screening	• To be offered to all patients

4.3.2 Clinical Staging

Clinical staging need to be completed by the gynecology department as part of the diagnosis of cervical cancer. The classification by the International Federation of Gynaecology and Obstetrics (FIGO), which is based on tumour size and the extent of disease in the pelvis and distant organs, is recommended for staging invasive cervical cancer.

FIGO Cervical Carcinoma Staging 2018[9]	

Stage I:	The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
	• IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
	  ○ IA1 Measured stromal invasion <3 mm in depth
	  ○ IA2 Measured stromal invasion ≥3 mm and <5 mm in depth
	• IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri
	  ○ IB1 Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
	  ○ IB2 Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
	  ○ IB3 Invasive carcinoma ≥4 cm in greatest dimension

Stage II:	The carcinoma invades beyond the uterus, but has not extended into the lower third of the vagina or to the pelvic wall
	• IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement
	  ○ IIA1 Invasive carcinoma <4 cm in greatest dimension
	  ○ IIA2 Invasive carcinoma ≥4 cm in greatest dimension
	• IIB With parametrial involvement, but not up to the pelvic wall

9 Bhatla et al., 2019

Stage III:	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes
	• IIIA Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
	• IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
	• IIIC Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
	  ○ IIIC1 Pelvic lymph node metastasis only
	  ○ IIIC2 Paraaortic 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. A bullous edema, as such, does not permit a case to be allotted to stage IV • IVA Spread of the growth to adjacent organs • IVB Spread to distant organs
NOTE:	**Palliative care should be offered to all patients and their caregivers and/or family members from the point of diagnosis. See the Palliative Care section below for more information.**

Necessary Histopathologic Parameters for Assessment of Cervical Cancer:

Histopathologic evaluation
- Dimensions of the tumour
- Stromal invasion/depth of the wall involved
- Tumour differentiation
- Lymphovascular space invasion (LVSI)
- Status of resection margins
- Status of parametria and vaginal cuff
- Number and status of lymph nodes

4.4 Treatment

4.4.1 Treatment of Pre-cancerous Lesions[10]

Access to treatment options for pre-cancerous lesions has been increasing in Eswatini and include cryotherapy and loop electrosurgical excision procedures (LEEP).

Cryotherapy is an ablative method that uses freezing to destroy abnormal tissues. Trained healthcare providers who have access to the necessary equipment and compressed gas can perform cryotherapy at all levels of the health system. The procedure takes about 15 minutes to complete. Procedure performed when lesion is less than 75% of surface area of cervix and when the Squamo - columnar junction (SCJ) is fully visible.

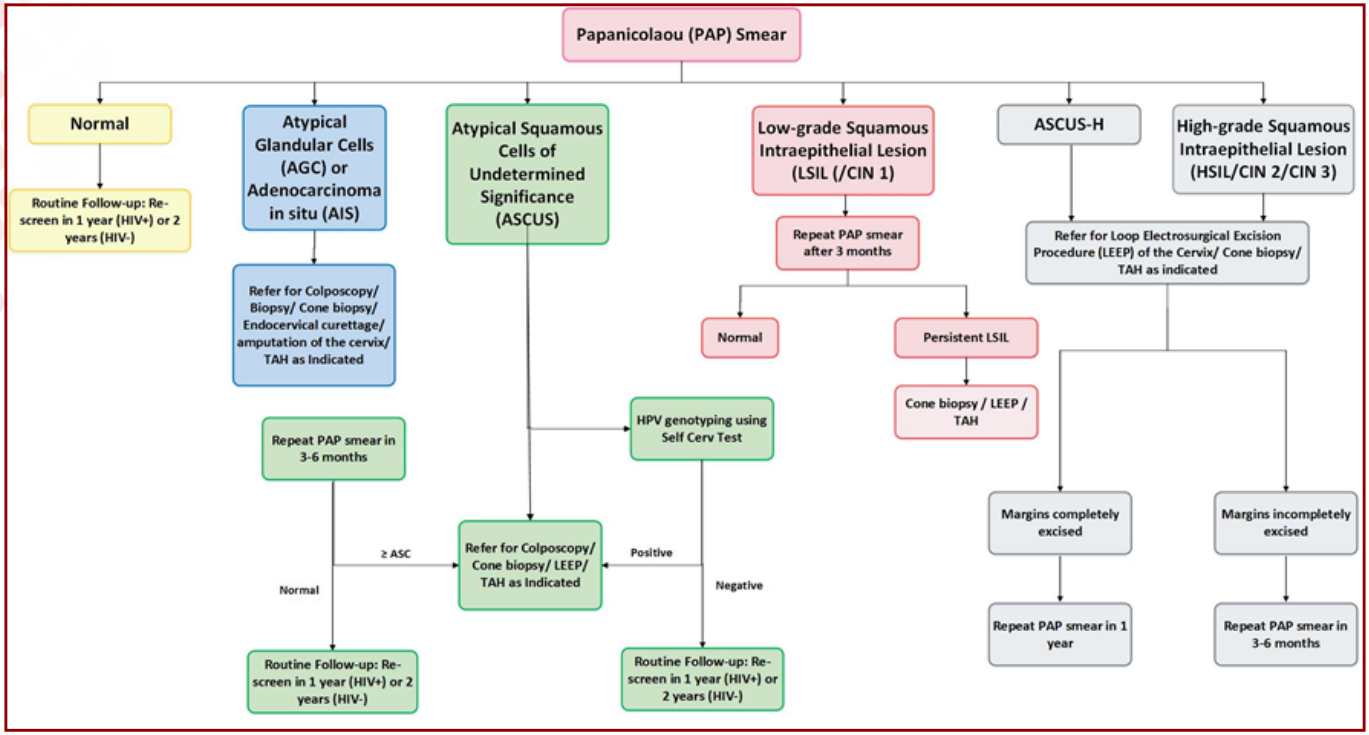
Thermocoagulation (cold coagulation) is an alternative method for the treatment of benign cervical intraepithelial lesions using a metallic probe heated to 100-120°C. The procedure leads to the thermal destruction of cervical tissue with a depth of destruction exceeding 4 mm after 30 seconds treatment.

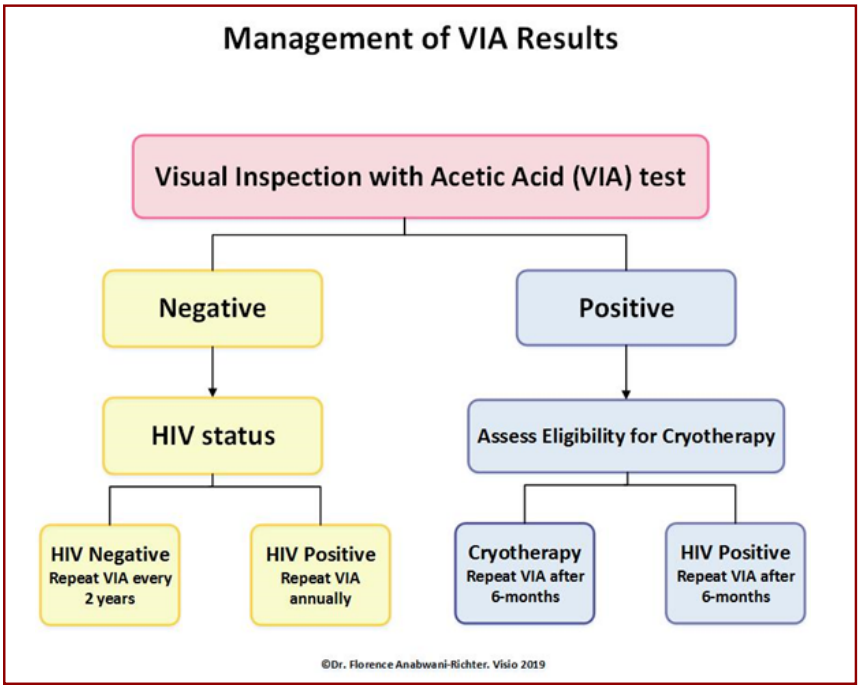
LEEP removes abnormal areas from the cervix using a thin wire loop that cuts the tissue and coagulates (haemostasis) at the same time. LEEP is performed by trained providers on an outpatient basis with local anesthesia and requires less than 30 minutes, but the patient may remain at the facility post-procedure to confirm bleeding has not occurred. Procedure performed for lesions not eligible for cryotherapy.

Conization (cold knife cone) of the cervix is a surgical procedure used to treat or diagnose cervical dysplasia. It is the excision of a cone-shaped portion of the cervix to remove a cervical lesion and the entire transformation zone. Practitioners can use this procedure when there are conflicting pap smear and biopsy specimens. It can be used if histological results are significantly less severe than the cytology result or if there is evidence of severe dysplasia, and even if there is stage 1A1 squamous cell cervical cancer. Conization can be done with a scalpel, a laser, or with an electrosurgical instrument typically referred to as a LEEP (Loop Electrosurgical Excision Procedure). The procedure is always performed in theater in conjunction with examination under anesthesia (EUA).

10 Aggarwal, 2014

Algorithm for Management of Patients on PAP Smear Results




Management of VIA Results
Visual Inspection with Acetic Acid (VIA) test
Negative
Positive
HIV status
Assess Eligibility for Cryotherapy
HIV Negative
Repeat VIA every 2 years
HIV Positive
Repeat VIA annually
Cryotherapy
Repeat VIA after 6-months
HIV Positive
Repeat VIA after 6-months
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Exclusion Criteria for VIA and Cryotherapy and Eligibility Criteria for Cryotherapy

Exclusion criteria for VIA	Exclusion criteria for cryotherapy	Eligibility criteria for cryotherapy/ thermo coagulation
• Women who are very ill • Women who are more than 20 weeks pregnant • Women less than 12 weeks after delivery • Women with cauliflower-like growth or ulcer; fungating mass • Women with previous history of treatment of cancerous lesions • Women with known allergy to acetic acid • Women with a history of total hysterectomy	• Women with a history of prior treatment for precancer • Women with suspected cancer • Women with known pregnancy and until 12 weeks postpartum • Women with a lesion occupying more than 75% of the surface area of the cervix • The cryotherapy probe does not cover the lesion or leaves space of more than 2 mm • The lesion extends more than 2 mm into cervical canal or onto the vaginal wall	• Women with a positive test and an entirely visible lesion on the ectocervix, not extending to the vaginal wall or into the endocervix • The lesion can be adequately covered with a 2.5 cm cryotherapy probe • Women with no evidence of pelvic inflammatory disease or cervicitis, and with no polyps • Women who are not pregnant • Women who have given consent for treatment

4.4.2 Treatment of Invasive Cervical Cancer[11]

Women diagnosed with early stage invasive cervical cancer can typically be cured with effective treatment, which underscores the need for early diagnosis and referral for treatment. Treatment of invasive cervical cancer is stage dependent and includes surgery, radiotherapy, and chemotherapy, which may be used in combination.

Cancer Stage	Summarized Recommended Treatment
Early stages – IA and IB (maximum IIA)	• Hysterectomy performed by local experienced gynaecologist at a referral hospital • Adjuvant radiation therapy if indicated through referral to South Africa
Later stages – II, III, IV	• Concurrent Chemoradiation standard of care for non-metastatic locally advanced disease, case to be discussed by the Tumour Board - Patient required to be re-staged by the gynecology department one week prior to referral • Chemotherapy – see chemotherapy protocols below

11 Denny, 2012; Marth et al., 2018

Special Treatment Considerations

Stage	Treatment	Issue
IA1	Conization or simple hysterectomy ± salpingo – oophorectomy and PLND if LVSI	Conservative surgery
IA2	Conization/radical trachelectomy or modified radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB1, IIA	Radical hysterectomy and PLND	Adjuvant CT/RT if risk factors (LVSI, G3, positive resection margins, multiple nodes)
IB2, IIB – IV	Combination CT/RT with cisplatin	NACT to large bulky tumors prior CT/RT

PLND, pelvic lymphadenectomy; LVSI, lymphovascular space invasion; CT, computed tomography; NACT, neoadjuvant chemotherapy; RT, radiation therapy

The "Sedlis criteria," which are intermediate risk factors used to guide adjuvant treatment decisions, include: (1) greater than one-third stromal invasion; (2) capillary lymphatic space involvement; or (3) cervical tumor diameters greater than 4 cm. However, potentially important risk factors for recurrence may not be limited to the Sedlis criteria. Additional risk factors for consideration include tumor histology (e.g., adenocarcinoma component) and close or positive surgical margins.

The following chemotherapy protocols are to be used for Stage 3 and 4 cervical cancers:

Stage 3	First-line	Cisplatin (if no renal impairment) concurrently with radiotherapy Tranexamic Acid
Stage 3 supportive therapy		Morphine + Bisacodyl + Pregabalin

Stage 4/ Recurrence	First line	Carboplatin + Paclitaxel Cisplatin + Bevacizumab* Metronomic (oral) Metformin + Cyclophosphamide + Celecoxib + Methotrexate Tranexamic Acid
Stage 4 supportive therapy		Morphine + Bisacodyl + Pregabalin
Small Cell Subtype		Etoposide + Carboplatin

*Metastatic cervical cancer becomes hypoxic which inhibits chemotherapy delivery. A vascular drug, Bevacizumab, has shown improvement in such cases

4.5 Cervical Cancer and Fertility Sparing[12]

Fertility-sparing approaches require very specialized skill and experience before being offered to patients. If expertise is not available, referral to experienced high volume centers is highly recommended. They may be considered in highly selected patients who have been thoroughly counseled regarding disease risk as well as prenatal and perinatal issues. Consultation with reproductive fertility experts is highly recommended and suggested.

Microinvasive disease (FIGO stage IA1 with no LVSI) is associated with an extremely low incidence of lymphatic metastasis, and conservative treatment with conization is an option for individuals with no evidence of LVSI. In stage IA1 individuals with evidence of LVSI, a reasonable conservative approach is conization (with negative margins) in addition to SLN mapping algorithm (if available) or pelvic lymphadenectomy.

The goal of conization is en-bloc removal of the ectocervix and endocervical canal. The shape of the cone can be tailored to the size, type, and location of the lesion (i.e., narrow long cone in cases of suspected invasive adenocarcinoma). The panel recommends cold knife conization as the preferred approach. However, LEEP (loop electrosurgical excision procedure) is acceptable if adequate margins, proper orientation, and a non-fragmented specimen without electrosurgical artifact can be

12 JNCCN, 2019

obtained. Endocervical curettage should be added as clinically indicated.

Select patients with stage IA2 or IB1 cervical cancer, especially for those with tumors of less than 2 cm in diameter, may be eligible for conservative surgery. Radical trachelectomy may offer a reasonable fertility-sparing treatment option for patients with stage IA2 or IB1 cervical cancer with lesions that are less than or equal to 2 cm in diameter. In a radical trachelectomy, the cervix, vaginal margins, and supporting ligaments are removed while leaving the main body and fundus of the uterus intact. Laparoscopic pelvic lymphadenectomy accompanies the procedure and can be performed with or without SLN mapping. Due to their aggressive nature, tumors of small cell neuroendocrine histology are considered inappropriate for radical trachelectomy. Trachelectomy is also inappropriate for treating gastric type cervical adenocarcinoma and adenoma malignum (minimal deviation adenocarcinoma) due to their diagnostic challenges and potentially aggressive nature.

Vaginal radical trachelectomy (VRT) may be used for carefully selected patients with lesions of 2 cm diameter or less. Abdominal radical trachelectomy (ART) provides a broader resection of the parametria than the vaginal approach and is commonly used in stage IB1 lesions. Multiple case series have evaluated safety and outcomes with vaginal versus abdominal approaches to radical trachelectomy, including systematic reviews on VRT and ART. A limited number of studies have specifically examined this approach in patients with larger stage IB1 tumors between 2 cm and 4 cm in diameter and reported safe oncologic outcomes. However, as expected, more patients in this subgroup will require adjuvant therapy that may reduce fertility.

4.6 Cervical Cancer in Pregnancy

- If micro-invasive carcinoma is suspected, a cone biopsy should be considered under general anaesthesia.
- Prophylactic cerclage may decrease bleeding and premature labour.
- Conservative approach only if firm desire to continue the pregnancy.
- **Neo-adjuvant chemotherapy is an option.**

Recommended to wait until 14 weeks gestation to start chemotherapy. Folic acid antagonists (e.g. methotrexate) and idarubicin are not safe in pregnancy. Pharmaco-dynamics and pharmaco-kinetics of chemotherapy may change due to increased GFR and liver metabolization. Interval of 3 to 4 weeks between last chemotherapy and delivery (as a rule, no

chemotherapy should be administered after 35 weeks of pregnancy with main concern being bone-marrow suppression at the time of delivery). No obvious increased risk for congenital malformations after intra-uterine exposure to chemotherapy during second and third trimesters.

- Caesarean section delivery route of choice.
- **Radiotherapy is a relative contra-indication.**

Radiotherapy with proper screening of uterine cavity may be applied to the upper body during pregnancy with relative safety. Chest radiotherapy should preferably be given with the fetus in the cephalic position after 28 weeks (to protect fetal neurological system). If chemo-and radiotherapy is needed as adjuvant treatment, radiotherapy is often postponed until after delivery.

4.7 Survivorship and Follow-up

Patients must be informed that they will require long-term follow-up once treatment has concluded. Patients that have completed treatment should be brought down from tertiary care to a regional hospital with a gynecologist for long-term follow-up.

No definitive agreement exists on the best post-treatment surveillance. A clinical visit with gynecological examination including a pap smear is usually performed every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. CT or PET/CT scan should be performed as clinically indicated.

5 Breast Cancer

5.1 Prevention

While there are no definitive measures to prevent breast cancer, there are life-style related risk factors that can be controlled by patients, including:[13]

- Drinking alcohol
- Being overweight or obese
- Not being physically active
- Not having children
- Not breast feeding
- Use of hormonal birth control
- Hormone therapy after menopause

Some risk factors cannot be controlled by patients, including:

- Being female
- Being age 35-65
- Having a family or personal history of breast or ovarian cancer including a first degree relative or male relative with breast cancer or history of ovarian cancer
- Inheriting genetic mutations such as BRCA1, BRCA2
- Previous radiation exposure to the chest for other conditions in childhood or early adulthood

The following prevention steps may reduce the risk of developing breast cancer in some patients:[14]

- Achieve and maintain a healthy weight
- Be physically active
- Limit or avoid alcohol
- Preventive surgery for women with very high breast cancer risk – such as those with a known BRCA gene mutation

5.2 Screening

General population screening for breast cancer should begin at age 35, except for high risk clients who should commence screening 8-10 years earlier than index. The following are considered at high risk for developing breast cancer:

- Children who have had radiation to the chest
- Familial breast and ovarian cancer

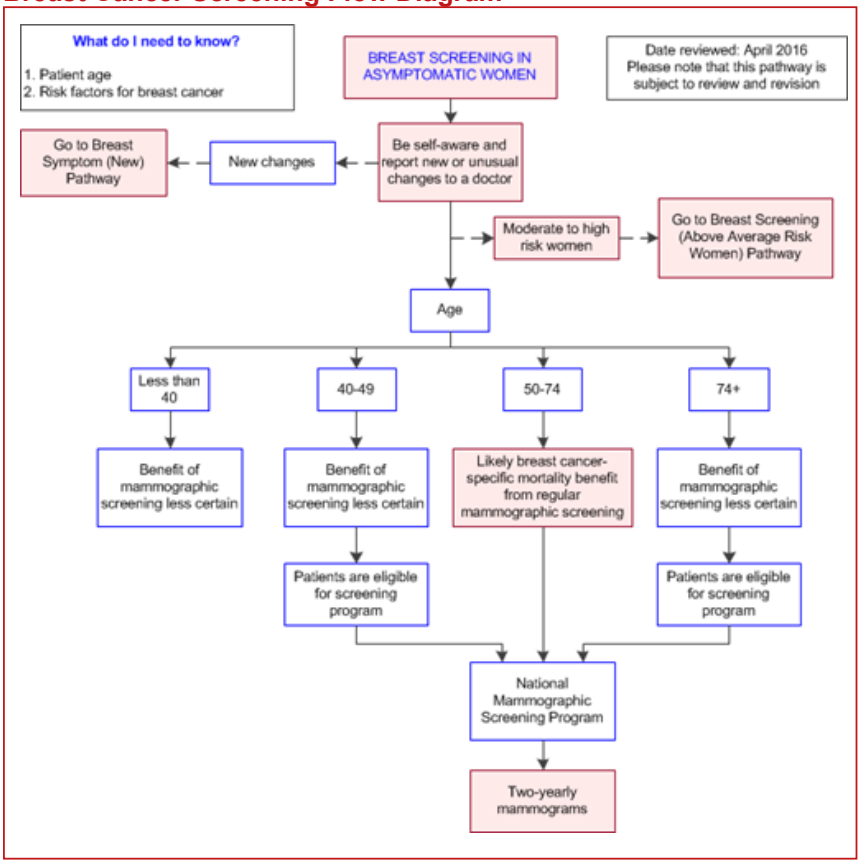
13 American Cancer Society, 2019b
14 American Cancer Society, 2019a

- History of male breast cancer in family
- History of breast cancer in first degree relative under the age of 50

The following screening methods are recommended in Eswatini:

- Clinical breast exam
- Mammography with or without breast ultrasound biennially
- Self-breast exams – no longer explicitly recommended as the above methods detect disease earlier

Breast Cancer Screening Flow Diagram

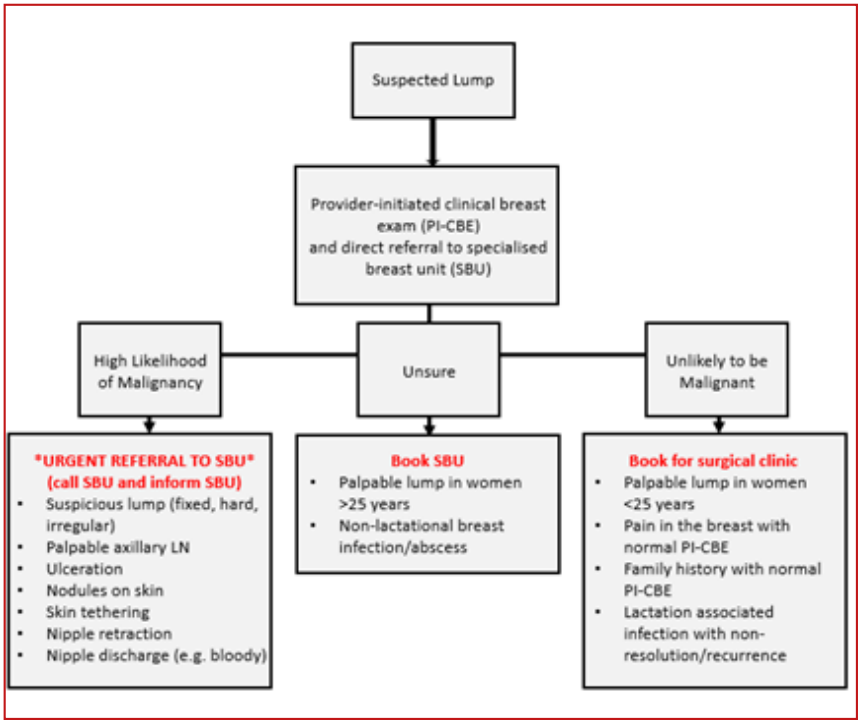


The trend for breast cancer in the African black population has shown earlier age at diagnosis of breast cancer in comparison to the white population.[15] Eswatini sees a similar trend for breast cancer age at diagnosis.[16]

15 Iqbal, Ginsburg, Rochon, Sun, & Narod, 2015
16 Ferlay et al., 2019; UICC, 2018

5.3 Early Referral Flow Chart

A dedicated specialized breast cancer unit (SBU) will be established to expedite diagnosis and treatment. This, at minimum, will include a trained mammographer, radiologist, pathologist, and a breast surgeon. The clinic will be established at the national referral hospital, which will advise regional hospitals on the referral system through planned technical support visits and consultations.



5.4 Diagnosis

A clinical assessment, tissue biopsy and mammogram are all required for breast cancer diagnosis.

The following table summarizes the recommended diagnostics for breast cancer:

Diagnostic Category	Investigation

Biopsy	• Biopsy techniques:
	  ○ Excision
	  ○ Lumpectomy
	  ○ Trucut biopsy
	• Ultrasound guided biopsies are preferred

Pathology	• A full pathology report including immunohistochemistry (IHC)

Laboratory Tests	• A full biochemistry report, including:
	  ○ KFT
	  ○ LFT
	• FBC and differential count

Radiology	• Echocardiogram report
	• Contrasted CT scan – to include chest, abdomen and pelvis to rule out metastasis
	• Chest X-ray prior to surgery to rule out effusions
	• Bone scan in locally advanced breast cancer
	• For all locally advanced breast cancers upon recommendation of radiologist if CT does not show metastasis: Diffusion weighted imaging (DWI) with MRI to image spine
	  ○ Note: DWI is recommended in place of a bone scan if not available
	• Bilateral mammogram required for every patient for staging
	  ○ Mammogram should include ultrasound bilaterally and axillary
	  ● lymph nodes, routine supraclavicular ultrasound

5.4.1 Clinical Staging of Breast Cancer (TNM)

Clinical Staging of Breast Cancer –TNM Definitions

Tumour	Node	Metastasis
Tis: Carcinoma in situ (DCIS, LCIS, Pagets) T1: < 2 cm T1mic: < 1 mm T1a: > 1 mm, < 5 mm T1b: > 5 mm, < 1 cm T1c: > 1 cm, < 2 cm T2: > 2 cm, < 5 cm T3: > 5 cm T4: Any size with extension to CW and/or skin (invasion of dermis alone does not count) T4a: Extension to CW (not include pec only) T4b: Ulceration and/ or ipsilateral satellite nodules an/or oedema (peau d'orange) of skin T4c: Both T4a and T4b T4d: Inflammatory (A rapid onset of a brawny erythema, edema, and a peau d'orange appearance and/or abnormal breast warmth, with or without a lump that can be felt. The erythema covers at least a third of the breast).	cN0: no regional nodes cN1: Movable, ipsilateral level I, II axillary nodes cN2: Fixed or matted ipsilateral level I, II axillary nodes OR isolated IMN nodes cN2a: Fixed I/II axillary cN2b: Isolated IMN (no axillary) cN3: Ipsilateral infraclav (level III axillary) OR IMN w level I/II OR SCV cN3a: Level III cN3b: IMN w axillary nodes cN3b: SCV pN0(i+): ITC detected by H&E or IHC pN0(mol+): detected on PCR but not histology or IHC pN1: Micromets OR 1-3 axillary nodes, IMN pN1mic: > 0.2 mm, < 2 mm pN1a: 1-3 axillary nodes, at least one > 2 mm pN1b: IMN pN1c: 1-3 axillary nodes AND IMN pN2: 4-9 axillary nodes OR IMN pN2a: 4-9 axillary nodes pN2b: IMN without axillary nodes pN3: > 10 axillary nodes OR Level III OR IMN w I/II axillary OR SCV pN3a: > 10 axillary nodes pN3b: IMN with axillary nodes pN3c: SCV nodes ITC: isolated tumor cell clusters less than 0.2 mm; excluded from positive node counts	M1: distant mets > 0.2 mm in any organ

C: clinical, p: pathologic, IMN: Internal mammary node, SCV: supraclavicular

Clinical Staging of Breast Cancer

Nodal status/ Metastasis	T stage			
	T_1	T_2	T_3	T_4
N_0	I	IIa	IIa	IIIb
N_1	IIb	IIb	IIIa	IIIb
N_2	IIIa	IIIa	IIIa	IIIb
N_3	IIIc	IIIc	IIIc	IIIc
M_1	IV	IV	IV	IV

Note: Shaded boxes constitute the heterogeneous group of clinically determined LABC.

Clinical staging to be completed by an experienced surgeon as part of breast cancer diagnosis.

5.5 Treatment[17]

Treatment for breast cancer is stage dependent and relies on a combination of surgery, chemotherapy and radiation. It is important to note that there is only up to a 12-week window post-surgery to begin radiation to derive the maximal clinical benefit.

5.5.1 Surgical Treatment

The ESMO consensus guidelines (2019) endorses that all patients with TNBC and HER2-positive with tumours > 2cm receive neoadjuvant chemotherapy in order to get an understanding of their basic disease biology (chemotherapy sensitive or resistant). In our setting, all TNBC and HER_2/NEU positive disease are to receive neo-adjuvant chemotherapy, irrespective of stage, due to difficulties in accurate measurement of tumour size.

Surgical options:

- Breast conserving surgery (BCS). This is always followed by whole breast radiotherapy. It should be offered to patients that meet the BCS criteria, and availability of timely radiotherapy is guaranteed.
- Mastectomy; radical or modified and axillary lymphadectomy
- Axillary nodal clearance (ANC)
- Sentinel lymph node (SLN) biopsy
- Prophylactic contralateral mastectomy with +/- reconstruction. This requires input from the Genetic counselor for BRCA and familial

17 Cardoso et al., 2019, 2018

gene mutations. The gynaecologist should be involved through an MDT to assess for bilateral salphingo-oophorectomy (BSO).

5.5.2 Chemotherapy for Breast Cancer

For eligible patients, the following chemotherapy protocols are recommended in Eswatini:

First Line	Epirubicin* + Cyclophosphamide + Taxane (paclitaxel or Docetaxel) Docetaxel + Cyclophosphamide Anastrozole** Trastuzumab**
Second Line	Carboplatin + Paclitaxel Gemcitabine + Cisplatin
Third Line	Capecitabine Vinorelbine Metronomic (oral) – Cyclophosphamide + Methotrexate CMF: 5-Flourouracil + Methotrexate + oral Cyclophosphamide
Hormonal Therapy	Tamoxifen or Aromatase inhibitors, Trastuzumab **

**Doxorubicin can be used as an alternative but required echocardiograms and evaluation by surgeon after 2 cycles. Epirubicin is less stringent cardiac baseline functions in relation to Doxorubicin.*
***Require IHC, can also be used in both neo-and adjuvant setting*

Chemotherapy in Pregnant Patients

- No chemotherapy in the first trimester
- Anthracyclines, cyclophosphamide and taxanes can be used in both second and third trimesters
- Notify the MGH high risk clinic for patient assessment
- Discuss with cardiology for Echocardiography, and high-risk clinic assessment thereafter
- If in third trimester, it is preferable to have upfront surgery followed by adjuvant chemotherapy after delivery
- No radiotherapy or radiation-related investigations are to be offered at any stage of the pregnancy

5.6 Survivorship and Follow-up

Mammograms and evaluation by a surgeon are required. Patients who receive neo-adjuvant or adjuvant therapy are to be followed in the SBU for five years at the following intervals:

- Year 1: every 4 months
- Year 2: every 6 months
- Years 3-5: annual checkups and then discharge after year 5

6 Lymphomas

6.1 Prevention

There is no definitive prevention strategy for lymphoma, but patients should be advised to avoid specific risk factors that may increase risk of Non-Hodgkin's lymphoma, including:

- HIV infection
- H. pylori – patients should be treated with antibiotics
- Poor diet and lack of exercise

6.2 Screening

No routine screening is available for lymphomas, patients are suspected based on clinical presentation or symptoms. Some common signs and symptoms include:

- Enlarged lymph nodes
- Chills
- Weight loss
- Fatigue (feeling very tired)
- Swollen abdomen (belly)
- Feeling full after only a small amount of food
- Chest pain or pressure
- Shortness of breath or cough
- Severe or frequent infections
- Easy bruising or bleeding

High-risk groups for lymphoma are patients with:

- EBV-infection
- HTLV-1
- Kaposi Sarcoma
- Immunosuppression – HIV or non-HIV related
- H. pylori infection
- Autoimmune disorders such as Sjogren's syndrome and Hashimoto's thyroiditis
- Exposure to environmental factors including pesticides, radiation and chemotherapy

6.3 Diagnosis

The following table summarizes the recommended diagnostics for lymphoma:

Diagnostic Category	Investigation
Biopsy	• A whole node excision biopsy by a Medical Officer • Bone Marrow Aspirate Trephine (BMAT)
Pathology	• A full pathology report with IHC and cell of origin defined • Blood smear

Laboratory Tests	• A full biochemistry report, including:
	  ○ KFT
	  ○ LFT
	  ○ Uric acid
	  ○ LDH
	  ○ CMP
	• FBC and differential count
	• Erythrocyte sedimentation rate (ESR)
	• Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus and HIV tests

Radiology	• Echocardiogram report • Contrasted CT scan – must include neck, chest, abdomen and pelvis • PET/CT scan for Deauville scoring, if available

6.4 Treatment[18]

For eligible patients, the following chemotherapy protocols are recommended in Eswatini for adult patients with Hodgkin's or Non-Hodgkin's lymphoma:

Adult Hodgkin's Lymphoma	First-line	ABVD – Doxorubicin + Bleomycin + Vinblastine + Dacarbazine
Adult Non-Hodgkin's Lymphoma	First-line	RCHOP21 – Cyclophosphamide + Doxorubicin + Vincristine + Prednisone + Rituximab
	T-cell	CHOEP – Cyclophosphamide + Doxorubicin + Vincristine + Prednisone + Etoposide

6.5 Survivorship and Follow-up

When available, a post-treatment scan, inclusive of one PET, should be done. Lactate dehydrogenase (LDH) testing and clinical examination are to be done quarterly in the first year and twice annually in years 2-5 following treatment. After five years, patient is to be discharged to a regional internist.

18 Hutchings et al., 2018; Labianca et al., 2010; Vitolo et al., 2016

7 Common Childhood Cancers

The common childhood cancers are leukemias, lymphomas, brain tumours, Wilm's tumours (Nephroblastoma), Neuroblastoma, and retinoblastoma. For detailed information, please refer to the Paediatric Cancer Protocols.

Leukemias

Common childhood leukemias include acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and chronic myeloid leukemia (CML).

7.1 Prevention

No prevention methods are recommended for leukemia. The following are risk factors for leukemia in children:

- Age distribution peaks:
    - ALL peaks 2-3yrs. olds
    - AML < 2yr. olds
    - CML two peaks <1 yr. or early teens
- Males are at higher risk than females
- Previous Haemophilus influenza type b infection in nonvaccinated children
- Genetic abnormalities: Down's syndrome, Fanconi's Anaemia, Bloom's syndrome, ataxia Telangiectasia
- Large birth weight babies
- Previous radiation exposure
- Maternal abdominal X-ray during pregnancy

7.2 Screening

No routine screening is recommended for leukemia. There are variable suggestive symptoms and signs of leukemia in adults that may be indicative of leukemia and warrant further investigations.

Variable suggestive symptoms:

- Malaise
- Fatigue
- Lethargy
- Prolonged or recurrent fever
- Irritability and/or protracted crying
- Growth restriction/failure to thrive
- Dyspnoea/effort intolerance
- Dizziness
- Palpitations
- Bleeding diathesis (epistaxis, bleeding gums and/or easy bruising)
- Bone pain
- Prolonged cough
- Nausea
- Vomiting
- Headache (if CNS involvement)
- Repeated common childhood infections

Signs of leukemia in children:

- Pallor
- Petechiae
- Purpura
- Bruising
- Hepatosplenomegaly
- Lymphadenopathy
- Mediastinal mass
- Cranial nerve manifestations or focal neurology
- Testicular enlargement

All paediatric patients with suspicion of leukemia need to be referred to the pediatrician for work up and urgent transfer through Phalala Fund to a haematologist.

DO NOT DELAY REFERRAL FOR ALL ACUTE LEUKEMIAS.

7.3 Diagnosis

Diagnostic Category	Investigation
Biopsy	• BMAT • Tissue biopsy for peripheral involvement • Lumbar puncture if CNS involvement and indicated
Pathology	• A full pathology report with IHC • Immunophenotyping • Cytogenic analysis – karyotyping, FISH, flow cytometry

Laboratory Tests	• A full biochemistry report, including:
	  ○ UEC
	  ○ LFT
	  ○ Uric acid
	  ○ LDH
	  ○ CMP
	  ○ DIC (prolonged prothrombin time, low fibrinogen and fibrinogen degradation products)
	• FBC, differential count and blood film (high WCC with neutropenia, blasts)

Radiology	• ECG • Echocardiogram report prior to using anthracyclines or ERNA • Chest X-ray • Ultrasound of abdomen • CT of brain if neurological symptoms

7.3 Treatment[19]

Treatment options for childhood leukemia in Eswatini are minimal. Treatment requires a multi-disciplinary approach and requires a tertiary care center with transplant service. Defer routine immunization during therapy and for six months after chemotherapy.

Individualized chemotherapy protocols need to be developed for each patient by the oncologist in consultation with the disciplinary team. Chemotherapy can be started in Eswatini prior to referral to an appropriate treatment center to improve clinical outcomes.

19 Creutzig, Kutny, Barr, Schlenk, & Ribeiro, 2018; Hunger & Mullighan, 2015

Simple Chemotherapy Regimen for Acute Lymphoblastic Leukemia (ALL)

Agent	Dose/Route	Days
Induction (4 weeks)		
Prednisone	60 mg/m^2/day PO in three divided doses	1 – 28
Vincristine	1.5 mg/m^2 IV (max dose 2 mg)	Days 1, 8, 15, 22
Methotrexate	Age-specific[a] given IT	Days 1, 15
Consolidation (4 weeks): start when ANC > 1,000/µL and platelets > 100,000/µL		
6-Mercaptopurine	50 – 75 mg/m^2/day PO	1 – 28
Vincristine	1.5 mg/m^2 IV (max dose 2 mg)	1
Methotrexate	Age-specific[a] given IT	Days 1, 8, 15, 22
Maintenance (continue for 3 years from diagnosis); start when ANC < 1,000/µL and platelets > 100,000/µL. Adjust doses of 6-MP and MTX to maintain ANC > 1,000/µL and platelets > 100,000/µL		
Repeat 12 weeks cycles		
6-Mercaptopurine (6 – MP)	50 – 75 mg/m^2/day PO	1 – 84
Methotrexate (MTX)	20 mg/m^2 PO or IM/IV	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78
Vincristine	1.5 mg/m^2 IV (max dose 2 mg)	Days 1, 8, 15
Prednisone	40 mg/m^2/day PO in three divided doses	1 – 21
Methotrexate	Age-specific[a] given IT	Day 1
Perform bone marrow aspirate at end induction, start maintenance, and periodically during maintenance. Cranial irradiation (2,400 cGy given as 200 cGy/day Monday through Friday for 12 days) should be given between consolidation and maintenance if possible.		

PO ***oral,*** **IV** ***intravenous,*** **IM** ***intramuscular,*** **IT** ***intrathecal,*** **ANC** ***absolute neutrophil count.***

[a] Age-specific intrathecal methotrexate: 1 – 2 years 8 mg; 2 – 3 years 10 mg; 3+ years 12 mg

Basic Chemotherapy Regimens for Acute Myeloid Leukemia (AML)

AML – BFM Study Group AML – BFM 93	*Induction*: AIE (ARAC + IAD + VP – 16) *Consolidation*: **High-risk patients**: HD – ARAC + MTZ (HAM) + 6-week consolidation with 6-TG + prednisone + vincristine + doxorubicin + ARAC + cyclophosphamide **Standard risk patients**: 6-week consolidation (see above) without HAM *Intensification*: HD – ARAC + VP – 16 (HAE) *CNS prophylaxis*: Intrathecal ARAC + cranial irradiation *HSCT*: allogeneic HSCT in high-risk patients if matched related donor is available *Maintenance*: 6-TG daily + ARAC monthly for a total of 12 months CR 82%, 5-year OS 57%
Medical Research Council MRC AML12 Trial	*Induction I*: ARAC + DAUNO + VP – 16 (ADE) versus MTZ + ARAC + VP – 16 (MAE) *Induction II*: same as induction I but with ARAC shortened from 10 to 8 days *Consolidation 1*: Amsacrine + ARAC + VP – 16 *Consolidation 2*: HD – ARAC + L-asparaginase *Consolidation 3 – 4*: HD – ARAC + MTZ *CNS prophylaxis*: Triple intrathecal methotrexate + ARAC + hydrocortisone *HSCT*: allogenic HSCT in standard or poor risk patients with matched related donor available CR 90%, 10 – year OS 61%
NOPHO – AML 93	*Induction I*: ARAC + 6 – TG + VP – 16 + DOXO *Induction II*: same as Induction I for good responders, or ARAC + MTZ for poor responders *Consolidation 1*: HD – ARAC + MTZ *Consolidation 2*: HD – ARAC + VP - 16 *Consolidation 3*: HD – ARAC *Consolidation 4*: HD -ARAC + VP – 16 *CNS prophylaxis*: Intrathecal methotrexate *HSCT*: allogenic HSCT recommended to all patients with matched family donor CR 92%, 5 – year OS 65%

6 – TG 6-thioguanine, ARAC cytarabine, CNS central nervous system, DAUNO daunorubicin, DOXO doxorubicin, HD – ARAC high – dose cytarabine, HSCT hematopoietic stem cell transplantation, IDA idarubicin, MTZ mitoxantrone, VP – 16 etoposide

7.5 Survivorship and Follow-up

These patients require lifelong follow-up, as they're at risk for recurrence, and at high risk for lymphomas. Specialist MDT clinics should be created for them.

8 Adult Leukemias

Adult leukemia, according to these treatment protocols, include acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL).

8.1 Prevention

No prevention methods are recommended for leukemia. The following are risk factors for leukemia in adults:

- Any age group, > 60 years at highest risk
- Previous chemotherapy and radiation exposure
- Congenital disorders: Down's syndrome, Fanconi's Anaemia, congenital neutropenia, neurofibromatosis
- Benzene exposure

8.2 Screening

No routine screening is recommended for leukemia. There are variable suggestive symptoms and signs of leukemia in adults that may be suggestive of leukemia and warrant further investigations.

Variable suggestive symptoms:

- Malaise
- Fatigue
- Lethargy
- Prolonged or recurrent fever
- Irritability and/or protracted crying
- Growth restriction/failure to thrive
- Dyspnoea/effort intolerance
- Dizziness
- Palpitations
- Bleeding diathesis (epistaxis, bleeding gums and/or easy bruising)
- Bone pain
- Prolonged cough
- Nausea
- Vomiting
- Headache (if CNS involvement)
- Repeated common childhood infections

Signs of leukemia in adults:

- Pallor
- Petechiae
- Purpura
- Bruising
- Hepatosplenomegaly
- Lymphadenopathy
- Mediastinal mass
- Cranial nerve manifestations or focal neurology
- Gouty arthritis
- Hyper-viscosity due leukocytosis
- Testicular enlargement

8.3 Diagnosis

Diagnostic Category	Investigation
Biopsy	• BMAT • Tissue biopsy for peripheral involvement • Lumbar puncture if CNS involvement and indicated
Pathology	• A full pathology report with IHC • Immunophenotyping • Cytogenic analysis – karyotyping, FISH, flow cytometry

Laboratory Tests	• A full biochemistry report, including:
	  ○ UEC
	  ○ LFT
	  ○ Uric acid
	  ○ LDH
	  ○ CMP
	  ○ DIC (prolonged prothrombin time, low fibrinogen and fibrinogen degradation products)
	• FBC, differential count and blood film (high WCC with neutropenia, blasts)

Radiology	• ECG • Echocardiogram report prior to using anthracyclines or ERNA • Chest X-ray • Ultrasound of abdomen • CT of brain is neurological symptoms

8.4 Treatment[20]

Treatment options for adult leukemia in Eswatini are minimal. Treatment requires a multi-disciplinary approach and requires a tertiary care center with transplant service.

Individualized chemotherapy protocols need to be developed for each patient by the oncologist in consultation with the disciplinary team. Chemotherapy can be started in Eswatini prior to referral to an appropriate treatment center to improve clinical outcomes. Refer to appendix for the detailed chemotherapy regimen.

8.5 Survivorship and Follow-up

Leukemia survivors require long term follow-up by a specialist Haematologist or physician.

20 Dombret & Gardin, 2016

9 Kaposi Sarcoma

9.1 Prevention

Kaposi Sarcoma (KS) in Eswatini is typically associated with poor management of HIV infection. Therefore, prevention of KS is centered around lowering the risk of HIV infection, and for those who are HIV-positive, ensuring viral suppression is achieved and maintained through proper adherence to antiretroviral therapy (ART). If a patient is resistant to their ART regimen, prompt identification of patients failing treatment can prevent development of KS and other conditions associated with advanced HIV disease.

9.2 Screening

No recommended routine screening tests for KS exist for the general population. Patients living with HIV are at increased risk of developing KS and should have a thorough skin examination during ART refill visits. KS tends to develop in several areas at one time so identification of one skin lesion during a skin examination often means there are multiple areas of KS that may not be visible. Evaluation for KS through total skin and oral mucosal examination should be provided to all patients presenting for ART initiation. The incidence of KS is particularly high in the first 6 months following ART initiation, due to immune re-constitution inflammatory response (IRIS). As such, monthly follow-up should be done during this six-month period. Three monthly follow-ups are recommended for a year, then bi-annually thereafter.

All healthcare providers should be equipped to perform a total skin and mucosal examination and are expected to be able to identify symptoms suspect of KS.

9.3 Diagnosis

Diagnosis of KS should be confirmed by pathology prior to beginning treatment. The following table indicates the full investigations that should be performed at the time of diagnosis:

Diagnostic Category	Investigation
Biopsy	• Tissue biopsy
Pathology	• A full histology report

Laboratory Tests	• A full biochemistry report, including:
	  ○ KFT
	  ○ LFT
	• FBC and diff
	• Stool for occult blood

Radiology	• CT scan if indicated • Chest X-ray to exclude TB or pulmonary KS
Other	• Endoscopy to be guided by GIT symptomatology

9.3.1 Kaposi Sarcoma Staging[21]

The staging is to be completed by the referring physician or medical officer using the ACTG criteria. Patients with poor-risk factors (see the table below) are to be referred for initiation of chemotherapy by the oncology department/MDT at the tertiary hospital.
ACTG Staging for HIV-associated Kaposi Sarcoma is recommended.

ACTG Staging for HIV-Associated KS

Parameter	Good Risk (0)	Poor Risk (1)
Tumour (T)	Kaposi sarcoma confined to skin and lymph nodes Minimal oral disease: nonnodular Kaposi sarcoma confined to palate	Tumour-associated oedema or ulceration Extensive oral Kaposi sarcoma Gastrointestinal Kaposi sarcoma Kaposi sarcoma in other nonmodal viscera
Immune status (I)	CD4 count > 200 cells/µl	CD4 count < 200 cells/µl

21 Régnier-Rosencher, Guillot, & Dupin, 2013

Systematic illness (S)	No history of opportunistic infection or thrush No "B" symptoms: Unexplained fever Night sweats > 10% involuntary weight loss Diarrhea lasting > 2 weeks Performance status > 70 (Karnofsky score)	History of opportunistic infection or thrush "B" symptoms present Performance status < 70 (Karnofsky score) Other HIV-related illness (e.g. neurological disease, lymphoma)

The multifocal nature of Kaposi sarcoma makes it difficult to stage using the standard tumour, node, metastasis (TNM) system used for most solid tumours, and other AIDS-related factors contributing to disease burden must also be considered. Therefore, a system developed in the pre-cART era by the AIDS Clinical Trials Group (ACTG) is used instead and is summarized in this table.

STAGES	CHARACTERS
Stage – I	Localized skin lesions involving one limb only
Stage – II	Widespread skin lesions involving more than one limb
Stage – III	Kaposi's sarcoma involving the viscera and/or lymph nodes
Stage – IV	Generalized Kaposi's sarcoma involving the skin, viscera, and/or lymph nodes

9.4 Treatment[22]

If the patient is HIV-positive, they should be started on ARVs first, except if other urgent, life-saving treatment is required. See the following flow chart for a summary of treatment options for KS. A multi-disciplinary team is required for all non-cutaneous and complicated cases of KS.

The major goals of treatment for KS are:
- Alleviate the symptoms
- Shrink tumours
- Prevent disease progression

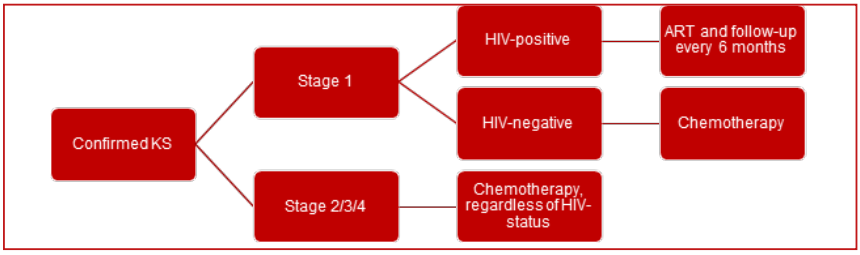
KS treatment can be categorized into:
- HAART
- Local therapy (intralesional chemotherapy, radiotherapy, surgery)

22 Mosam et al., 2012

- Systemic therapy (chemotherapy) (algorithm)

Treatment options depend very much on the tumour behaviour (extent of disease and rate of growth), and the host status (CD4 count, psychosocial impact and other medical illnesses). Although KS is a systemic multi-focal disease, local therapies do offer significant palliation for many patients. Systemic therapy is indicated for:

a. Extensive tumour burden (>25 skin lesions)
b. Visceral involvement
c. Extensive oedema
d. "B" symptoms
e. Treatment failure of local therapy



9.4.1 Radiotherapy for Kaposi Sarcoma

Radiotherapy is currently not available in Eswatini. Patients with KS in need of radiotherapy must be referred through an MDT to a facility with radiotherapy facilities, or private means if available to the client.

9.4.2 Chemotherapy for Kaposi Sarcoma

The choice and duration of using various modalities must be titrated against response per treatment goals. For eligible patients, the following chemotherapy protocols are recommended in Eswatini for patients with KS:

First-line	Vincristine + Bleomycin	
Second-line	Paclitaxel	Second line to be initiated if there is no response after six cycles of first line.
Third-line	Vincristine + Bleomycin + Doxorubicin* *Doxil preferred	
Pulmonary KS	Vincristine weekly Paclitaxel Etoposide	

The lifetime maximum dose of Bleomycin is 400 IU

9.5 Survivorship and Follow-up

Following treatment of non-complicated KS, patients should be followed up by their primary doctor at ART clinics according to the ART schedule. A multi-disciplinary team must follow-up complicated non-cutaneous KS patients. Patients are to be followed up 3 monthly in the first year, then bi-annually thereafter.

A skin map (see Appendix) is necessary before referral to a dermatologist in the event of KS recurrence. If patients fail on multiple regimens, immune exhaustion should be explored.

10 Prostate Cancer

10.1 Prevention

While there are no proven ways to prevent prostate cancer, healthy living and eating choices may reduce the risk of prostate cancer. Men should choose a healthy, low-fat diet, rich in fruits and vegetables, exercise regularly, and maintain a healthy body weight.

10.2 Screening

Routine screening is not recommended per the ACS. When screening is done, it should be a prostate specific antigen test (PSA) and digital rectal exam (DRE) at 50 years if life expectancy is > 10 years. United States Preventive Services Task Force (USPSTF) discourages routine prostate cancer screening in men < 75 years. Prostate screening should be done every two years for all men above age 50 with any of the following risk factors:

- Discussion should take place at age 45 for men at high risk (African-American, 1st degree relative with prostate cancer at early age)
- Discussion should take place at age 40 (age at which AUA recommends routine screening) for men at very high risk (several 1st degree relatives with prostate cancer at early age)

Screening for prostate cancers is done through a digital rectal examination (DRE) where a trained healthcare worker feels the surface of the prostate for any irregularities, in conjunction with annual PSA readings and rectal or pelvic ultrasound.

Population based screening for prostate cancer will not be routinely offered.

Signs and Symptoms

- Most detected on screening PSA: biopsy for PSA > 4 or PSA-DT < 2 yrs.
- Advanced cases: urinary urgency/frequency, dysuria, nocturia, hematuria, poor erectile function, bony pain, bladder outlet obstruction, urinary retention, chronic renal failure, rectal bleeding

10.3 Diagnosis and Staging

Diagnosis of suspected cases of prostate cancer requires the following:

Diagnostic Category	Investigation
Biopsy	• 12 cores TRUS-guided biopsy
Pathology	• A full histology report

Laboratory Tests	• Prostate specific antigen (PSA) test
	  ○ PSA doubling time
	  ○ PSA density
	  ○ PSA velocity
	  ○ PSA ratio, free to bound

Radiology	• Ultrasound pelvis and abdomen • Chest X-ray • If PSA >20 bone scan should be performed, or MRI DWI (high risk) if bone scan unavailable • MRI pelvis (prostate specific sequences)
Other	• Endoscopy on symptoms

10.3.1 Prostate Cancer Staging (TNM)

T – Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Clinically unapparent tumour not palpable or visible by imaging

T1a Tumour incidental histological finding in 5% or less of tissue resected at TURP or open prostatectomy

T1b Tumour incidental histological finding in more than 5% of tissue resected at TURP or open prostatectomy

T1c Tumour identified by needle biopsy (e.g. because of elevated prostate- specific antigen [PSA] level)

T2 Tumour confined within the prostate1

T2a Tumour involves one half of one lobe or less

T2b Tumour involves more than half of one lobe, but not both lobes

T2c Tumour involves both lobes

T3 Tumour extends through the prostatic capsule2

T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement

T3b Tumour invades seminal vesicle(s)

T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, bladder, rectum, levator muscles, and/or pelvic wall

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M – Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s)

1 Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified asT1c.

2 Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

3 Metastasis no larger than 0.2 cm can be designated pN1 mi.

4 When more than one site of metastasis is present, the most advanced category should be used.

10.3.2 Risk Stratification

Prognostic Risk Grouping for Prostate Cancer (D'Amico)[23]

Recurrence Risk Group		Factors	5-10YR OS
LOW	VERY LOW	All of T1c, PSA <10, Gleason <7, <3 biopsy cores positive, ≤50% involvement in each core, PSA density < 0.15ng/ml	>95%
	LOW	All of T1-2a, Gleason <7, PSA <10	

23 Hernandez, Nielsen, Han, & Partin, 2007

INTERM	LOW	ONLY ONE of T2b-c, Gleason 7 (3+4), PSA ≥ 10 <20	75-90%
	HIGH	>ONE of T2b-c, Gleason 7 (4+3), PSA ≥ 10 <20	
HIGH	HIGH	Any of T3a, Gleason >7, PSA ≥ 20	60-80%
	VERY HIGH	T3b-T4	

10.4 Treatment

Treatment for prostate cancer depends on its stage, risk group, patient comorbidities, expected life expectancy, and hormone sensitivity status (metastatic disease).

Stage	Recommended Treatment
Very low risk	For life expectancy < 10yrs, observation For life expectancy 10-20yrs, active surveillance For life expectancy ≥ 20yrs, active surveillance, Radiotherapy (EBRT or brachytherapy), Radical Prostatectomy (RP)+/- pelvic Lymph Node Dissection (LND) if >2% risk of LN involvement (Roach or Partin tables)
Low risk	For life expectancy < 10yrs, observation For life expectancy ≥ 10yrs, RT alone, RP +/- pelvic LND, or active surveillance If RP + margins → adjuvant RT (preferred) or expectant management
High Risk	Radiotherapy (3DCT/IMRT with IGRT +/- brachytherapy boost) + long-term Hormone Therapy (2-3 yrs., neoadjuvant, concurrent, and adjuvant). 4-6 months of Androgen Deprivation Therapy (ADT) considered for select patients with single adverse feature with GS 6-7. Consider whole pelvis Radiotherapy. Consider RP with pelvic LND only for selects pts with low-volume disease and no fixation. Adjuvant RT +/- short term ADT for + margins or pT3 disease
Node positive	Lifelong or long-term ADT (≥ 2 yrs.) alone or combined with RT (3D/IMRT +/- brachy boost)

Metastatic	Long-term ADT or orchiectomy +/- palliative Radiotherapy +/- bisphosphonates. For hormone refractory disease, docetaxel + prednisone prolongs survival vs mitoxantrone + prednisone **Consider intermittent ADT on a benefit-risk assessment
Adjuvant or salvage radiotherapy after radical prostatectomy	Restage to determine if disease local or systemic – biopsy if local salvage options being considered. MRI may help detect nodes. Other imaging modalities controversial/limited utility in this setting. Adjuvant Radiotherapy indicated for: • Persistent local disease on imaging or biopsy • pT3 disease or + margins Salvage RT indicated for: • Rising PSA after RT Best candidates for salvage had pre-treatment low risk disease, PSA velocity < 2 ng/mL in year before diagnosis, pathologic GS ≤ 7, positive margins, negative LN, no SVI, time to PSA failure > 3 yrs. after RP, low PSA at time of salvage (<1 ng/mL) Short-term ADT considered for pts with high risk features
Residual disease or recurrence after radiotherapy	ADT or observation if metastatic or not candidate for local therapy. Surgery, brachytherapy, or cryotherapy if biopsy positive & no evidence (or low risk) of metastasis. Salvage RP provides 5-yr PSA control in 85% of pts with pre-op PSA < 4, 55% with pre-op PSA 4-10, 30% with pre-op PSA > 10. Has high risk of morbidity – incontinence (50-70%), erectile dysfunction, bladder neck contracture or stricture (15-30%)

Radiotherapy is currently not available in Eswatini

10.4.1 Chemotherapy for Prostate Cancer[24]

Chemotherapy regimens for Intermediate Risk, High Risk, and Stage IV prostate cancer are as follows:

Intermediate or High risk	Goserelin
Stage 4 – HSPC	Goserelin
	Docetaxel + Prednisone
	Zoledronic Acid
Stage 4 – CRPC	Docetaxel + Prednisone
	Enzalutamide + Prednisone
	Abiraterone + Prednisone
	Mitoxantrone

Supportive Care

- Hot flushes
  - Depot Provera 1 Amp 3 monthly if significant
- Obstructive bladder symptoms
  - Oral selective α1 blockers e.g. Alfazocin 10mg daily, Tamsulosin 0.4mg daily
- Irritative bladder symptoms
  - Oxybutynin 5mg tds PO
- Bone mineral density preservation
  - After Bilateral Orchidectomy or on Zoladex
  - Calcium 2 tabs TDS PO
  - Vit D 50 000 Units every 2 weeks PO

Caution: Discontinue if high number of lytic bone metastases i.e. risk of hypercalcaemia

- Incontinence
- Erectile dysfunction
- Psychosexual support

10.5 Survivorship and Follow-up

Follow-up post-surgery is done using PSA testing, symptomatology, and clinical examination for non-metastatic cancers. The frequency of follow-ups should be every six months for the first two years and annually for up to five years following surgery.

Metastatic patients are to be followed up by the oncologist and surgeon on an individualized basis.

24 James et al., 2015; Parker, Gillessen, Heidenreich, & Horwich, 2015

11 Colorectal Cancer

11.1 Prevention

There are no definitive methods for preventing colorectal cancer, but routine screening can detect abnormal growths early before invasive cancer develops. Healthy lifestyle choices such as a diet low in red meat and high in fruit and vegetables, plus adequate physical activity may help to reduce the risk of colorectal cancer.

11.2 Screening

Risk factors for colorectal cancer include:

- Age > 50 years
- Lifestyle factors:
  - Smoking
  - High red meat consumption
  - Sedentary lifestyle
  - Obesity, type II diabetes
  - Excessive alcohol intake
- Family history – first degree relative with history of colorectal cancer or adenomatous polyps
- Having inherited syndromes; Lynch syndrome and familial adenomatous polyposis
- Any previous history of colorectal pathology such as polyps, Crohn's Disease, irritable bowel syndrome, ulcerative colitis
- Any history of rectal bleeding
- Recurrent bowel problems including constipation or diarrhea

High risk patients:

- Family history of colon cancer, aged < 60 years
- Benign colon disease, e.g. polyps
- History of abdominal or pelvic radiation
- Previous history of colon cancer in index patient
- Having inherited syndromes; Lynch syndrome and familial adenomatous polyposis
- Inflammatory bowel syndrome

This high-risk population will be screened with scheduled colonoscopy and stool occult blood tests. The general public will not be offered routine screening. It is advised that a baseline colonoscopy at age 50 is offered.

11.3 Diagnosis and Staging

Diagnostic Category	Investigation
Biopsy	• Biopsy tissue

Pathology	• A full pathology report, no cytology required
	• Full panel of MSI proteins in young patients < 60 years:
	  ○ MLH1
	  ○ MSH2
	  ○ MSH6
	  ○ PMS2

Laboratory Tests	• Chemistry
	  ○ KFT
	  ○ LFT
	  ○ Carcinoembryonic Antigen (CEA)
	• FBC with differential count

Radiology	• Ultrasound of abdomen • CT Scan of abdomen and chest • MRI pelvis
Other	• Colonoscopy and sigmoidoscopy • Endoscopy and gastroscopy

TNM Staging Table

Tumor	
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propia
T1	Invasion of the submucosa
T2	Invasion into the muscularis propria
T3	Invasion through the muscularis propria into the perocolorectal tissues
T4a	Invasion through visceral peritoneum
T4b	Invasion or adherence to other organs or structures
Node	
N0	No lymph node metastases
N1	Metastasis in one to three lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in two to three regional lymph nodes

N1c	Tumour deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastases in four or more lymph nodes
N2a	Metastasis in four to six regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
METASTASES	
M0	No distant metastases
M1	Distant metastases present
M1a	Metastasis confined to one organ or site (e.g. liver, ovary lung, nonregional node)
M1b	Metastasis in more than one organ/site or the peritoneum

TNM, tumor, node, metastases
Adapted from the American Joint Committee on Cancer. *AJCC Cancer Staging Manual.* 7th ed. New York: Springer; 2010.

Colon Histology Post-Operative (poor prognostic factors):

Perforation/Obstruction	Tumour spill/rupture at time of surgery
Inadequate/positive margins	Inadequate/positive LN dissection (<12)
Extra nodal tumour deposits	MSI-H
T3/T4	Poor differentiation
Lympho-vascular invasion	Peri-Neural Invasion

11.4 Treatment[25]

All colon cancers must be referred for surgery and adjuvant therapy dependent on pathologic findings. Surgical intervention is to be decided by a multi-disciplinary team. Rectal cancers should be discussed in MDT, with treatment options of surgery, neo-adjuvant chemo-radiotherapy, radiotherapy, and chemotherapy. The recommend chemotherapy protocols for colorectal cancer are as follows:

First-line Advanced	Modified FOLFOX – Oxaliplatin + 5-Flourouracil + Leucovorin XELOX – Oxaliplatin + Capecitabine
Metastatic Options	FOLFIRI – 5-Flourouracil + Leucovorin + Irinotecan Cetuximab + Irinotecan 5-Flourouracil + Leucovorin FOLFIRI + Bevacizumab FOLFOX + Bevacizumab
Palliative	Irinotecan

11.5 Survivorship and Follow-up

If treated by surgery alone, the surgeon is to follow-up with colorectal cancer patients for five years. A CEA test should be done at every follow-up visit, and a colonoscopy at one-year post-surgery and every 3-5 years thereafter.

If the patient received adjuvant chemotherapy, they must be jointly followed-up by the surgeon and oncologist for eight years.

Patients under the age of 50 must be followed-up for the duration of their lifetime, and family counselling and screening are required, regardless of treatment.

25 Labianca et al., 2010

12 Palliative Care

Palliative care is important for all patients throughout their cancer diagnosis and treatment journey, regardless of cancer stage at diagnosis. Patients with advanced cancer are particularly in need of palliative care to minimize suffering when treatment may no longer effective.

12.1 Principles of Palliation

The World Health Organization defines palliative care as an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.[26]

Palliative care in Eswatini:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten or postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications

12.2 Palliative Care at Diagnosis

Palliative care at diagnosis should include a meeting with the patient and family in addition to a holistic assessment of the patient. The meeting with the family and patient is to communicate the following:

- The diagnosis or possible diagnosis
- Upcoming treatment procedures and treatment plan, ensuring the

26 WHO, 2002

patient clearly understands the purpose of each
- Education on decision making and the patient's rights regarding care
- Education on palliative care services available and how to access them (e.g. hospices, NGOs, etc.)

The holistic assessment of the patient must include evaluation of:
- Pain at diagnosis
- Other accompanying symptoms
- Assess the patient for possible psychological conditions; look out for changes in mood, and general outlook on life
- An identified support system and potential socioeconomic stressors
- Spiritual beliefs and practices

Breaking Bad News

The task of breaking bad news:
"If we do it badly, the patients or the family may never forgive us; if we do it well, they may never forget us" (Buckman, 1992).

Remember to always ask before you tell. Do not assume the patient or family has no idea about the disease process or their treatment and care preferences. It is essential to have a logical and systematic approach to sharing medical information. The **SPIKES** protocol has been shown to be effective:

1. **S**etting – physical context. The context of the interview means the physical context or setting and includes five major components: arranging the space optimally, body language, eye contact, touch, and introductions.
2. **P**erception – finding out how much the patient and/or family knows or suspects. Before providing further information, it is always important to determine what the patient knows about the medical condition and its effect on the future.
3. **I**nvitation – finding out how much the patient and/or family wants or is willing to know. This is the single most crucial step in any information-giving discussion. It is far easier to proceed with giving the news if there is a clear invitation from the patient to do so.
4. **K**nowledge – sharing medical information. Use the least amount of medical jargon to the patient and/or family to ensure the information shared is well understood. Care should be taken to avoid losing important information in translation.
5. **E**motions and **e**mpathetic responses – responding to exhibited feeling by the patient and/or family. In this entire process, do not lose

human emotional reactions. In many respects, the patient's reactions to his or her medical condition and the professional's response to those reactions define their relationship and determine whether it offers support for the patient. Therefore, the professional's ability to understand and respond sensitively to the emotions expressed by the patient is central to all communication in palliative care.

6. **S**trategy and **s**ummary – advance care planning. This stage is a two-way process that puts together the above steps, patient and/or family wishes, and the physician's medical advice. It is recommended that this is written done in duplicate, with a copy going with the patient. The patient should be clearly informed of the unlimited amount of time this plan can be changed if they so wish.

12.3 Palliative Care During Treatment

Palliative care is provided throughout treatment. Specific services to be offered are:

- Assessment of pain management and performance status:
    - Identification of side effects
    - Pain assessment
    - Symptom management
    - Medication adjustment or dose adjustment
    - Education on break through doses
- Education on non-pharmacological interventions
- Identification and education about ways to improve the quality of life of the patient – e.g. changes to the home to increase mobility
- Periodic family conferences to reassess socioeconomic stressors and spiritual beliefs and address barriers with the family
- After consulting with the treating oncologist on prognosis: counselling patient and family/caregivers on death, dying and advanced directives (e.g. wills, DNR, power of attorney)

The Dying Patient

The terminal phase of a patient's illness refers to the last few hours or days of a patient's life; the stage when death is imminent. A patient may have a recognized terminal illness for much longer, but the terminal phase may still be an unpredicted event for both family and professional careers. Care provided to the dying patient is important both for the patient – to ensure physical comfort in the face of challenging symptoms and dignity in death – and for the family – as the experience of caring for a dying family member impacts the bereavement process. The fact that patients are particularly vulnerable at this stage of their illness seems self-

evident, but it is often at this stage that care is withdrawn by the doctor with the attitude of that nothing more can be done. In fact, the patient may need more accurate assessment and management of symptoms, and especially the assurance of ongoing care and non-abandonment.

The palliative care team has a role in supporting the patient and family through the terminal phase in whatever setting the patient chooses for receiving palliative care. A patient does not need to be admitted to hospital to die. When patients are in hospital or in a nursing home, it is important that family members are given the opportunity to be present during the dying process.

Symptom Control in the Terminal Phase

1. **Rationalize regular medication**: the burden of taking many tablets should be reduced and some regular medication discontinued e.g. thyroxine, and hypertensives, vitamins.
2. **Route of administration**: as the patient deteriorates it may be difficult to administer oral medication and it is important to use alternate routes, e.g. subcutaneous, rectal. The use of a syringe driver facilitates delivery of medication essential for symptom control by continuous subcutaneous infusion. Explanation to families is important so that they understand that the deterioration of their loved one is the result of the illness and not the syringe driver.
3. **Planning care**: it is important to anticipate symptoms that may develop in the terminal phase so that medication to relieve these symptoms is available when required.
4. **Common symptoms in the terminal phase:**
   - Pain – regular analgesia is still needed but requirements for pain medication do not usually increase significantly.
   - Nausea and vomiting – can be reduced by regular medication: cyclizine, haloperidol or metoclopramide. Haloperidol is commonly used as it also reduces anxiety and agitation.
   - Anxiety, restlessness, agitation – these symptoms can be very distressing to the family and caregivers and can be difficult to control. It is important to try and identify the cause of this distress, which may be a simple reversible cause such as urinary retention, constipation or infection.
   - Agitation and restlessness respond to benzodiazepines – valium, midazolam which are also useful for easing breathlessness and as anticonvulsants.
   - Respiratory secretions – hyoscine butyl bromide is useful in reducing excess respiratory secretions.

- Dyspnoea – this is an extremely distressing symptom; reversible causes should be determined and treated. Congestive cardiac failure should be treated aggressively. Bronchospasm can be treated by nebulized bronchodilators. Oxygen therapy is beneficial to patients with chronic obstructive airways disease but is ineffective in controlling symptoms at the end of life. Low dose morphine is useful is reducing the sensation of dyspnoea. Non-pharmacological interventions are important, such as nursing the patient in a sitting position, a draft of air blowing across the face from an open window or fan. Benzodiazepines may be required to relieve anxiety resulting from and exacerbating dyspnoea.
- Mouth care – patient may have a dry mouth because of the illness or because of drug therapy. It is important to keep the mouth clean and moist and to treat infections such as oral candidiasis. Sodium bicarbonate solution or soda water are effective as mouth washes and partially frozen drinks or chips of ice can be sucked to keep the mouth moist. Petroleum jelly prevents sore, cracked lips.
- Pressure care – special mattresses and frequent turning and lifting of the patient is important and the family needs careful explanation of the importance of preventing pressure sores. Pressure sores should be covered, and it is important to administer an extra dose of analgesic prior to dressing changes. Metronidazole can be applied locally to offensive infected ulcers.

Psychosocial Support of Patient and Family

Psychosocial support by palliative care professionals facilitates the patient and family's expression of emotional pain, fear or anger, assists in the containment of these emotions, and allows end of life tasks to be completed. The important messages that need to be conveyed at the end of life are:

1. Forgive me
2. I forgive you
3. Thank you
4. I love you
5. Goodbye

Psychosocial Support Includes

1. Pre-bereavement grief counseling
2. Emotional and practical support for the family caregivers
3. Respect of confidentiality
4. Assisting the patient and family to come to terms with changing body

image, changing roles

12.4 Bereavement Counselling

Bereavement counselling is to be provided by the psychology department. Bereavement support requires willingness to understand the cultural context and belief systems of the person concerned and conversations should be empowering to them.

Grief Language[27]

- **Loss:** is closely associated with changes in our lives. There are many types of loss. A few examples are retrenchment, rape, divorce, illness, or the death of a loved person or animal.
- **Grief:** the feelings and the physical, cognitive, spiritual and social impact of the loss.
- **Bereavement:** the process associated with loss and grief, the state of having suffered a loss and responding to the loss, the learning to live with the loss.
- **Mourning**: the expression of sorrow.
- **Unresolved grief:** the grief process is impeded or interrupted in some way over time and adjustment to the loss cannot be made.

Anticipatory Grief

When death is seen to be a probable outcome of illness, both patient and family may begin to grieve. This form of grieving is a preparation for what is seen as an inevitable future separation from loved ones. Sometimes the extremely ill person starts to separate him/herself from others before the others are ready to accept this – this can lead to problems in communication, and health professionals can support family members and help them to understand what is happening.

Possible Symptoms of Grieving

Physical	Emotional	Behavioural	Cognitive	Spiritual
Dry mouth	Numbness	Passive or very active	Denial/ disbelief, shock	
Tightness in throat/chest	Yearning	Searching	Confusion	Loss of faith
Dizziness Breathlessness	Sadness	Crying, sighing	'Am I going crazy?'	Comfort from faith

27 Parkes, 1987

Butterflies or a huge 'hole' in tummy	Anger Guilt Anxiety	Indecisiveness, sleep disturbance, changes in appetite	Sense of the presence of the person	Search for meaning
Loss of energy	Loneliness	Forgetful, social withdrawal	Preoccupation with the deceased	Changes in relationship with Divine
Loss of sexual desire	Relief	Mood swings, substance abuse		Alienation

The Process of Normal Grief

Death, loss and grief are part of the human life cycle and affect us all. The way we grieve is an individual matter and is influenced by many factors. There are many ways of grieving.

Worden's Four Tasks of Mourning (1982, 1991)

1. Task I: To accept the reality of the loss
2. Task II: To experience the pain of the grief
3. Task III: Adjust to life without the deceased
4. Task IV: to emotionally relocate the deceased and move on with life

The Helping Relationship: Bereavement Support[28]

Providing bereavement support requires experience and a good working knowledge of communication skills.

Health professionals must accept that there are no simple solutions in bereavement work. The only solution that the person grieving a loved one is looking for is to have that person back in full health. The role of the health professional – who is there to support the bereaved person – is to walk alongside, to be fully present to the other person and prepared to be a 'compassionate witness' to the pain and the longing expressed.

28 Weingarten, 2003

13 Annexes

13.1 Additional Lymphoma Treatment Protocols

The following protocols may be used if treatment available.

13.1.1 Hodgkin's Lymphoma

Regimen Name	Details
ABVD	• Each cycle 28 days long. Chemo given day 1 and 15 followed by 2-week rest before next course • LVEF >50% - Adriamycin maximum dose 450mg/m^2. Patients >60 or at risk or with low baseline need repeat ERNA or ECHO after 2nd cycle • Bleomycin test dose given with 1st dose – 0.5u IVI over 15 minutes. Patient then observed for 2 hours before giving rest of Bleomycin IMI. Bleomycin max dose 300u. Give 1g paracetamol po with Bleomycin. • Give with Kytril 1mg or Zofran 8mg IVI • Adriamycin 25mg/m^2 IV day 1 and 15 • Bleomycin 10u/m^2 IM day 1 and 15 (limit to 15mg due to ampule size for cost-saving purposes) • Vinblastine 6mg/m^2 (max 10mg) day 1 and 15 • DTIC 375mg/m^2 IV day 1 and 15

OPEC	• This regimen can be used if patient is not able to tolerate anthracyclines due to poor cardiac function or as palliation in patients relapsing after ABVD who do not qualify for or refuse ASCT
	  ○ Vincristine 1.4mg/m2 (max 2mg) IV day 1 and 8
	  ○ Prednisone 40mg po day 1-14
	  ○ Etoposide 200mg/m2 po day 1-5
	  ○ Chlorambucil 6mg/m2 po day 1-14
	• Rest period of 14 days follows the above. Can give up to 8 cycles

ChiVPP	• Based on MOPP regime. Useful for patients who require curative treatment but are not able to tolerate anthracyclines
	• Procarbazine not registered in SA but we can get MCC approval to use it. Diet sheet must be given with procarbazine
	• Course given every 28 days. Repeat until 2-3 cycles after remission. Minimum 6 cycles, maximum 8
	  ○ Chlorambucil 6mg/m^2 po day 1-14
	  ○ Vinblastine 6mg/m^2 (max 10mg) IV day 1 and 8
	  ○ Procarbazine 100mg/m^2 po day 1-14
	  ○ Prednisone 40mg po day 1-14

Burkitt Lymphoma Protocol

Diagnosis

Mostly made on histology of a node or mass, in some cases by bone marrow or even flow cytometry of ascites or pleural fluid.

Findings Classic of Burkitt

BL cells express surface IgM, Bcl-6, CD19, CD20, CD22, CD10, and CD79a, and are negative for CD5, CD23, and TdT
Medium-sized cells with abundant, basophilic cytoplasm, often containing lipid vacuoles; round nuclei with clumped chromatin and multiple nucleoli; and a diffuse, monotonous pattern of infiltration are characteristic of classic BL. 7,13A “starry sky” appearance has been described in this type of NHL because of its abundant proliferative rate, frequent apoptosis, and numerous macrophages containing ingested apoptotic tumor cells. Ki 67>95%.

Eighty percent of BL cases harbor t (8;14), resulting in the juxtaposition of the c-myc gene on chromosome 8 with IgH enhancer elements on chromosome 14 which drive c-Myc mRNA and protein production. In the remaining 20% of BL cases, translocations occurring between chromosomes 2 and 8, t (2;8) (p12;q24), or chromosomes 8 and 22, t(8;22)(q24;q11).

Work Up Before Chemotherapy

- Clinical examination
  - Exclude emergencies like airway obstruction and spinal cord compression
  - Exclude clinical features which may indicate CNS disease
- FBC, Diff

- Bone marrow aspirate and trephine with cytogenetics if not dine on histology
- HIV
- Chemistry
  - Renal function, potassium, urate, calcium, phosphate and LDH to exclude spontaneous tumour lysis or identify patients at high risk for tumour lysis.
  - Elevated liver enzymes which may indicate infiltration
- Chest x- ray
  - To exclude evidence of mediastinal disease while awaiting the CT scan
- Ultrasound abdomen if creatinine is elevated
  - To exclude obstruction of the ureters and other masses
- CT chest, abdomen and pelvis ASAP
- CT or MRI brain if any suspicion of CNS disease

Management

Manage emergencies like tumour lysis, spinal cord compression or airway obstruction urgently (see Oncologic Emergencies chapter).

- Hydration with 166ml/h if renal function and output permit
- Allopurinol 600mg stat and 300mg daily (renal function permitting)
- Citrosoda 10ml 6 hourly

Newly diagnosed patients with HIV need to be counselled and started on ARV's.

Debulking treatment

- Day one: Corticosteroids at 1 mg/kg
- Day two: Add cyclophosphamide 500mg iv and vincristine 2 mg iv
  - Check tumour lysis bloods from day one every hour depending on results

The debulking chemotherapy is pre- treatment for all patients and is not counted as part of the formal chemotherapy regimen.

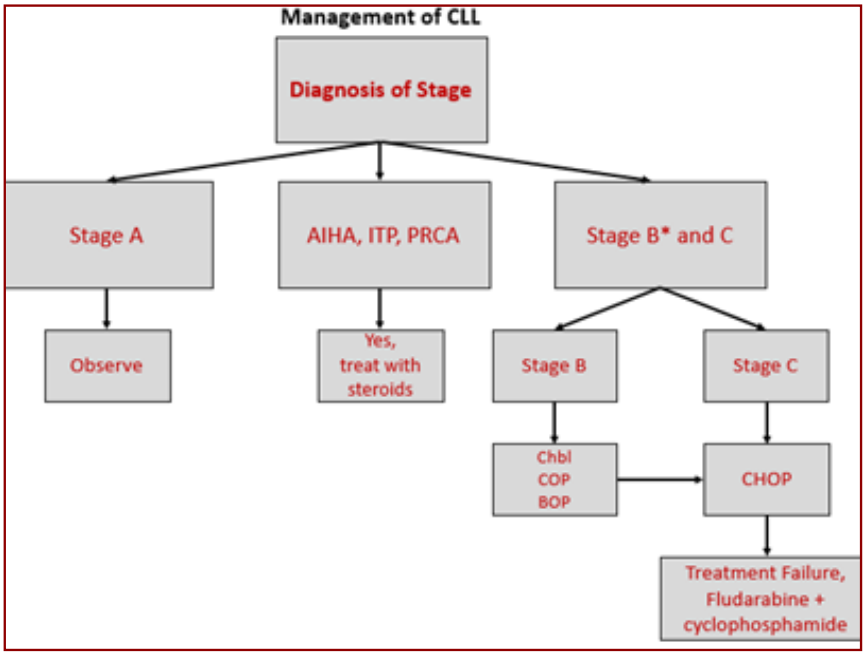
Specific Chemotherapy

NB: ENSURE THAT ANY PLEURAL FLUID OR ASCITES HAS RESOLVED BEFORE PATIENTS RECEIVE HIGH DOSE METHOTREXATE IN ANY PROTOCOL (Methotrexate can accumulate in third space fluids leading to prolonged exposure to high levels and resultant toxicity).

Type of Lymphoma	Chemotherapy
Sporadic Burkitt lymphoma	• High cure rate possible • Patients of all stages managed with either ***COPADAM/CYVE or Codox – M IVAC with 2 cycles of each***. • Due to bed pressures in F4 CODOX is currently preferred and should ideally be with Rituximab which is currently not policy for state patients yet, but can be done for medical aid and military patients
Immunodeficiency Burkitt lymphoma with CNS disease	• These patients are considered incurable and depending on performance status management can vary from absolute palliation and hospice referral from the beginning to outpatient management with ***high dose CHOP and IT chemotherapy*** or even high dose methotrexate in the ward. • Management to continue till 6 cycles of CHOP has been given or patients performance status deteriorates
Immunodeficiency Burkitt lymphoma (bone marrow does not show leukemia)	• Treated with ***Modified Milano Protocol*** • Patients will be in hospital most of the time, but weekend passes are possible when patients are not neutropenic • Staging scans must be booked for the week before the patients start the final cisplatin-based chemotherapy. • Patients should ideally be taken of Tenofovir for the cisplatin chemotherapy – discuss with ID • Please ensure hydration at 166ml/hour during cisplatin infusions and avoid any nephrotoxic drugs
Immunodeficiency Burkitt leukemia	• CODOS- M IVAC X 2 cycles each without Rituximab.

13.1.3 Chronic Lymphocytic Leukemia (CLL)

- Differentiate from PLL, mantle cell leukemia and other B proliferative malignancies.
- Stage A, B, or C.
- Presence or absence of AIHA, ITP or PRCA.



***Indications for therapy in stage B:** B symptoms, progressive lymphadenopathy > 10cm, progressive splenomegaly > 6cm, marrow failure, lymphocyte count doubling in less than 6 months.*

Intention to Treat According to Performance Status:

Clinical	Cytogenetic	Therapy 1	Therapy 2	Therapy 3
Go-Go	Normal	Flu Cy	CHOP / COP	Allo SCT
	Del 13	Flu Cy	CHOP / COP	Allo SCT
	Del 11q	Flu Cy	Allo SCT	
	Del17p	Solumedrol	Alemtuzumab	Allo SCT
Go Slow		COP / chlorambucil Cyclophosphamide	CHOP / cyclophosphamide	
No Go		Cyclophosphamide, chlorambucil		
Short response (< 12 months)	“” “”	CHOP / FND / alemtuzumab	Allo SCT	
Transformation		CHOP / FND / DHAP	Allo SCT	

Go-go: age <65, food performance status, no comorbidities, has good transport.
Go-slow: Age 65-75, or reduced performance status, no transport, some organ failure

No go: Older patient with significant comorbidity and organ dysfunction.

REGIMEN	
Oral Chlorambucil	A well tolerated drug which can be used safely in older patients In frail elderly patients a daily dose of 2-4mg can be given An alternative is to give 0.2mg /kg daliy for 4-6 weeks with adjustment according to the blood counts and response

CVP / COP	• Our first-line regimen for low-grade B-cell lymphomas and occasionally used for palliation
	  ○ Cyclophosphamide 750mg/m^2 IV day 1
	  ○ Vincristine 1,4mg/m^2 IV day 1 (max 2mg)
	  ○ Prednisone 100mg po daily day 1-5
	  ○ Antiemetic – metoclopramide 10mg IV
	• Cycle repeated every 21 days
	• Restage after 4 cycles – aim for 6 cycles (sometimes we go to 8 cycles)

GSH COP	• This regimen was developed at GSH for poor performance patients with indolent B-cell lymphomas or CLL
	• Give chemo weekly for 6 weeks followed by a rest period of 6 weeks; then repeat for 6 weeks with a second rest period of 6 weeks
	  ○ Cyclophosphamide 500mg/m^2 IV day 1
	  ○ Vincristine 1,4mg/m^2 IV day 1 (max 2mg)
	  ○ Prednisone 30mg po daily day 1-7
	  ○ Antiemetic – metoclopramide 10mg IV

Fludarabine + Cyclophosphamide (Flu-Cy)	This is the regimen of choice for younger CLL patients with a good performance status. Rituximab can be added if patients are from military hospital or have a medical aid which authorizes biological agents **NB** *Patients with creatinine clearance of < 50 need dose reduction of Fludarabine and it cannot be used at all if the creatinine clearance is <30* Fludarabine should be used with extreme caution in patients of 60 and older as severe prolonged cytopenia can occur **Days 1 – 3** Fludarabine 30 mg/ m^2/d as short iv infusion followed by **cyclophosphamide** 250 mg/m^2 over 30 minutes on the same day. • Beware tumour lysis. • Start PCP prophylaxis with co-trimoxazole or dapsone. • Neutropenia protocol (as per ALL) • Repeat every 28 days. • Modify dose for cytopenia, other toxicities • Reassess after 3 courses and continue for 6 courses if objective response.

ALL (pH negative)

Remission Induction

VAAP	Weekly for 5 weeks:
Day 1 to end of VAAP	Prednisone 60mg/m^2 orally per day for 4 weeks, reduced to 20mg/m^2 during week 5 and stop at end of week 5
Day 1 of each of the 5 weeks	Vincristine 1.4mg/m^2 (no dose capping) iv as 30 min infusion in 200 ml N saline or as 10 min iv bolus
Day 1 of each of the 5 weeks	L-asparaginase (following vincristine) 10,000 iu/m^2 (max 15,000iu) in 200 ml N saline over 1 h (check for hypersensitivity)
Day 1 of each of the 5 weeks	Adriamycin 20mg/m^2 as a rapid saline drip following asparaginase

CNS Prophylaxis

Once blasts have cleared from the peripheral blood, perform weekly lumbar puncture injecting ***cytosine arabinoside 30 mg, methotrexate 12 mg and decadron 1mg, all loaded in one syringe***. Take CSF to the Haematology lab for a cytospin – the first LP is particularly crucial to diagnose or exclude CNS involvement.

Patient should receive 5 doses of intra-thecal chemotherapy during induction. Keep record and catch up after VAAP before CEM.

Supportive Care on VAAP

Prevention/Management of Tumour Lysis

Patients with ALL, particularly with high white cell counts and bulky nodes, are at high risk for tumour lysis with potentially life-threatening hyperkalemia and renal failure. High urate and existing renal impairment indicate a particularly high risk.

Preventative measures

- Hydrate with ½ normal saline one liter 6 hourly if renal function permits
- Allopurinol 600mg stat and 300mg daily if renal function permits
- Citrosoda 10ml 6 hourly
- In discussion with consultant start treatment with steroids alone or steroids and vincristine to decrease risk of major lysis and add rest of drugs when safe
- Check tumour lysis bloods

Anti-microbial prophylaxis

Patients must remain on co-trimoxazole 2 tablets daily or Dapsone 100mg daily till treatment for the ALL is completed. The only exception is for transplant patients from stem cell infusion to engraftment.

Patients on VAAP should also be on neutropenic prophylaxis:

- Fluconazole 400mg daily
- Ciprofloxacin 500mg twice a day

Special blood product support while on VAAP

- If fibrinogen < 1.5 g/L infuse cryoprecipitate 1000-2000U
- Platelet count >50 x109/l and fibrinogen >1.5g/L are required for safe lumbar puncture. If lower transfuse with platelets and/or cryoprecipitate.

GIT complications

- Chlorhexidine mouthwash 6 hourly
- Patients must be on lactulose and monitored for the severe constipation which can occur on vincristine
- Monitor for oral and other mucositis as well as herpetic lesions.

Confirmation of remission during VAAP

Book bone marrow for day 28 – the day of 5th VAAP. If not in CR, discuss further management.

Consolidation therapy

Start with CEM1 on day 42 of induction therapy if in remission and neutrophil count >1.5 x10^9/l or as soon thereafter as granulocyte count allows. Ensure that there are no 3rd spaces (e.g. pleural effusion) and that liver and renal functions are normal.

CEM1 / 2	
Day 1-5	**Cytosine arabinoside**, 100 mg/m^2/day in 4 divided doses as continuous infusion. Bolus daily **Etoposide** 100mg/m^2/d.
Day 1	**Methotrexate** 3500mg/m^2 as 4-hour infusion.
Days 2-4	**Folinic acid (**Leucovorin**)** rescue (15mg/m^2, 6 hourly, for 2-3 days commencing 24 hours after methotrexate infusion is started. Increase dose if levels are >/=10. Methotrexate blood levels are expected to drop by 1 log each at 24 & and 48 hours of starting the drug infusion.

VCD:

3 - 4 weeks after CEM1 or as soon as neutrophils are >1.5 x10^9/l

Day 1.

Cyclophosphamide 60 mg/kg (over 2 hours)
with
MESNA 60 mg/kg in 5 divided 2 hourly doses. First dose before cyclophosphamide.

Day 2-3

Vincristine 1mg/m^2 daily continuous infusion for 2 days.

Days 1-4

Dexamethasone 25mg/m^2 ivi days one to four.

Patients are followed as outpatients after VCD.
CEM 2 given once neutrophils are >1.5 x 10^9/l after VCD

Patients who have hyperleukocytosis (white cell count > 100) must be given good hydration and hydroxyurea 3-4g twice a day to lower the white cells, but the definitive treatment is to start induction ASAP.

NB – Get ERNA result – consider mitoxantrone or other modification if ejection fraction is low.

Day 1-7

- Cytarabine at 100 mg/m2/day, given as a daily dose continuous infusion over 24 hours in 200ml 0.9% saline
- Etoposide bolus injection each of 7 days at a dose of 100 mg/m2/day over 30 minutes in 200ml N saline.

Days 1, 2, 3

- Daunorubicin 75 mg/m2/day as 30 min infusion in 200ml N saline. On completion, the line must be flushed with 100ml saline.

ERNA before consolidation – discuss dose adjustments if needed. Remember lifetime maximum dose of Daunorubicin is 500mg/m^2.

Consolidation:
Same regime as induction, except Daunorubicin 60 mg/m^2/day.

CNS prophylaxis
Administer one injection of triple intrathecal chemotherapy (cytarabine 30 mg, methotrexate 12 mg and dexamethazone 1 mL) with induction once blast have cleared from peripheral blood and one with consolidation. **NB** the CSF must be sent for cytospin.

Salvage regimen for patients requiring re-induction

FLAM
Day 1-3 Mitoxantrone 10mg/m2 ivi over 30 minutes
Day 1-5 Fludarabine 30mg/2 ivi over 30minutes
Day 1-5 Cytarabine 2g/m2 ivi over 4 hours after the fludarabine
Day 1-5 Dexamethasone eye drops (or other available steroid eye drops) 2 hourly

Please note the correct order of infusion is mitoxantrone followed by

fludarabine, followed by cytarabine.

Please make sure that patients getting high dose cytarabine have normal renal function and are monitored for any signs of cerebellar dysfunction

Patients who achieve remission with FLAM will be given a consolidation with FLAM before proceeding to high dose therapy. Please check the ERNA and consider reducing mitoxantrone dose to 8mg/m^2 if needed.

Post remission therapy

Following consolidation all patients who are in remission and have a good performance status will receive either an autologous stem cell transplant or an allogeneic transplant.
Patients with t (8;21) and inversion 16 receive an autologous stem cell transplant.

Patient with standard risk AML will receive and allogeneic stem cell transplant if they have a matched sibling donor and an autologous stem cell transplant if they do not.

Patients with secondary AML and all other poor risk AML will receive an allogeneic stem cell transplant either from a matched sibling donor or a haplo-identical donor.

13.2 Commonly Used for Chemotherapy Adverse Effects[29]

Bleomycin: allergic reaction (use 1mg test dose before first dose), pulmonary toxicity (acute pneumonitis, chronic fibrosis-400units lifetime dose for adults), fever, skin toxicity (hyperkeratosis, peeling), mucositis

Carboplatin: hypersensitivity reaction, blood count depression, nausea and vomiting, alopecia

Cisplatin: blood count depression, nausea and vomiting, tinnitus, hearing loss, peripheral neuropathy (late), renal damage (lessened with proper administration-see below), hypomagnesemia, allergic reaction

Cyclophosphamide (Cytoxan): alopecia, blood count depression, nausea and vomiting, stomatitis, cystitis (keep well hydrated), amenorrhea,

29 Chabner, 1990

sterility, late bladder cancer, SIADH

Dactinomycin (Actinomycin D): local irritant (extravasation), alopecia, blood count depression, nausea and vomiting, stomatitis, diarrhea

Doxorubicin (Adriamycin): local irritant (extravasation), alopecia, blood count depression, nausea and vomiting, stomatitis, cardiomyopathy (risk= underlying heart disease and age; keep total lifetime dose below 500mg/m^2)

Etoposide (VP-16): blood count depression, allergic reaction, hypotention, fever, alopecia

5-Fluorouracil: alopecia, blood count depression, nausea and vomiting, stomatitis, diarrhea, conjunctivitis, chest pain, hand-foot syndrome, ataxia (rare)

Leuprolide: hot flashes, impotence, gynecomastia, tumor flare

Levamisole: rash, diarrhea, nausea

Megestrol: edema, nausea, rash, hypertension, hot flashes

Methotrexate: blood count depression, stomatitis, acute renal failure

Paclitaxel (Taxol): allergic reaction, alopecia, blood count depression, nausea and vomiting, sensory neuropathy, myalgias, ventricular bradycardia, hypotension

Prednisone: insomnia, dyspepsia, hypertension, edema, euphoria, depression, hyperglycemia, osteoporosis

Procarbazine: blood count depression, nausea, flu-like syndrome, amenorrhea, sterility, hypersensitivity

Tamoxifen: hot flashes, edema, menstrual irregularities, skin rash, hair thinning, thrombosis

Vincristine (Oncovin): local irritant (extravasation), alopecia, sensory and motor neuropathy, constipation, jaw pain, hoarseness, SIADH, sterility, amenorrhea

13.3 Skin Map

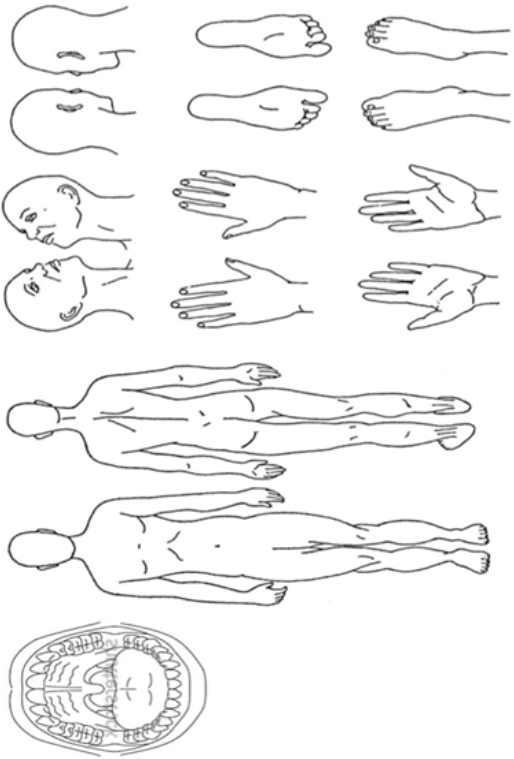
SKIN CANCERS ASSESSMENT FORM

Patient Name .....
Sex .....
DOB .....
Hospital Number.....

Date: .....

Diagnosis: .....

NOTES



Assessor's Name: .....

Signature: .....

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