Republic of Botswana

Ministry of Health & Wellness

National Guidelines for the Management of Cervical, Breast, Colon, Head & Neck Cancers

FIRST EDITION, 2020

Contents

Acronyms and Abbreviations

AJCC	American Joint Committee on Cancer
ALND	Axillary Lymph Node Dissection
BCS	Breast Conservation Surgery
CBC	Complete Blood Count
CBE	Clinical Breast Examination
CEA	Carcinoembryonic Antigen
CKC	Cold knife Conization
CMF	Cyclophosphamide/ Methotrexate/Fluorouracil
CNB	Core Needle Biopsy
CXR	Chest X-Ray
DCIS	Ductal Carcinoma in situ
ECC	Endo Cervical Curettage
ECOG	Eastern Cooperative Oncology Group
ENE	Extranodal Extension
ER	Estrogen Receptor
ESMO	European Society for Medical
EUA	European Urology Association
FBC	Full Blood Count
FNA	Fine Needle Aspiration
GLOBOCAN	Global Cancer Incidence, Mortality and Prevalence
GP	General Practitioner
GPH	Gaborone Private Hospital
HRCTV	High Risk Clinical Target Volume
IARC	International Agency for Research on Cancer
IHC	Immunohistochemistry
ITC	Isolated Tumor Cell
IUD	Intrauterine Device
LCIS	Lobular Carcinoma in situ
LEEP	Loop Electrosurgical Excision Procedure
LFT	Liver Function Tests
LMICs	Low- and Middle-Income Countries
LVEF	Left Ventricular Ejection Fraction
MDT	Multidisciplinary Team
MOHW	Ministry of Health and Wellness
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NPC	NASOPHARYNX Cancer
NRH	Nyangabgwe Referral Hospital
PMH	Princess Marina Hospital
PR	Progesterone Receptor
RFT	Renal Function Tests
RT	Radiotherapy
SBE	Self-Breast Exam
TNM	Tumor Node Metastasis
VDC	Village Development Committee
VIA	Visual Inspection with Acetic Acid
WHO	World Health Organization

Foreword

Cancer is one of the major NCDs and it is the second leading cause of death globally, accounting for an estimated 9.6 million deaths in 2018. Globally, nearly one in six deaths is due to cancer. Approximately two thirds of all cancer deaths occur in low- and middle-income countries. Around one third of deaths from cancer are due to the 5 leading modifiable behavioural risks factors: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use. Overall, the burden of cancer incidence and mortality is rapidly growing worldwide; this reflects both aging and growth of the population as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socioeconomic development. According to GLOBOCAN 2012 estimates, more African women die from cancer than from complications related to pregnancy and childbirth.

In Botswana, cancers account for 7% of all deaths. According to the population-based Botswana National Cancer Registry (BNCR), over 21, 000 adult cancers were diagnosed and registered between 2003 and 2017. An average of 1, 400 cancers are registered annually with the vast majority being diagnosed late. Some contributing factors to the incidence of cancer in Botswana are the high HIV prevalence as well as increasing life expectancy. Using data from the BNCR for the period 2003-2017, top 3 cancers diagnosed in the general population are Kaposi's sarcoma, cervical and breast cancers; top 3 cancers diagnosed in women are cervical, breast and Kaposi's sarcoma whereas Kaposi's sarcoma, esophageal and prostate cancers are the most common cancers diagnosed in men. Lastly cervical, breast, and esophageal cancers are the top 3 leading causes of cancer deaths in Botswana.Currently there are four public hospitals in Botswana that have been capacitated to provide cancer treatment. Two of the hospitals have developed Multi-Disciplinary Team (MDT) clinics offering varied services such as haematology, breast cancer, gynaecology-oncology, and palliative care services. They serve to coordinate care, provide multidisciplinary care, and provide linkages with HIV care and follow-up care. The Botswana National Essential Medicines List (EML) for cancer is 85.4% aligned with the WHO EML.

Following the development of the Botswana National Multi-Sectoral Strategy for the Prevention and Control of Non-Communicable Diseases (2018-2023), it was deemed necessary to develop the national cancer diagnosis and treatment guidelines which will serve as a tool to standardize and improve the quality of cancer care by providing evidence-based care, improving the efficiency of care, reducing inappropriate variations in practice as well as to provide more rational basis for referral. These guidelines bear a sharp focus on early detection, quality treatment, care and support. I urge all clinicians in our health care system to read and follow these guidelines across the cancer care cascade to ensure good patient outcomes.

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Acknowledgements

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PURPOSE AND CONTENT OF THE GUIDELINES

Evidence-based treatment guidelines are essential for promoting effective and economically efficient clinical care worldwide. It also facilitates program planning by the Ministry of Health and other health policy makers, monitoring and evaluation, and research for oncology programs. Effective guidelines must be tailored to serve specific epidemiologic and resource contexts.

When implemented effectively, treatment guidelines help provide consistent care and increased treatment efficacy to patients, quality standardized guidance to providers at all levels of care and makes demand for chemotherapy and other surgical and diagnostic medical supplies for oncology more predictable. Thus, national guidelines are a critical element of advancing cancer care and control in low- and middle-income countries (LMICs). This is the first set of guidelines drafted for Botswana.

Objectives

- Implement standardized national cancer control and treatment guidelines for the most prevalent cancers in Botswana

Methods

A group of experts convened to develop cancer screening, medical, pathological, surgical and radiation oncology guidelines for the most prevalent cancers in Botswana. The initial guidelines were drafted using National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), European Urology Association (EUA) Guidelines, Cape Town and Rwanda Cancer Care Guidelines, as well as relevant published literature. Oncology trained clinicians developed a first adaption for serial review by generalists and national oncologists and surgeons. Final review by international experts (medical, radiation and surgical oncologists) in each cancer site was performed, followed by a final in-country technical review meeting and formal approval by the MOHW.

Results and Content:

The current guidelines summarize expert opinions and are recommended for use at all cancer referral centers, primary care centers and district hospitals in Botswana. The recommendations are grouped under either "minimal" or "ideal". Minimal recommendations refer to screening interventions, procedures and therapy currently available in Botswana. Ideal refers to therapies that are either available only in the private sector or anticipate becoming available in Botswana in the future.

Role for Palliative Care

There is ample data to support the role and benefit of palliative care as part of oncology therapy for all cancer patients. This care modality primarily focuses on relieving suffering and improving quality of life for patients and their families, but is not curative treatment. It provides patients of any age or disease stage with relief from symptoms, pain, and stress, and should also be provided with curative treatment.

In Botswana, all patients with known cancer diagnoses or high suspicion for cancer, but with poor performance status should not be transferred to a cancer referral center. We strongly recommend phone or e-mail consultation with an oncologist prior to recommending palliative care only, as performance status can be confounded by the disease, in certain cancer subtypes. Decision-making about palliative care and hospice should be in line with current national palliative care guidelines. In the future, telemedicine will play an important role in remote clinical consultations, which will lead to decentralization and strengthening of palliative care services for cancer patients in Botswana.

Essential Package of Services for Given Cancer, By Facility Level

Level	Key Personnel	Screening, Diagnosis Treatment & follow up Interventions
Community	Health educators, VDC	• Community members' sensitization regarding cancer symptoms. SBE teaching (including practical sessions) and cervical cancer screening promotion by primary level clinicians • Patients self-refer to health posts and primary clinics
Health posts, primary clinics	Nurses, occasionally GP	• CBE for breast cancer screening performed by nurses • Refer patients with palpable breast masses or other findings concerning for cancer to district hospitals
District Hospital (primary and secondary hospitals)	GPs, nurses, in some cases specialists (internists, OB/GYN, surgeons)	• Clinical history taken, and physical exam and ultrasound performed by GPs • Refer patients with solid or complex mass to cancer specialty center for Core Needle Biopsy CNB (not FNA if complex mass or palpable nodes) • Patients with simple cysts should have follow up exam to determine stability; if highly symptomatic cyst drainage may be performed; abscesses should be drained and treated • Consider other diagnostic strategies (e.g. Ziehl-Nielsen stain) when unusual characteristics • Patient who have completed curative intent treatment are 5 years out from their initial diagnosis, should follow up annually at the district hospital
Cancer Specialty (Referral) Center – NRH, PMH, Maun, Serowe	Med Oncologist, Rad Oncologists, Pathologists, Radiologists, Internists, General Surgeons, OB/GYNs	• Ultrasound-guided core needle biopsy by trained internist, general surgeon, GP or interventional radiologist. For some cases, pathological specimen will be excisional • If negative pathology, consider repeat biopsy for patients with concerning physical exam or historical features • If positive pathology, determination of treatment plan • Provision of chemotherapy, surgery and radiotherapy • For patients who are on palliation only, referral to local district hospital for long term follow up

Booklet 1

1. Cervical Cancer Management Guidelines

1. CERVICAL CANCER MANAGEMENT GUIDELINES

1.1 Overview

Cervical cancer is the fourth most common cancer in women and the seventh overall worldwide. Cervical cancer is highly preventable and treatable if detected early. However, a large majority of the global burden occurs in less developed countries. In Botswana, cervical cancer is the most common cancer among women and represents 29% of all cancers diagnosed and 23 % of cancer associated death in women (GLOBOCAN 2012 IARC). Of the patients with invasive disease in Botswana approximately 66% are HIV positive (*Grover et al. JGO 2016).*

1.2 Screening

Refer to the appendix for existing national guidelines for screening.

1.3 Common findings at presentation

- For localized disease - cervical mass, vaginal bleeding, post-coital spotting, foul smelling discharge, pelvic/abdominal mass, pelvic and back pain, sciatica, leg swelling, renal failure
- For metastatic disease – symptoms and signs from lung (e.g. dyspnea, pleuritic chest pain), liver (hepatomegaly, jaundice), and/or bone pain (bone metastasis).

1.4 Pathology

- Diagnostic biopsy of cervical mass should be done when the mass is large enough to be visualized grossly.
- Cold knife cone (CKC) biopsy: This procedure is performed on lesions without a grossly visible lesion or concern for malignancy on Papanicolaou test, visual inspection with acetic acid (VIA) or colposcopy. CKC should be performed on all patients with microinvasive cancer on biopsy.
- Loop electrosurgical excision procedure (LEEP): The LEEP procedure is used as part of the diagnosis and treatment for precancerous lesions (CIN2/3). This procedure uses electrocautery to excise premalignant lesions.

1.5 Imaging modalities/Investigations for staging

Minimal:

- FBC (including platelets), LFT, RFTs
- HIV testing and CD4 count and HIV viral load in women with positive HIV test
- CXR
- Abdominal/pelvic ultrasound with special attention to renal tract and liver (imaging studies are optional for stage < 1B1)
- Selected skeletal x-rays and/or bone scan where indicated (clinical suspicion for skeletal metastases)

Ideal:

- CT scan of chest/abdomen/pelvis, with IV and oral contrast
- Optional - EUA Cystoscopy/proctoscopy (stage >/=1B2) if suspected invasion of the bladder or rectum

1.6 Staging

Table 1. Carcinoma of the Cervix Uteri[a] (FIGO staging-2018)

Stage	
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma, which can be diagnosed only by microscopy with deepest invasion ≤5 mm.
IA1	Measured stromal invasion of ≤3.0 mm in depth.
IA2	Measured stromal invasion of >3.0 mm and <5.0 mm in depth.
IB	Invasive carcinoma with measured deepest invasion >/= 5mm (greater than stage IA), lesion limited to the cervix uteri (largest extent of the lesion is no longer considered).
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
II	Cervical carcinoma invades beyond the uterus, but has not extended to the lower third of the vagina or to the pelvic wall.
IIA	Involvement limited to upper 2/3rd of vagina without parametrial involvement.

IIA1	Invasive carcinoma ≤4.0 cm in greatest dimension.
IIA2	Invasive carcinoma >4.0 cm in greatest dimension.
IIB	With obvious parametrial invasion, but not up to the pelvic wall.
III	The tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney [c] and/or involves pelvic and/or para-aortic lymph nodes.
IIIA	Tumor involves the lower third of the vagina with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause).
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
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.

Staging Summary (WHO):

Stage	
I	Confined to the cervix
II	Extends beyond the cervix without involving the pelvic walls or lower 1/3rd of vagina with invasive carcinoma
III	Denotes extension to pelvic walls, which may cause hydronephrosis, or invasion of the lower third of the vagina
IV	Distant disease in liver, bones, lungs or any tumor outside of the pelvis or invades the bladder or rectal mucosa

1.7 Treatment

All patients should be discussed at a multidisciplinary conference prior to therapy if available. At Princess Marina Hospital (PMH), this conference is held on Wednesday at 8am in the Women's health clinic. Referrals to this clinic can be made by sending an email to gynmdt@gmail.com or by calling +267 3621630/1634.

STAGE IA1 (No lymphovascular invasion)

- Conization only: Provided cone margins are negative (preferably non-fragmented specimen with 3mm negative margins), no vascular/lymphatic invasion, and <3mm depth of invasion, in patients wishing to preserve fertility and amenable to regular follow-up. If cone margins are positive, perform a simple hysterectomy as below.
- Perform a simple hysterectomy in patients not considering fertility-preservation options. Lymphadenectomy not required. Patients should have negative cone margins prior to undergoing simple hysterectomy in order to be sure the stage is still 1A1 (repeat cone[s] can be performed but the patient should have ≤3 mm invasion).

STAGE IA1 WITH LVSI AND STAGE IA2

- Pelvic radiation (RT) + brachytherapy (total point A dose or high-risk clinical target volume (HRCTV) 70-80 Gy), if there is high surgical risk.
- Modified radical hysterectomy and pelvic lymph node dissection.

STAGE IB1, IB2, AND IIA1

- Pelvic RT + brachytherapy (total point A dose or HRCTV: 80-85 Gy)
- Radical hysterectomy with pelvic lymph node dissection +/- para-aortic lymph node dissection

STAGE IB3 AND STAGE IIA2

- Definitive pelvic RT + concurrent platinum-based chemoradiotherapy + brachytherapy (total point A dose or HRCTV > 85 Gy)
- If diagnosed post-operatively, give adjuvant radiotherapy or concurrent chemoradiotherapy based on the SEDLIS criteria (GOG 92) and Peters criteria respectively (GOG 109).[1]

STAGE IIB, IIIA, IIIB, IVA

- Definitive concurrent chemoradiotherapy with brachytherapy (total point A dose or HRCTV > 85 Gy)
- For curative patients, transfuse to hemoglobin of 10 gm/dl.
- If patients have severe renal dysfunction and poor performance, consider palliative radiation alone or best supportive care only.

[1] See Appendix

METASTATIC DISEASE (STAGE IVB):

- All therapy is palliative. Palliative chemotherapy with paclitaxel and cisplatin can be considered after a discussion of the risks/benefits and non-curative nature of the therapy. Individualized RT may be used for pelvic disease and symptom management.

RECURRENT DISEASE:

- Restaging scans and surgical exploration in selected cases to rule out distant metastatic disease.
- If local/regional recurrence in patients with no prior RT or failure outside of previously treated field consider tumor-directed concurrent cisplatin-based chemoradiotherapy +/- brachytherapy
- In patients with previous radiotherapy, only options are chemotherapy alone or best supportive care.

1.8 Follow up

1. After curative therapy:
    - Patients should be seen initially within 3 months post-concurrent chemoradiotherapy
    - History and clinical examination every 6 months for two years, followed by every year for three additional years.
    - No pap-smears needed for follow up.
    - No routine blood work or x-rays unless clinically indicated.
    - If a suspicious lesion is noted on examination, biopsy should be done.

2. After palliative therapy:
    - History and clinical examination as clinically indicated.
    - Blood work and x-rays as clinically indicated.
    - Symptom management as needed.

1.9 Drug regimens

<u>Concurrent Chemoradiotherapy</u>

- Cisplatin
  40 mg/m2 (maximum dose of 70mg) on days 1, 8, 15, 22, 29, 36; given 4 hours before radiation

Chemotherapy for recurrent or metastatic disease

- Carboplatin/Paclitaxel
  Carboplatin AUC 5 or 6 IV over 1 hour on day 1
  Paclitaxel 175mg/m2 IV over 3 hours on day 1
  21-day cycles x 6-9 cycles
- Carboplatin
  400mg/m2 or AUC 5 or 6 IV on day 1; 28-day cycles
- Paclitaxel
  175 mg/m2 IV over 3 hours on day 1; 21-day cycle
- Gemcitabine/Cisplatin
  Gemcitabine 1000mg/m2 IV on d1, d8
  Cisplatin 50mg/m2 once on d1
  21-day cycle

1.10 Current Gaps

- Pathology services are not readily available in all locations.
- Limited capacity for imaging.

1.11 Implementation Goals

In the next year:

- Optimize utilization of tissue processing and slide scanner at NHL to facilitate turnaround of histopathological review.
- Expand MDT to centers beyond PMH.

In the next 2 to 5 years:

- CT capacity for staging (available to be used routinely for staging)
- Build more capacity for radical hysterectomy and lymph node dissection.

1.12 APPENDIX

CERVICAL CANCER HISTOLOGICAL SUBTYPES

- Squamous (70-80%)
- Adenocarcinoma (10-15%)
- Other epithelial

SURGICAL OPTIONS

- LEEP and Cold knife conization (CKC) – Goal is en bloc removal of the squamocolumnar transformation zone and lesions involving the ectocervix and endocervical canal; the shape of the LEEP/cone can be tailored to the size, type, and location of the lesion (that is narrow long cone in cases of suspected adenocarcinoma in-situ or lesions involving the canal). LEEP is the preferred approach for preinvasive disease and CKC is the preferred approach if invasive carcinoma is suspected.

- Simple/Extrafascial Hysterectomy for stage IA1 disease who do not desire future fertility.

- Modified Radical hysterectomy– Preferred over simple hysterectomy for patients with stage IA2 – IB1 disease due to its wider margin of resection that includes aspect of the cardinal and uterosacral ligaments, upper vagina, pelvic nodes and at times para-aortic lymph nodes.

- Pelvic lymph node dissection

RADIOTHERAPY OPTIONS

All treatment including brachytherapy and external beam radiation (EBRT) should be concluded within 56 days of initiation.

- Brachytherapy.
  It can be administered by intrauterine catheter, ovoid or intravaginal cylinder at high dose rate. The isotope used at Gaborone Private Hospital (GPH) is 192-Iridium.

- Concurrent chemoradiotherapy:

In patients with intact uterus

- EBRT 1.8 to 2 Gy given 5 days per week, for an initial dose of 45 Gy-50Gy
- Primary cervical tumor is then boosted using brachytherapy with an additional dose to point A or HRCTV for a total dose of 80Gy to small-volume tumors, to >/= 85Gy for larger volume tumors.
- Unresected nodes may be evaluated for boosting with an additional 10- 15Gy

Post-hysterectomy

- EBRT 1.8 Gy x 28 fractions given 5 days per week, for an initial dose of 50.4 Gy
- Unresected nodes may be evaluated for boosting with an additional 10- 15Gy

- Radiotherapy Planning

Radiation therapy is applied using the four fields technique. If CT simulator available, contour nodal volume to be treated for field borders.

- Anterior and posterior areas: Upper limit: the gap between L4-L5.
- Lower limit: the lower edge of the obturator foramina lateral limits: 2 cm outside the bone pelvic wall, according to the parametrial involvement.
- Lateral fields:
  · Anterior limit: middle portion of the pubic symphysis.
  · Posterior limit: S2-S3 (rectal half).
  · Upper and lower limits: the same limits are preserved of anteroposterior fields.

DOSE MODIFICATION AND TOXICITY

- The full blood count, serum creatinine, urea, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course of chemotherapy.

- If renal toxicity is noted, a repeat course of Cisplatin Injection should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the urea is below 25 mg/100 mL.

- Encourage patient to maintain adequate hydration 24 hours following chemotherapy.

- Delay chemotherapy for 1 week if platelet <75,000/mm3 and/or absolute neutrophil count (ANC) <1500/mm3

- If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); initiate sodium thiosulfate antidote; elevate extremity.

Anti-emetic

1. Highly emetogenic

- Cisplatin

Granisetron 3mg IV and Decadron 10-20mg ivi
Dexamethasone 4mg twice a day po 3 days + Metoclopramide 10mg 8 hourly prn + if needed Ondansetron 8mg 8hourly 3days (or 5 days if major problem). Add in prochlorperazine supps for severe nausea.

2. Lower emetogenic risk
Taxanes; Gemcitabine; 5FU

Dexamethasone 4-8mg ivi

(NB: Remember premed with Taxanes. Give Betamethasone 8mg bd 6 doses or dexamethasone 8mg at least 4 hours before treatment);

Phenergan 25mg and cimetidine pre-paclitaxel

SEDLIS CRITERIA

SEDLIS CRITERIA: ELIGIBILITY FOR CONSIDERING EXTERNAL PELVIC RADIATION AFTER RADICAL HYSTERECTOMY IN NODE-NEGATIVE, MARGIN-NEGATIVE, PARAMETRIA-NEGATIVE CASES[1,2,3]

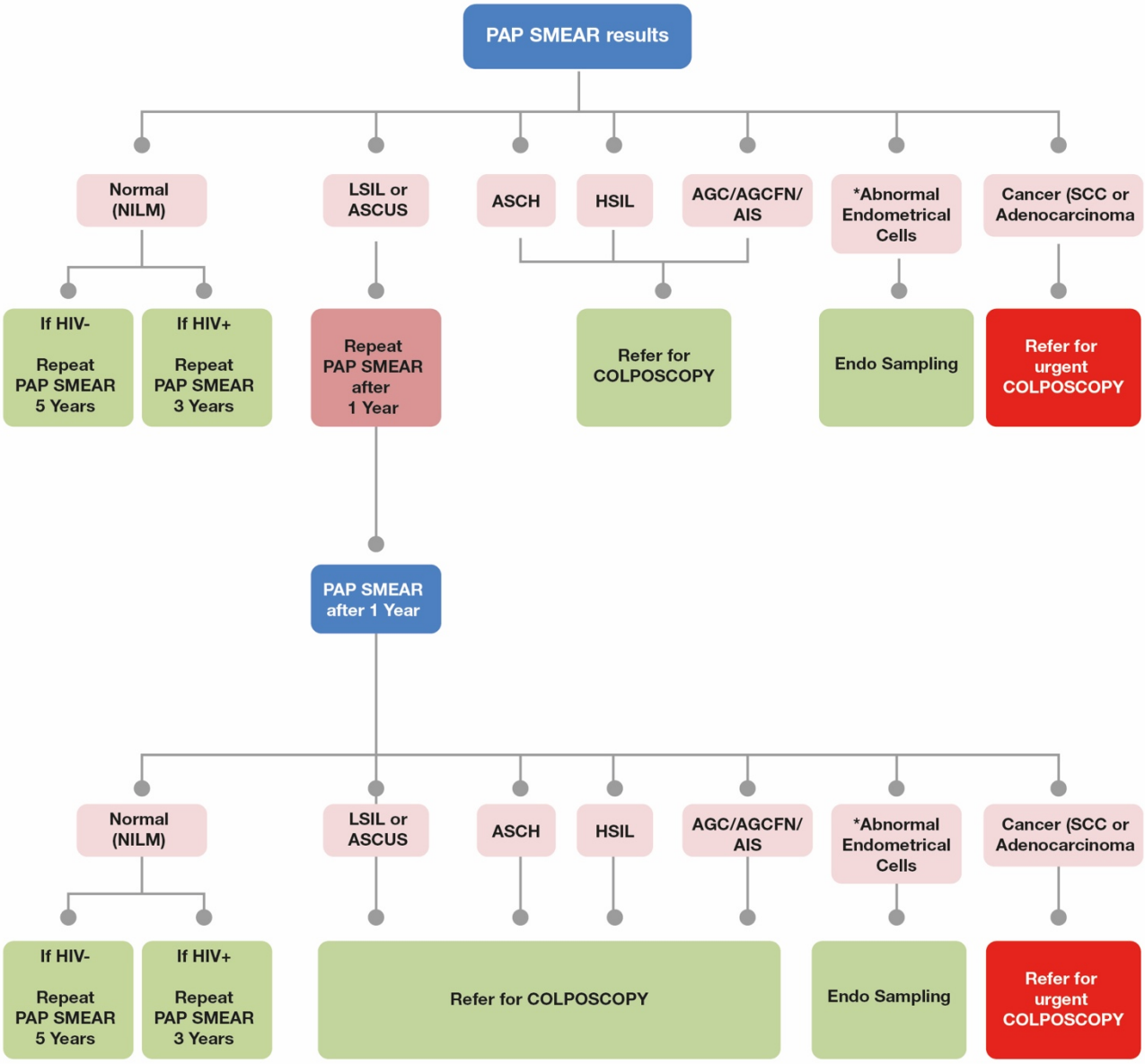
LVSI	Stromal Invasion	Tumor Size (cm) (Determined by clinical palpation)
+	Deep 1/3	Any
+	Middle 1/3	≥2
+	Superficial 1/3	≥5
-	Middle or Deep 1/3	≥4

LVSI: Lymphovascular space invasion

PETERS CRITERIA: ELIGIBILITY FOR CONSIDERING ADJUVANT CONCURRENT CHEMORADIOTHERAPY

Must meet one or more of the following criteria: Positive Margins and/or Parametria Involvement and/or Positive Lymph Nodes

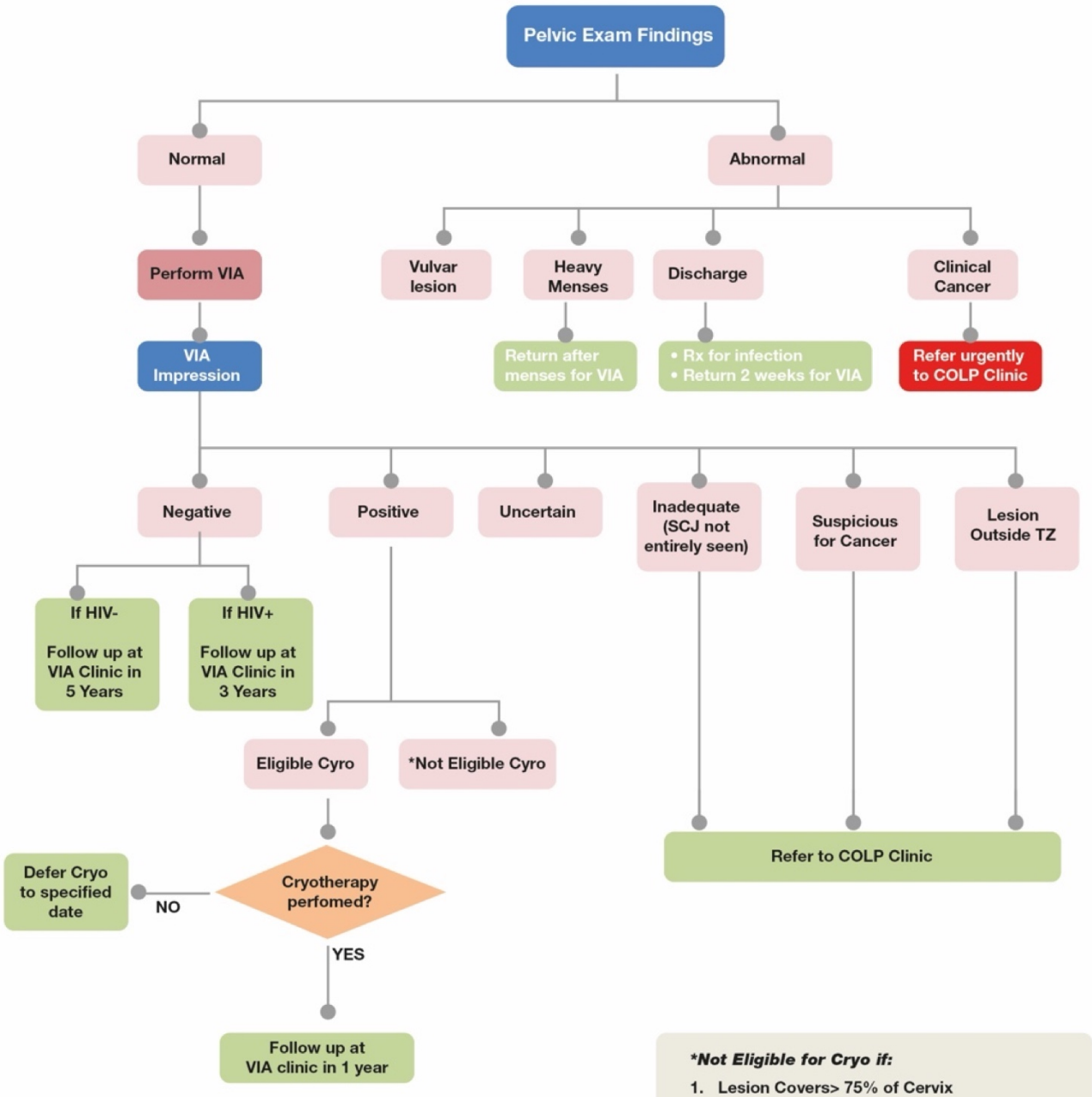
ALGORITHM #1
PAP SMEAR RESULTS - MANAGEMENT ALGORITHM



*All women with PAP Amear showing:

1. ABNORMAL ***Endometrial Cells*** regardless of age
2. Presence of NORMAL Endometrial Cells in a patient ***40 Years or Over*** should be referred for Endometrial sampling

ALGORITHM #2
VIA CLINIC: INITIAL VIA

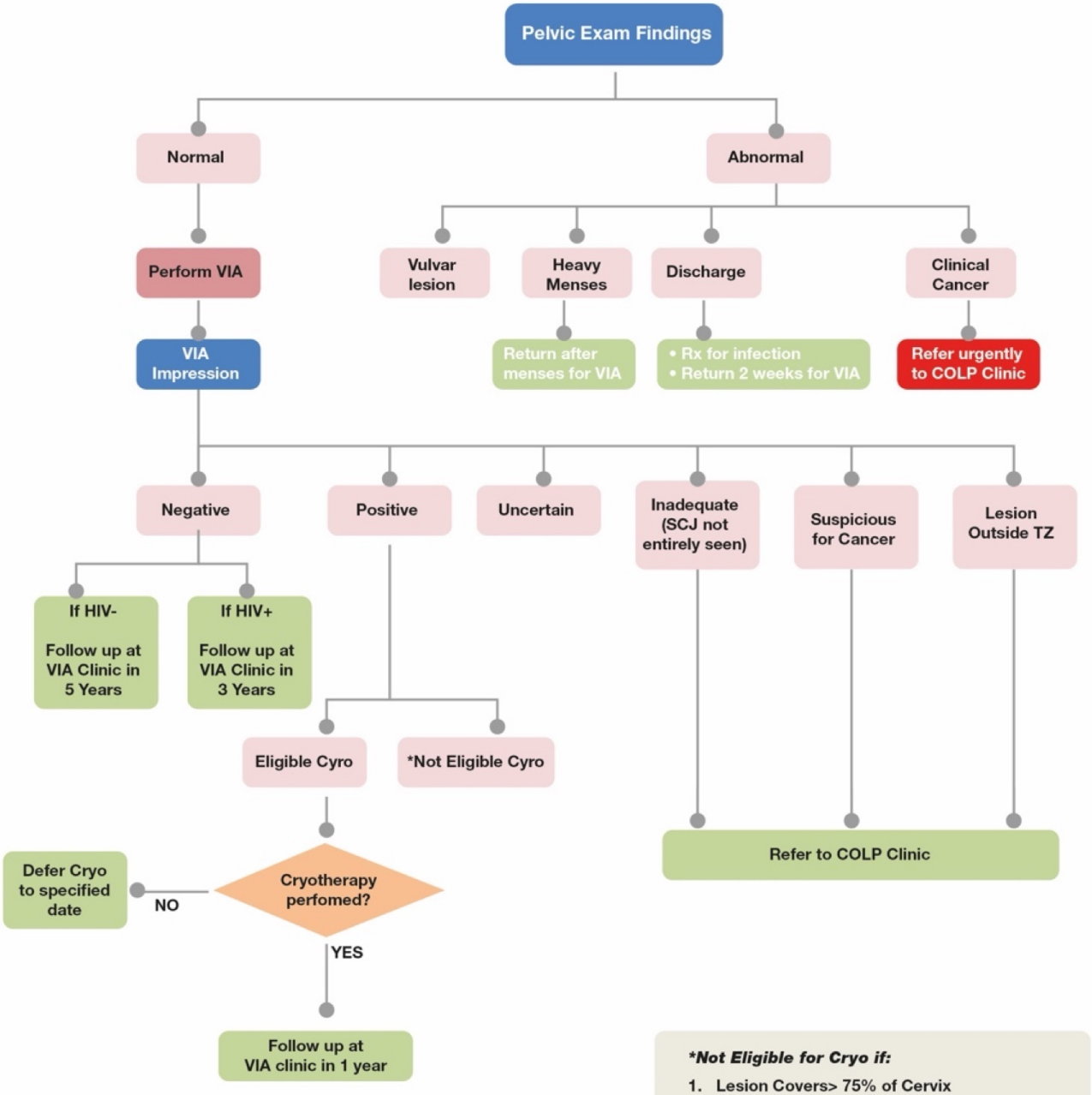


Consult if unsure at any stage.

Not Eligible for Cryo if:

1. Lesion Covers> 75% of Cervix
2. Extends into cervical os
3. Lesion too thick for cryo
4. Atypical vessels / Punctuations / Mosaicism
5. Suspicious for Cancer
6. Lesion outside TZ

ALGORITHM #3
VIA CLINIC: FOLLOW-UP VIA (including Unscheduled)



Not Eligible for Cryo if:

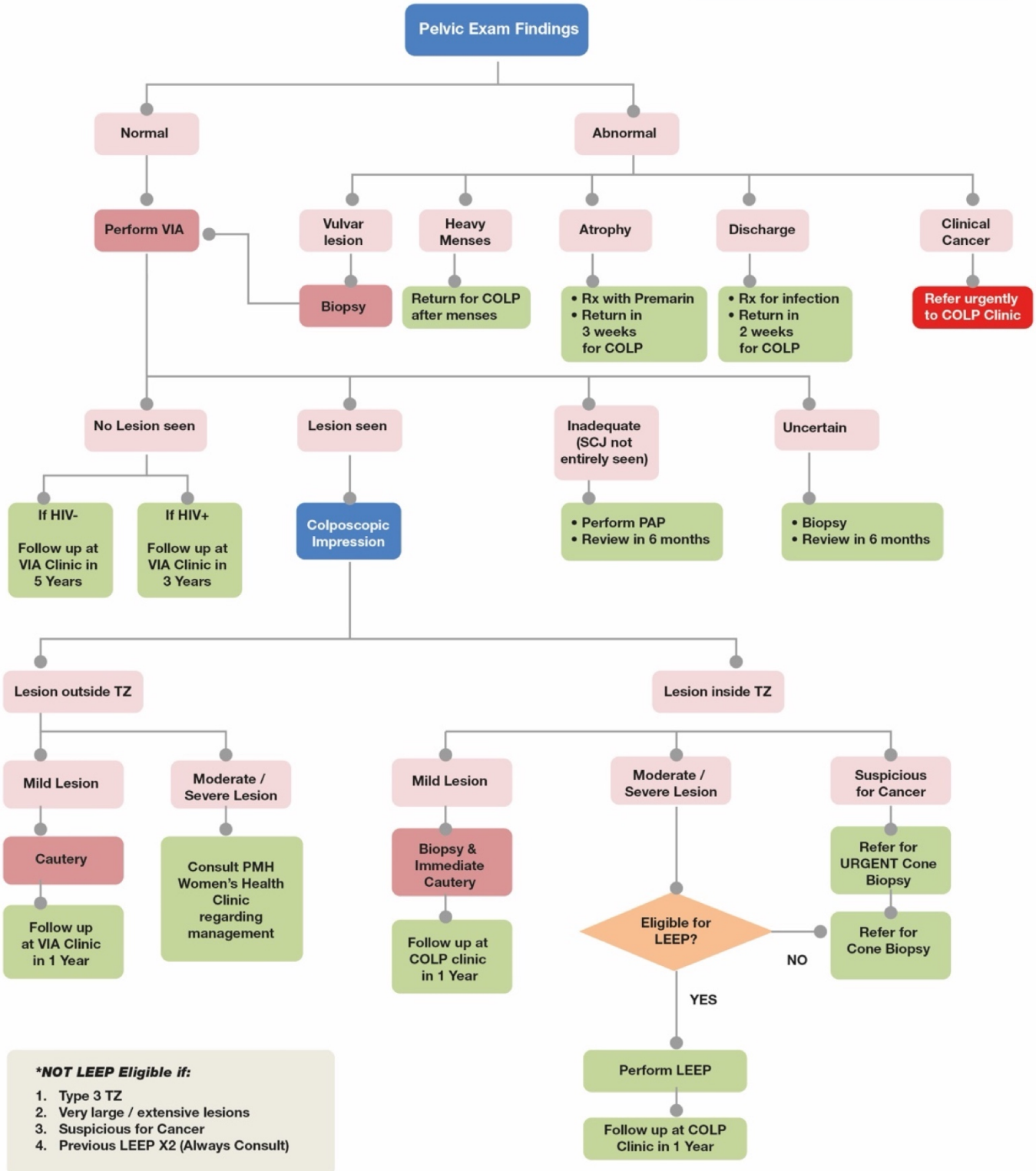
1. Lesion Covers> 75% of Cervix
2. Extends into cervical os
3. Lesion too thick for cryo
4. Atypical vessels / Punctuations / Mosaicism
5. Suspicious for Cancer
6. Lesion outside TZ
7. Previous Cryo X2 (Always consult)

Consult if unsure at any stage.

ALGORITHM #4
VIA CLINIC: INITIAL COLP (If VIA Referred)

***Perform PAP Smear** prior to Acetic Acid aplication:*

If during speculum exam, SCJ is not entirely seen. THEN, if COLP exam inadequate → send PAP.
(If adequate → discard PAP.)

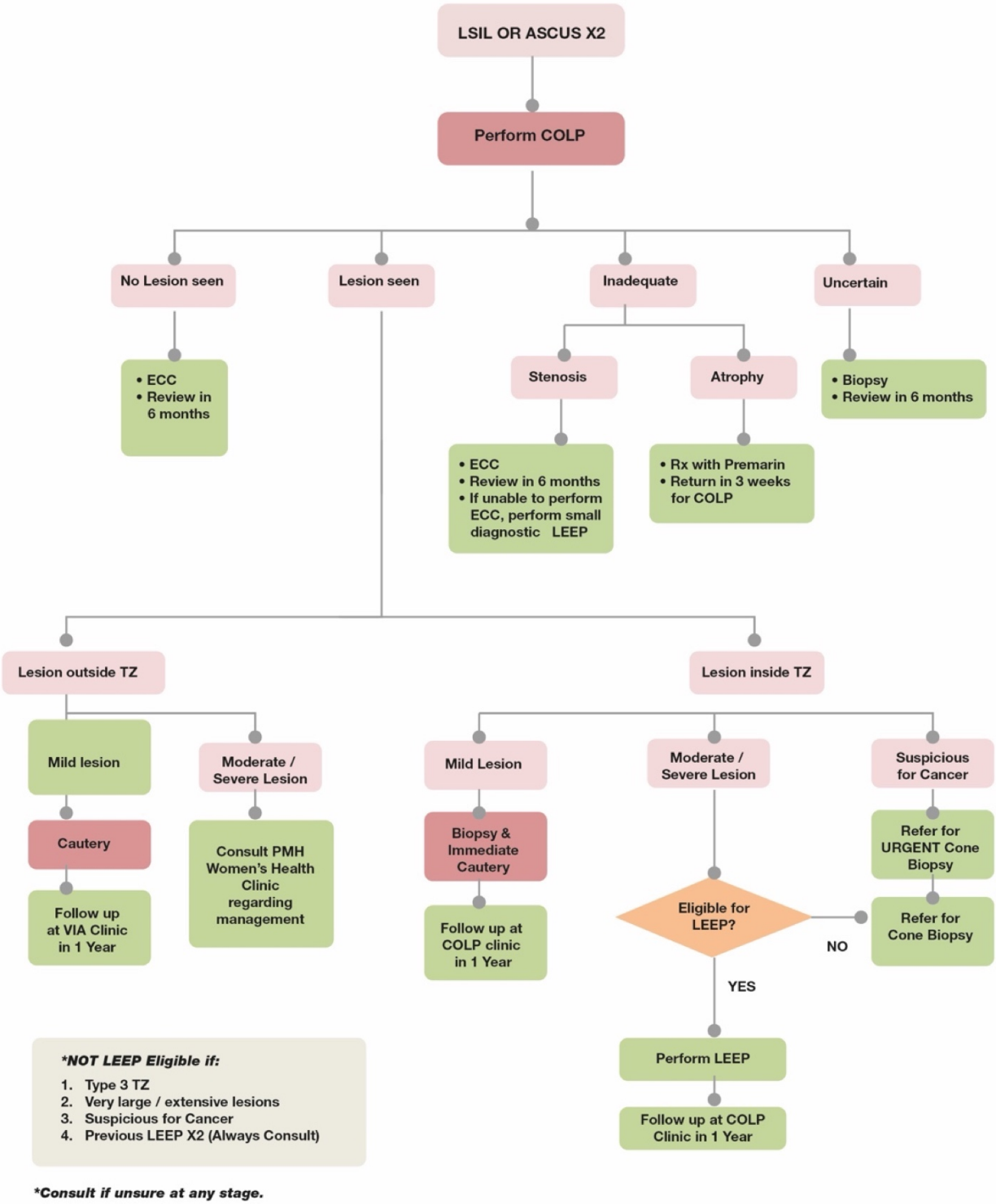


NOT LEEP Eligible if:

1. Type 3 TZ
2. Very large / extensive lesions
3. Suspicious for Cancer
4. Previous LEEP X2 (Always Consult)

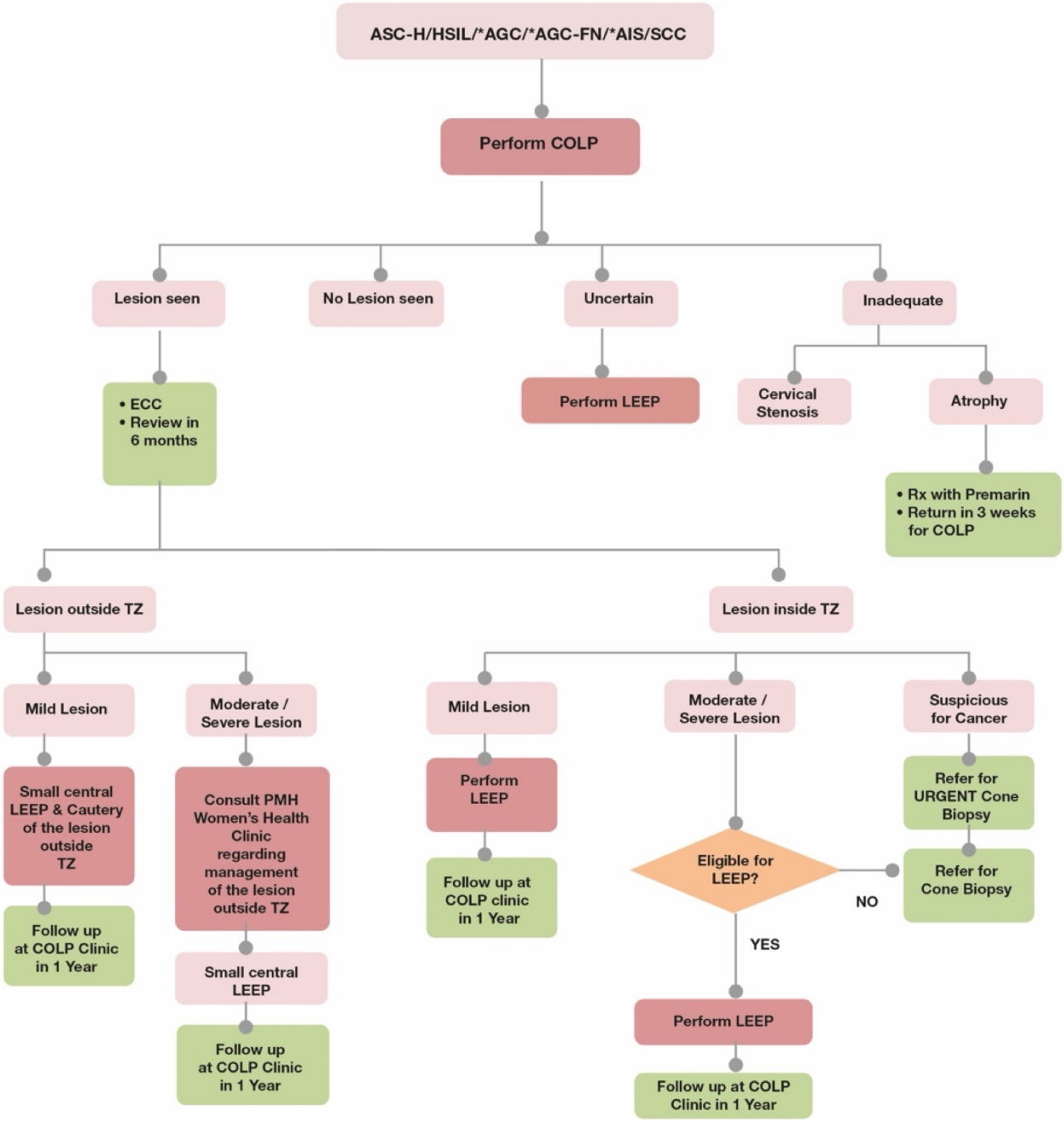
Consult if unsure at any stage.

ALGORITHM #5
COLP CLINIC: If PAP SMEAR REFERRED-LOW GRADE X2



Consult if unsure at any stage.

ALGORITHM #6
COLP CLINIC: If PAP SMEAR REFERRED-HIGH GRADE



AGC/AGC-FN/AIS:
Consultant must take place before Management decision

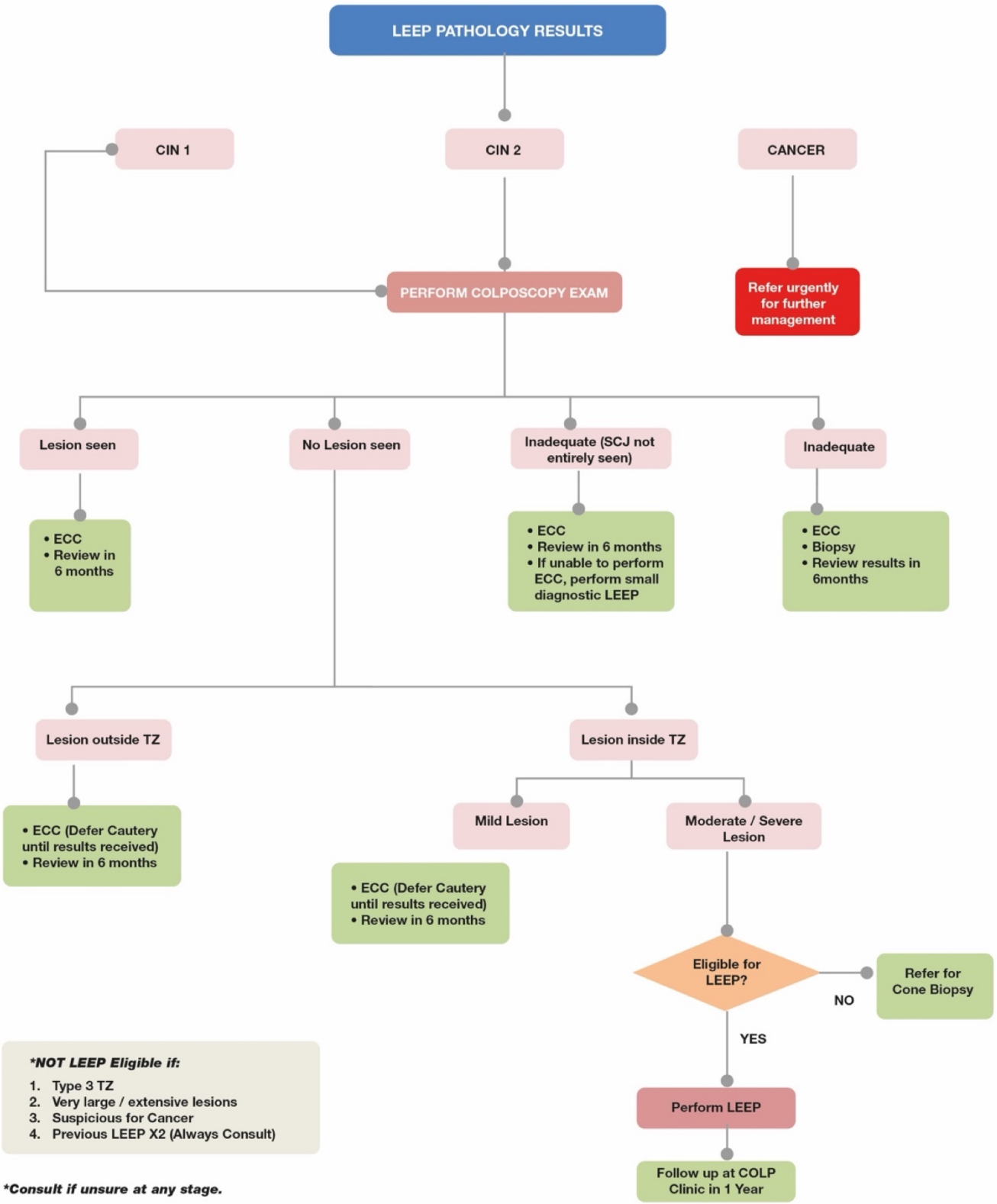
NOT LEEP Eligible if:

1. Type 3 TZ
2. Very large / extensive lesions
3. Suspicious for Cancer
4. Previous LEEP X2 (Always Consult)

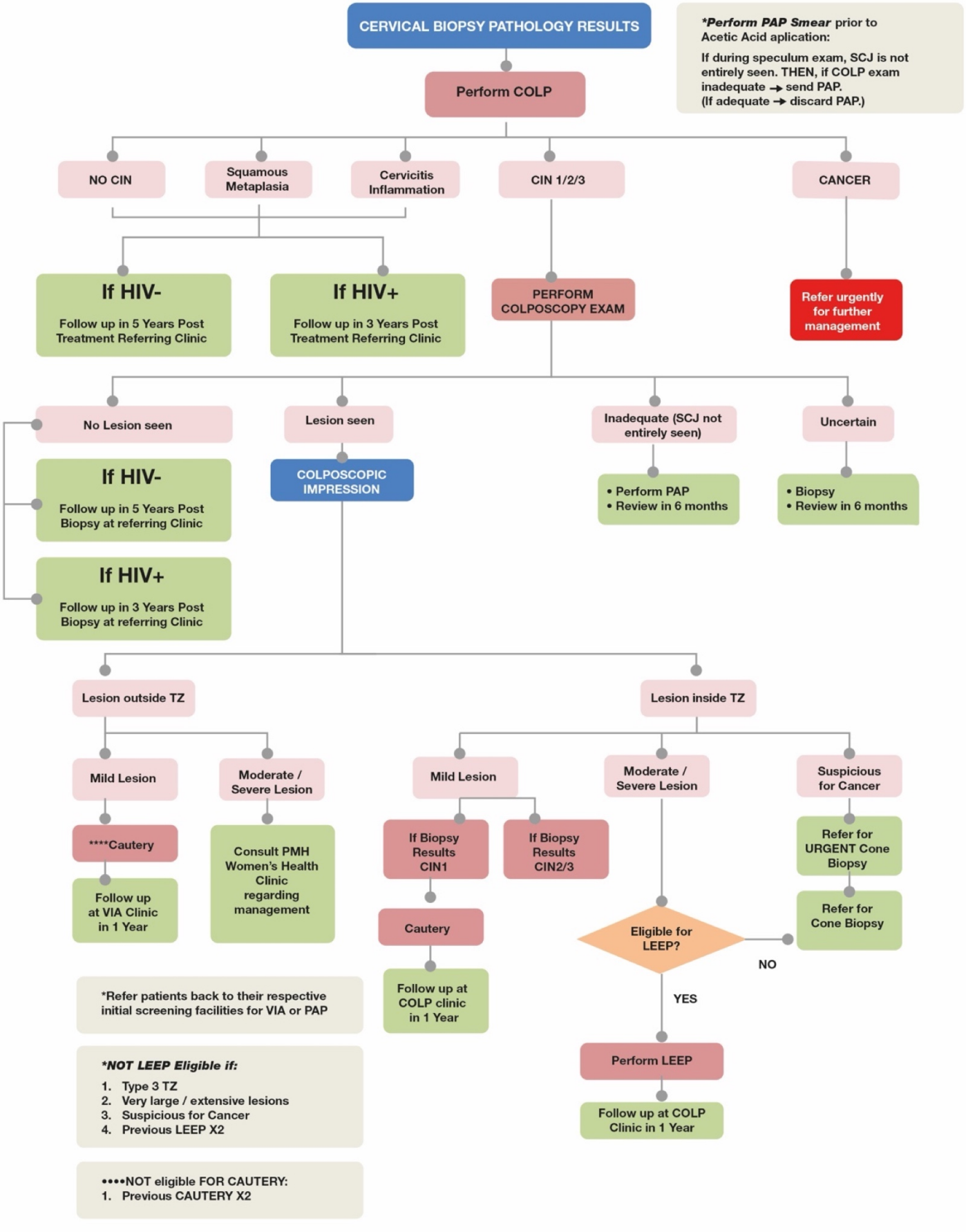
Consult if unsure at any stage.

ALGORITHM #7
COLP CLINIC: POST LEEP FOLLOW UP (CLEAR ENDO MARGINS)

ALGORITHM #7a
COLP CLINIC: POST LEEP FOLLOW UP (CLEAR ENDO MARGINS)

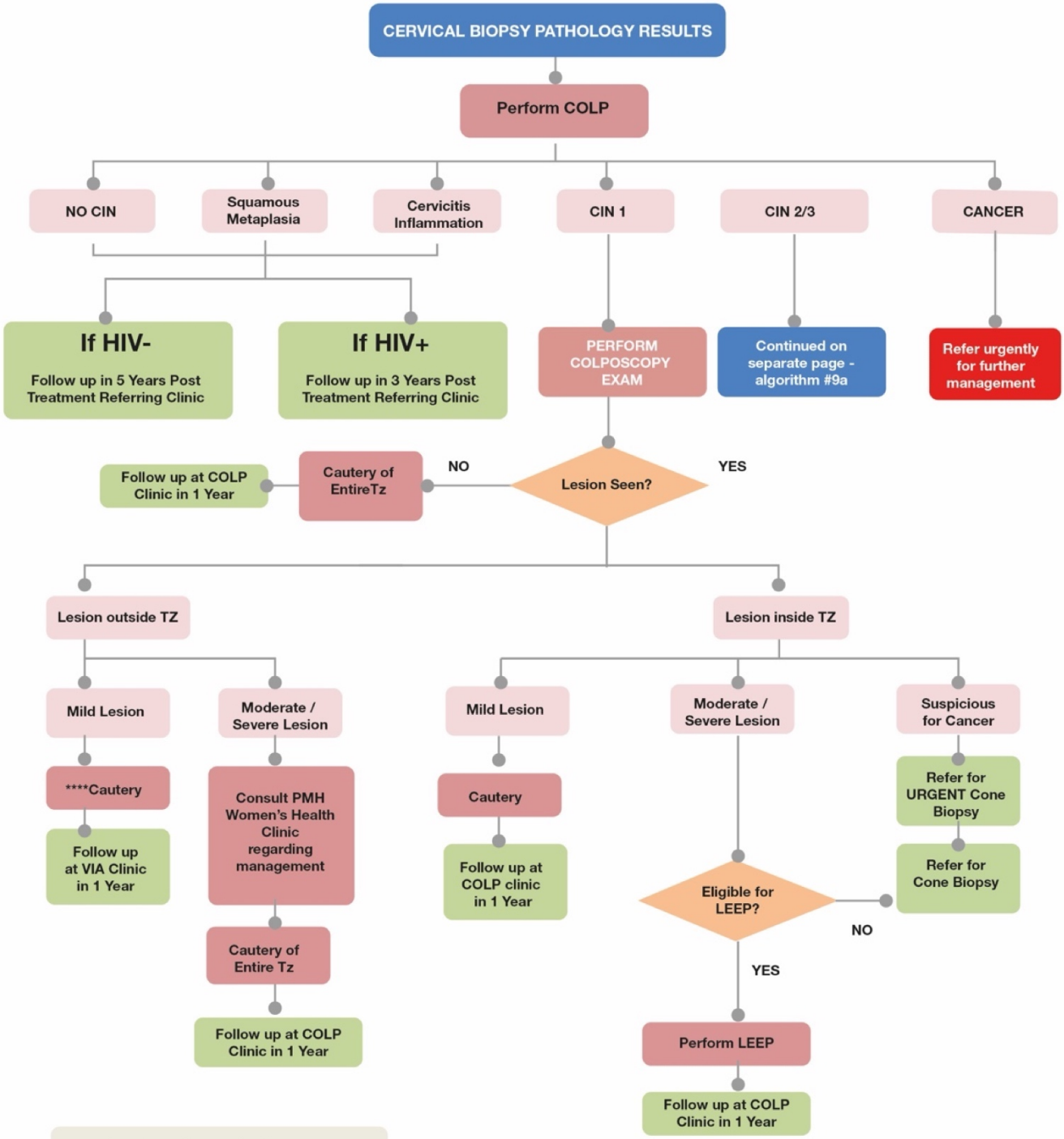


ALGORITHM #8
COLP CLINIC: POST CAUTERY - CERVICAL BIOSPY



Consult if unsure at any stage.

ALGORITHM #9
COLP CLINIC: POST CAUTERY - CERVICAL BIOSPY



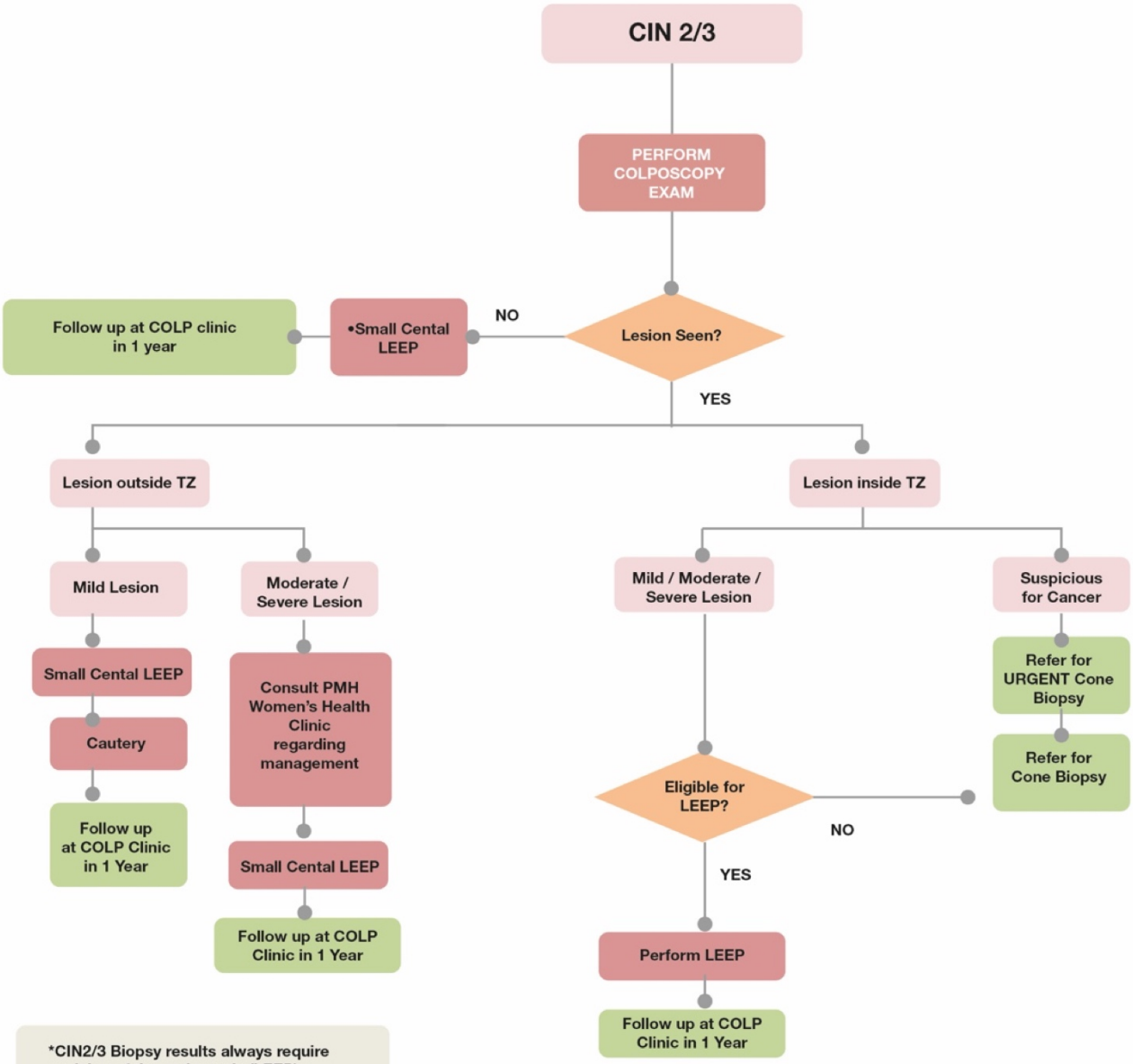
*Refer patients back to their respective initial screening facilities for VIA or PAP

NOT LEEP Eligible if:

1. Type 3 TZ
2. Very large / extensive lesions
3. Suspicious for Cancer
4. Previous LEEP X2

Consult if unsure at any stage.

ALGORITHM #9a
COLP CLINIC: POST DIAGNOSTIC - CERVICAL BIOSPY [CIN2/3]



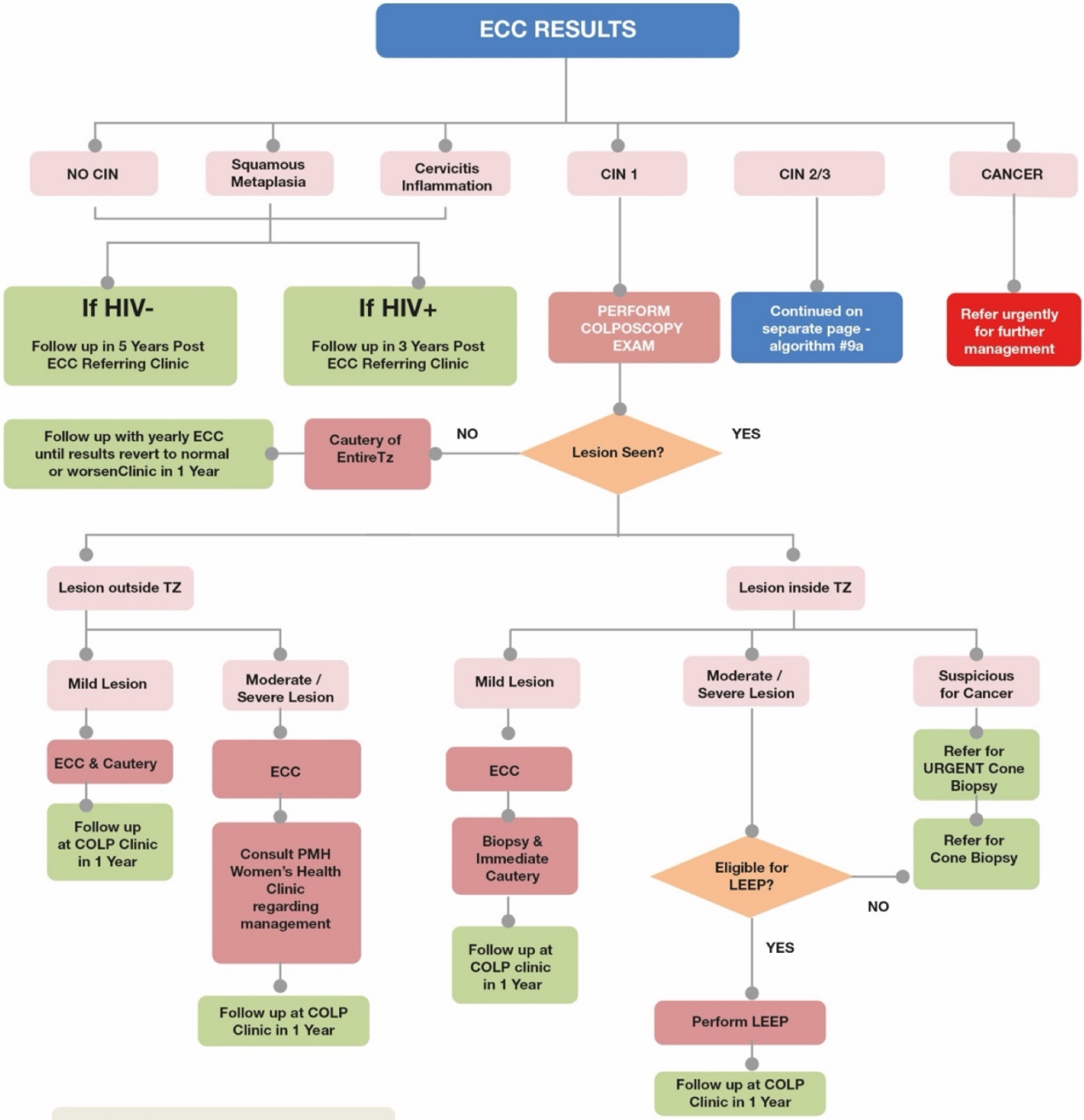
*CIN2/3 Biopsy results always require excision of the endocervix (LEEP)

NOT LEEP Eligible if:

1. Type 3 TZ
2. Very large / extensive lesions
3. Suspicious for Cancer
4. Previous LEEP X2

Consult if unsure at any stage.

ALGORITHM #10
COLP CLINIC: POST ENDO CERVICAL CURETTAGE (ECC)



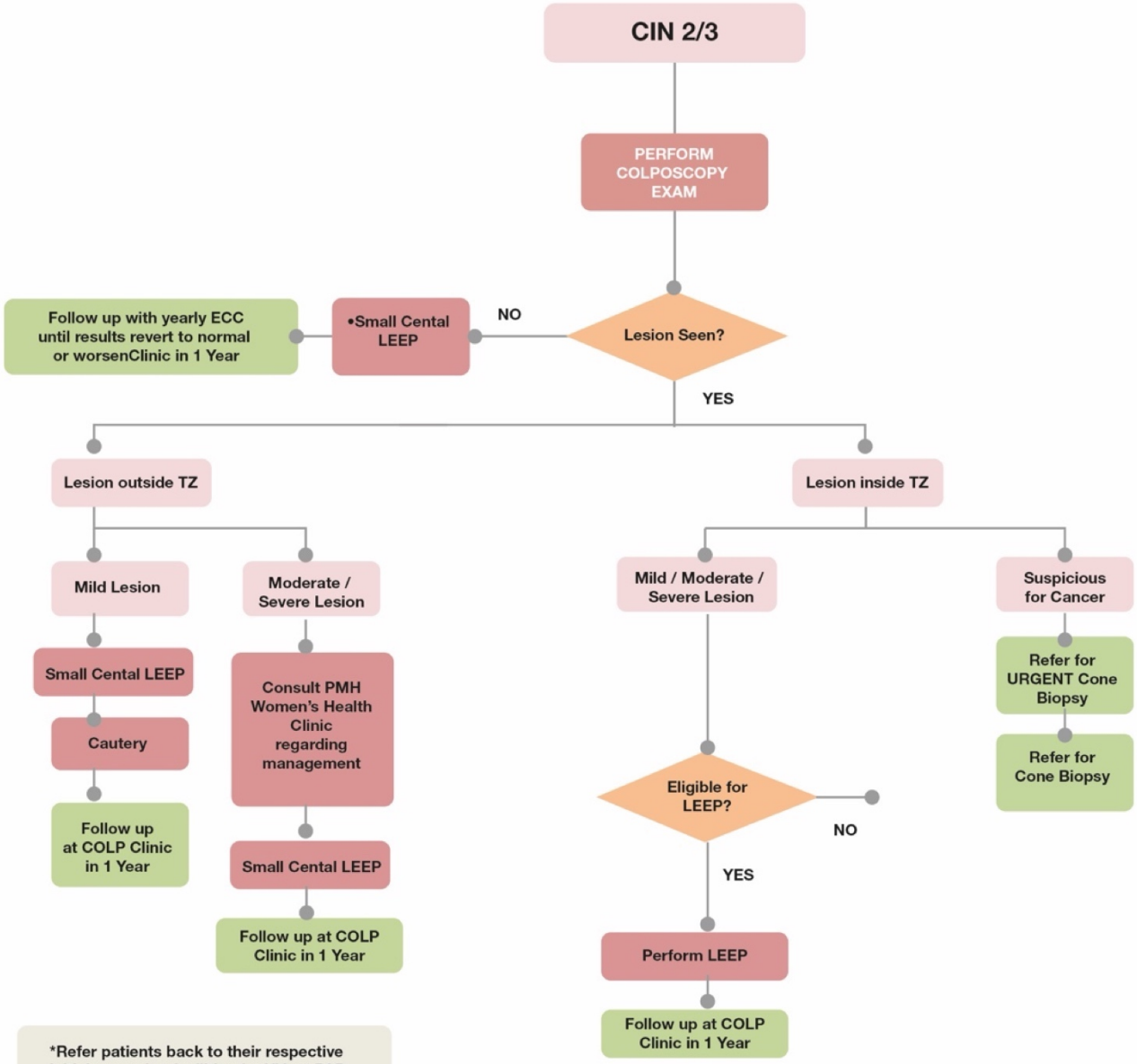
*Refer patients back to their respective initial screening facilities for VIA or PAP

NOT LEEP Eligible if:

1. Type 3 TZ
2. Very large / extensive lesions
3. Suspicious for Cancer
4. Previous LEEP X2

Consult if unsure at any stage.

ALGORITHM #10a
COLP CLINIC: POST ENDO CERVICAL CURETTAGE (ECC) [CIN2/3]



*Refer patients back to their respective initial screening facilities for VIA or PAP

NOT LEEP Eligible if:

1. Type 3 TZ
2. Very large / extensive lesions
3. Suspicious for Cancer
4. Previous LEEP X2

Consult if unsure at any stage.

Booklet 2

2. Breast Cancer Management Guidelines

BREAST CANCER MANAGEMENT

2.1 Overview

Breast cancer is the most common cancer affecting women worldwide, with nearly 1.7 million new cases diagnosed in 2012. This represents about 12% of all new cancer cases and 25% of all cancers in women. In Botswana, the incidence and mortality attributed to breast cancer has been on the rise. Breast cancer is the second most common cancer (second to cervical cancer) among women in Botswana and represents 9.5% of all cancers diagnosed in Botswana and 18% of all cancers diagnosed in women. Breast cancer accounts for 12.5% of cancer associated deaths in women. (GLOBOCAN 2012 IARC).

2.2 Screening

Screening should be offered to any average risk patient aged >30 years or increased risk patient >/= 25 years, or aged 10 years younger than the age of diagnosis of an affected first degree relative.*[2] The earlier screening age is supported by Botswana National Cancer Registry Data (1998-2009), which shows that 5% of breast cancers occur in women <30 years and 15% in women aged 30 – 40 years. Women are at increased risk if they have three or more risk factors – i.e. personal history of cancer or benign proliferative breast diseases, previous thoracic radiation, significant family history*, suggestion of familial history of cancer and known genetic mutation (Mcpherson et al. BMJ. 2000 Sep 9;321(7261):624-8). If a patient has symptoms, this is no longer a screening case and the clinician should refer to the diagnosis algorithm.

Botswana does not currently have a national screening program in place. However, the Ministry of Health (MOH) is exploring opportunities for implementation of a national screening program for breast cancer. This will encompass annual screening mammograms for women age 50-74, or starting at age 40 or 10 year less than the earliest diagnosed relative for patients at high risk of breast cancer.

Minimal

1. Clinical Breast Exam (CBE) performed by primary healthcare providers at the primary care level. Refer to "breast cancer screening" algorithm in appendix for age and frequency of screening guidelines stratified by risk status.
2. Teaching of patients to perform self-breast exam (SBE) by primary healthcare providers
3. All female patients should be counseled on breast awareness, and to return to health facility if they develop any symptoms (even if occurs before their next screening assessment is due)

Ideal

4. Screening mammography for women aged 50 – 74, may be performed at Private facilities that have the capacity to screen and follow-up abnormal mammograms. Women at higher risk could start screening at 40.

[2] *A woman's risk of breast cancer is two or more times greater if she has a first degree relative (mother, sister, or daughter) who developed the disease before the age of 50, and the younger the relative when she developed breast cancer the greater the risk.

2.3 Common findings at presentation

1. For localized disease - breast mass, axillary adenopathy
    a. For inflammatory breast cancer – enlarged breasts, warmth, edema, peau d'orange skin changes, erythema and induration

2. For metastatic disease – symptoms and signs from lung (dyspnea, pleuritic chest pain), liver (hepatomegaly, jaundice), bone (bone pain) or brain metastases (headache, focal neurological exam)

2.4 Investigations

Minimal

1. Imaging:
    a. Diagnostic mammogram OR dedicated breast ultrasound. If mammogram is not available, an ultrasound should be obtained (see ultrasound guidelines for palpable mass). If there is a palpable mass and mammogram or ultrasound are not available within 4 weeks, proceed with biopsy and the patient should be referred to surgery after diagnosis is confirmed.

    b. Imaging modalities for staging should include CXR and abdominal ultrasound (for stage III and/or abnormal LFTs).

    c. If ultrasound and CXR are abnormal. Consider follow-up imaging with CT of the Chest, Abdomen and Pelvis, however this should not delay initiation of therapy.

    d. Include CT head and/or MRI brain if patient has any symptoms suggestive of brain metastases. Symptoms include headaches, seizures, visual changes and altered mental status.

    e. If patient has bone pain or elevated alkaline phosphatase, staging should also include skeletal survey or local X-ray for bone pain

    f. Obtain a baseline echocardiogram if plan for combined anthracycline-based chemotherapy and trastuzumab (Perez et al. JCO 2004; 22(2):322-329, Guarneri et al. JCO 2006; 24(25):4107-4115). A cardiac echocardiogram is not routinely required for patients receiving anthracycline-based chemotherapy alone, unless there is clinical suspicion for underlying cardiac disease.

2. Biopsy/Pathology:

    1. Core needle biopsy (CNB) of the breast, is the diagnostic biopsy procedure of choice. This may be performed with or without ultrasound image guidance. It allows adequate histology to evaluate in situ vs invasive disease, and to assess estrogen receptor (ER), progesterone receptor (PR) and HER2 status. FNA is less optimal, but may be used when core needle biopsy is not available.

2. Surgical excisional biopsy can be performed if core needle biopsy and FNA are not readily accessible. However, this requires more resources and it is invasive and should only be performed only if alternative methods of biopsy are not available. **A mastectomy or lumpectomy should not be performed until a histological diagnosis has been established.**
3. ER, PR, HER2 testing should be obtained on all samples. HER2 testing is currently performed by IHC only in the public sector. Patients with HER2 3+ by IHC are regarded as positive. HER2 2+ is equivocal and should be sent for FISH, and HER2 0, 1+ are regarded as HER2 negative.

3. Labs:

    a. Complete blood count (CBC), liver function tests (LFT)

    b. Pregnancy test for pre-menopausal women

Ideal

1. Diagnostic mammogram AND dedicated breast ultrasound for workup

If bone disease is suspected, a bone scan instead of skeletal survey is ideal.

2. The routine use of magnetic resonance imaging (MRI) of the breast is not indicated except under the following circumstances:

    a. If there is major discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
    b. If breast density precludes accurate mammographic assessment and Breast Conserving Surgery is being actively considered
    c. To assess the tumor size, or presence of multifocal or multicentric disease if breast conserving surgery is being considered, especially for invasive lobular cancer. Although there it has not been shown that use of MRI to facilitate local-therapy decision-making has recurrence of survival benefit (Houssami et al. JCO 2008; 26:3248-3258)
    d. For patients with prior mediastinal RT before age 30
    e. Node positive disease with no obvious breast lump (occult primary)
    f. Paget's disease

2.5 Pathology Assessment and Reporting

1. Report type of procedure, i.e., excision, simple mastectomy, modified radical mastectomy, lymph node dissection

2. Report the largest focus of invasive carcinoma, and characteristics of additional foci of invasive carcinoma and DCIS for multifocal disease. The T classification pertains to the largest focus of invasive carcinoma. The size of all specimens in 3 dimensions should be reported.

3. Report should include histologic subtype, histologic grade, lymphovascular invasion and perineural invasion

4. Margins should be evaluated on all surgical specimens. Orientation of the surgical specimen, description of the gross and microscopic margins status is required for optimal margin evaluation. All reports should include distance, orientation and type of tumor in relation to the closest margin.

5. ER, PR and HER2 status should be reported for all samples of invasive breast cancer.

6. The total number of nodes assessed, including size of metastases, extranodal (or extracapsular) tumor invasion should be reported.

7. Treatment effect should be documented for patients who received preoperative therapy, and designated with "py" prefix

2.6 Staging

Staging is based on the AJCC TNM classification, 8th edition 2017. See appendix for full staging.

1. **Stage I:**
    a. tumor < 2 cm, no palpable lymph nodes or distant metastatic disease

2. **Stage II:**
    a. No evidence of primary tumor, and metastatic ipsilateral axillary lymph nodes (based on clinical exam)
    b. Tumor > 2 cm and/or metastatic ipsilateral mobile axillary lymph nodes
    c. Tumor > 5 cm, no palpable lymph nodes

3. **Stage III:**
    a. Tumor > 5 cm with metastatic lymph nodes
    b. Tumor involving the skin or chest wall
    c. Fixed or matted axillary lymph nodes
    d. Metastatic lymph nodes above or below the clavicle
    e. All inflammatory breast cancers are at least T4 and stage III

4. **Stage IV:**
    a. Distant metastatic disease (tumor spread to other organs) – bones, liver, lung, brain, etc

2.7 Treatment

General considerations for treatment

Clinicians should discuss fertility wishes with all premenopausal female patients and ensure adequate contraception on chemotherapy, ideally non-hormonal contraceptive (IUD). Pre-menopausal patients at risk for pregnancy should have a negative pregnancy test prior to initiating chemotherapy.

All new breast cases must be discussed at multidisciplinary team including oncologist, surgeon and pathologist. Patients coming from the Northern region should be referred to Nyangabgwe hospital, while patients from the Southern region of Botswana should be referred to Princess Marina Hospital. Patients in the regions of Serowe and Maun can be treated in these respective hospitals if an oncologist is on site. Over time, with increase in the capacity to provide palliative care locally, patients with end stage disease will not need to be referred to these facilities. This will be reassessed and implemented at a later stage.

EARLY STAGE DISEASE: ADJUVANT SYSTEMIC THERAPY

ER and/or PR Positive / HER2 negative

Adjuvant chemotherapy followed by adjuvant endocrine therapy. Consider (or discuss in tumor board) hormone therapy alone in patients with well-differentiated/low grade lobular carcinoma with tumor size <3cm, who have undergone an adequate node assessment by complete axillary dissection and are pathologically node negative.

Adjuvant chemotherapy

First line – Doxorubicin/Cyclophosphamide. In most patients with HER2-negative, estrogen receptor positive disease, addition of paclitaxel following administration of doxorubicin/cyclophosphamide mainly offers benefit in node positive disease Dose dense, i.e. dad-T is not administered as first line because there is no reliable access to GCSF.

1. Preferred first line for elderly (women > 70 years) and patients with Ejection Fraction (EF) <40% is Cyclophosphamide/ Methotrexate/Fluorouracil (CMF) or Docetaxel-cyclophosphamide.
2. See "Section B: Drug Regimens" for other permissible regimens below only if first line not available
3. PREDICT BREAST CANCER ONLINE TOOL: this can be used to assess post-op survival benefit with addition of chemotherapy, hormonal therapy or transtuzumab.

Hormonal therapy: premenopausal at diagnosis

1. Tamoxifen for 5 years
2. Consider ovarian ablation or suppression. This can be performed surgically with BSO, radiation therapy or medically with GNRH agonists. This has been shown to be of most benefit in patients with high-risk disease also treated with chemotherapy (results from SOFT and TEXT trials)
3. If remains still premenopausal after initial 5 years of tamoxifen. Consider tamoxifen for an additional 5 years, to complete 10 years of therapy
4. If postmenopausal after 5 years of tamoxifen, switch to aromatase inhibitor if available in patients with high risk disease, ie. increased number of positive lymph nodes. May also consider an additional 5 years of tamoxifen to complete 10 years of therapy (Davies et al. Lancet 2013;381(9869):805-816)

Hormonal therapy: postmenopausal at diagnosis

1. Tamoxifen
2. Aromatase inhibitors for 5 years
3. Women with a contraindication to aromatase inhibitors, or who are intolerant of the aromatase inhibitors should take tamoxifen for 5 years and consider an additional 5 years to

complete 10 years of therapy

ER and/or PR Positive / HER2 positive

Adjuvant chemotherapy regimens

1. Preferred first line regimen is AC followed by Paclitaxel plus trastuzumab (AC-TH)
2. Docetaxel/Carboplatin/Trastuzumab may also be used if available.
3. Other regimens if first line therapy not available
    a. AC followed by Docetaxel plus trastuzumab
    b. Docetaxel/Cyclophosphamide plus trastuzumab
    c. Paclitaxel plus trastuzumab (for N0 disease with T not greater than 3 cm)
4. Trastuzumab should be given three weekly to complete 1 year of therapy
5. Initiate adjuvant hormonal therapy following completion of chemotherapy. Hormonal therapy (and radiotherapy if needed) can be given concurrently with Trastuzumab
6. See Adjuvant endocrine therapy guidelines as above

ER and/or PR negative / HER2 positive

Adjuvant chemotherapy regimens

1. Adjuvant chemotherapy regimens with Trastuzumab as above.

Adjuvant hormone therapy – not indicated

ER and/or PR negative / HER2 negative (Triple Negative Breast Cancer)

Adjuvant chemotherapy

1. Preferred first line – Doxorubicin/Cyclophosphamide followed by Paclitaxel (AC-T) as above

Adjuvant hormone therapy – not indicated

LOCALLY ADVANCED DISEASE OR INOPERABLE DISEASE

Neoadjuvant chemotherapy is given prior to surgery. Administer all chemotherapy prior to surgery. If progressing while on adjuvant chemotherapy consider surgery and adjuvant radiotherapy. Hormone receptor status and HER2 testing should be performed on initial biopsy prior to or during initiation of neoadjuvant chemotherapy.

HER2 negative disease

Neoadjuvant chemotherapy

Preferred first line – Doxorubicin/Cyclophosphamide followed by Paclitaxel (AC-T) given prior to surgery. See "drug regimens" section for list of acceptable alternative regimens.

HER2 positive disease

Neoadjuvant chemotherapy regimens

1. Preferred first line regimen is AC followed by Paclitaxel plus trastuzumab (AC-TH)
2. Trastuzumab should be continued post-operatively to complete 1 year of therapy
3. Other permissible trastuzumab-chemotherapy regimens are as noted above.

ER and/or PR positive disease

Adjuvant endocrine regimens

1. Following surgery initiate adjuvant endocrine therapy as above (in addition to chemotherapy as indicated).
2. Endocrine therapy should only be administered sequentially following completion of chemotherapy (at least 3weeks post chemo) but can be initiated concurrently with trastuzumab.
3. In patients with poor performance status or in the elderly consider neoadjuvant endocrine therapy alone.

METASTATIC DISEASE

Endocrine Therapy for Stage IV disease

1. Premenopausal women: Tamoxifen and consider ovarian ablation/suppression.
2. Post-menopausal women: First line tamoxifen or aromatase inhibitor if available. Ideally after progression patients should switch to other hormonal therapy options based on availability. See appendix for available options for hormonal therapy.
3. If progression after third line hormonal therapy, initial single agent chemotherapy if good performance status
4. Patients with visceral crisis should be initiated on single agent chemotherapy as below. Visceral crisis is defined as the presence of symptomatic lung metastases, bone marrow deficiency, carcinomatous meningitis, or significant liver metastases resulting in clinical decompensation. These patients should be initiated on chemotherapy for more rapid control.

Chemotherapy Regimens for Stage IV disease

Preferred single agents

1. Paclitaxel (if not previously received or greater than 1 year since adjuvant or neo-adjuvant paclitaxel)
2. Capecitabine
3. Doxorubicin (if not previously received)
4. Cyclophosphamide (if not previously received)
5. Gemcitabine
6. Docetaxel
7. Vinorelbine, if available

Regimens for HER2 positive Stage IV disease

Preferred first line regimen

1. Trastuzumab alone or with:
    a. Paclitaxel +/- carboplatin
    b. Vinorelbine
    c. Docetaxel
    d. Capecitabine
    e. gemcitabine

Other regimen for trastuzumab-exposed disease

Lapatinib + capecitabine (available in private)

LOCALLY RECURRENT TUMOR (DISEASE AT SITE OF PRIOR BREAST SURGERY OR AXILLA)

1. Treatment in this setting may rarely provide a cure but will often provide symptomatic relief and/or prolong life.
2. Perform re-staging workup:
    a. Physical examination
    b. Complete blood count, liver function tests
    c. CXR and ultrasound
    d. CT chest/abdomen ideally
3. If found to have distant disease treat as for metastatic disease above
4. If locally recurrent tumor is resectable every patient should be considered for surgery if no evidence of metastatic disease.
5. If locally recurrent following mastectomy but no prior radiation, consider surgical resection if possible followed by radiation therapy to chest wall, supraclavicular and infraclavicular lymph nodes.
6. If symptomatic and/or rapidly-growing local recurrence with a performance status of 0,1, or 2 (see appendix) and did not receive chemotherapy before: treat as outlined above for locally advanced disease including surgery where possible.
7. If symptomatic and/or rapidly-growing local recurrence with an ECOG performance status of 0,1, or 2 (see Appendix B) and received chemotherapy AC/T chemotherapy before: treat with capecitabine (or taxane +- platins) and assess for response at 6-12 weeks. If not responding and ECOG PS of 0-2, switch to second line chemotherapy.

SPECIAL CONSIDERATIONS

1. Poor performance status or Elderly patients >70 years not fit for surgery and Hormone receptor positive
    a. Tamoxifen or AI (AI first line treatment of choice in post-menopausal patients) – for neoadjuvant settings
    b. Reassess operability at 3 -6 months
    c. If response for mastectomy (can consider up to 9 months after start of hormonal treatment)
    d. If no response switch to second line hormonal therapy
    e. If no further response for palliative radiotherapy
2. Breast cancer in men
    a. One percent of breast cancers occur in men, and men with breast cancer should be treated similarly to postmenopausal women. Tamoxifen is preferred for first line hormonal therapy. If an aromatase inhibitor is used, it should be given concomitantly with suppression of steroidogenesis.
3. Breast cancer in pregnancy: surgery and chemotherapy (AC-scheme) pre-partum are an option in second or third trimester, radiation an option post-partum. Typically try to avoid radiation. Ideally defer post-partum. Do not give chemotherapy within 3weeks of anticipated due date to avoid neutropenia and don't resume till after delivery.
4. Patients with favorable histology, including mucinous and tubular, benefit less from chemotherapy. They should receive hormonal therapy if hormone receptor positive and node negative. Consider chemotherapy for patients with node positive disease. If ER/PR negative, treat as usual breast cancer histology.

2.8 Follow up

1. For early stage or locally advanced disease after completion of curative intent treatment:
    a. History and clinical examination every 6 months for the first 2 years, then every year from year 3 to 5 at an oncology referral center, or in a local centre where CBE and Hormonal therapy management is acquired. Annual follow up at year 5 should be done up to year 10. Patients on hormonal therapy should be seen every 6 months for 5 years while on therapy. No routine blood work or x-rays unless clinically indicated.
    b. Ideally: Mammograms every 1 year for patients who received a lumpectomy, and mammograms in contralateral breast in patients who underwent mastectomy

2. For metastatic disease
    a. Follow up in clinic every 3 months indefinitely, or as clinically indicated, including home visits where feasible. Clinic visits should include symptom assessment, physical examination, performance status, weight
    b. Blood work – FBC, LFTs, RFT prior to each visit
    c. Imaging as clinically indicated, if concern for progression
    d. Ideally imaging studies should be performed every 2 to 3 months (unless in stable bone only disease, where symptoms or tumor markers are prioritized)
    e. Tumor markers are not routinely performed in Botswana and are optional in monitoring metastatic disease.

2.9 Drug regimens

1. Adjuvant Chemotherapy

- **AC-T**
  Doxorubicin 60 mg/m2 IV
  Cyclophosphamide 600 mg/m2 IV
  Given every 21 days (x 4 cycles in the adjuvant or neoadjuvant setting)
  Paclitaxel 175 mg/m2 IV every 21 days or 80 mg/m2 IV every 7 days (option for weekly paclitaxel 80 mg/m2 if practically feasible)

- **CMF**
  Cyclophosphamide 100 mg/m^2 p.o. days 1 through 14 (or 600 mg/m^2 iv days 1 and 8 if compliance problems)
  Methotrexate 40 mg/m^2 iv days 1 and 8
  5-Fluorouracil 600 mg/m^2 iv days 1 and 8
  Cycle repeated at 28-day intervals for 6 cycles only.

  Patients unable to attend clinic for IVI, substitute ORAL on day 8:
  Methotrexate 20 mg/m^2 po
  5-FU 500 mg/m^2 stat.

  Oral day 8 not recommended. Only use if unavoidable.

- **AC**
  Doxorubicin 60 mg/m2 IV.
  Cyclophosphamide 600 mg/m2 IV.

- **TC**
  Docetaxel 75mg/m2.
  Cyclophosphamide 600mg/m2.
  Cycle repeated at 21-day intervals for 4 (or 6 if Node pos) cycles.

2. HER2 positive regimens

- If on adjuvant therapy commence after completion of anthracycline component of chemotherapy
- trastuzumab loading dose of 8mg/kg IV followed by 6mg/kg IV three weekly. (a capping to 600 mg per cycle can be considered given the data of SC Trastuzumab (unidose of 600 mg)
- Adjuvant for 1 loading dose then 14 three weekly cycles. Should be administered concurrently if Paclitaxel is given total 15cycles Transtuzumab

- Metastatic for 1 loading dose then three weekly until progression
- Metastatic disease after progression on anthracycline
  Vinorelbine 25-30 mg/m^2 day 1+day 8 q21 x 6 + concurrent with trastuzumab three weekly as above

  Paclitaxel 175mg/m^2 q21 x 6+ in combination with trastuzumab three weekly as above

  Docetaxel 75mg/m^2 q21 x 6 + concurrent with trastuzumab three weekly as above

- Patients to have a repeat ejection fraction before cycle 1 and repeat every 4 cycles. To see the doctor every 4 cycles with ejection fraction result.

3. Endocrine therapy
   - Tamoxifen 20 mg orally per day
   - Letrozole 2.5 mg orally per day
   - Anastrozole 1 mg orally per day

4. Systemic chemotherapy for metastatic disease
   - Capecitabine 1000mg/m2 bid day 1-14 every 3 weeks. Dose reduction is recommended if not tolerated at full dose.
     Q21d until progressive disease

   - Paclitaxel 175 mg/m2 IV q 3 wks
     or
     70 mg/m2 IV q week (see above for comments about every 3-week vs weekly paclitaxel).
     In the metastatic setting weekly Paclitaxel has been shown to be superior to q3 weekly Paclitaxel and the latter should only be used when weekly visits for treatment is not tenable (Seidman et al. JCO 2008;26:1642-1649).

   - 5-Fluorouracil 500mg/m2 IV q week with leucovorin calcium 500mg/m2 IV bolus

   - Cyclophosphamide 600 mg/m2 q 3 wks

   - Doxorubicin 60 mg/m2 q 3 wks (total dose not to exceed 450 mg/m2)

   - Carboplatin Carbo AUC 5 day 1 IV +- a taxane or +-gemcitabine
     Cycle repeated at 21-day intervals

Calculate cockroft creatinine clearance

- Docetaxel 75mg/m2 q21
- 20 mg/m² Low dose Doxorubicin IV weekly
- Vinorelbine 25- 30 mg/m^2 IVI days 1 and 8 (cap dose at 50mg)
  Q21d
- Gemcitabine 800-1200 mg/m2 IV days 1,8, and 15.
  Q28d

2.10 Current Gaps and Implementation Goals

1. Gaps: limited capacity for core needle biopsy, limited capacity for bone scans, lymph node ultrasound
2. Long pathology turnaround time
3. Chemotherapy stock out leading to delays and interruptions in care delivery

2.11 APPENDIX

BREAST CANCER HISTOLOGICAL SUBTYPES

i. DCIS (Ductal carcinoma in situ)

- micropapillary
- papillary
- solid
- cribriform
- comedo (cytologically malignant, with the presence of high-grade nuclei, pleomorphism, and abundant central luminal necrosis)

ii. LCIS (lobular carcinoma in situ)

iii. Invasive

- Ductal
- Lobular
- Mixed Ductal and Lobular
- Invasive, NOS
- Comedo
- Inflammatory
- Medullary with lymphocytic infiltrate
- Mucinous (colloid)
- Papillary
- Scirrhous
- Tubular
- Other (squamous cell/ undifferentiated)

iv. Primary Lymphoma

v. Angiosarcoma

vi. Malignant Phylloides

vii. Carcinosarcoma/ metaplastic

SURGICAL OPTIONS FOR INVASIVE CANCER

In the Botswana breast cancer population, most patients present with stage III disease (Botswana Cancer Registry), however with neoadjuvant therapy, modified radical mastectomy or even possibly wide local excision can be performed.

1. Mastectomy

Modified radical mastectomy involves removal of the breast, pectoralis major fascia (but not the muscle) and selected axillary lymph nodes. Other mastectomy techniques like nipple sparing mastectomy and skin sparing mastectomy (Annals Surg 2010, Surg Onc 2006) are

good options where immediate breast reconstruction is an option but are not currently available as there are no available oncoplastic services in Botswana. The nipple-sparing and skin-sparing procedures are also contraindicated in cases of dermal lymphatic involvement.

Mastectomy is the standard treatment of clinically isolated breast tumour recurrence following BCS and radiation (Oncology 2000). This may be accompanied by axillary node dissection if not previously performed or clinically indicated.

2. Breast Conserving surgery (BCT)

Breast conservation surgery (BCS) accompanied by post-operative radiation produce acceptable cosmesis and adequate local disease control comparable to mastectomy (NEJM 2002, Cancer 2003). BCS may be performed in patients who meet the follow criteria: smaller monocentric tumours (Stage I and II, selected III), younger age, localization of tumor, patient compliance (Breast Surgery 3rd Edition 2007). A pre-operative diagnostic mammogram or MRI of the breast is required to rule out multicentric or multifocal disease. From the Consensus Conference on Breast Conservation (Milano, 2005) a reasonable clear surgical margin should be 1-10mm.
10-15% of patients with Invasive breast cancer will have clinical isolated breast local recurrence. Factors that are predictive to the chance of recurrence are age 35-40 years, size ≥ 5cm, lymphovascular invasion, close of positive margins (Oncology 2000).

BCS in contraindicated in the following scenarios: locally wide spread disease (tumor size is relative contraindication), persistently positive resection margins, multicentric or multifocal disease, diffuse malignant microcalcifications, first/Second trimester (cannot have radiation), already irradiated thoracic wall, patients with connective tissue disease.

4. Axillary Lymph Node Dissection (ALND)

While the minimum number of nodes that should be harvested is not well described, NCI/CALGB recommend that complete axillary lymph node clearance should be sufficient to remove evidence of all gross disease and should in general contain a minimum of six nodes. Sommer et al (J Clin Pathol 2004) suggested 16 nodes as target to ensure high level of confidence that the nodes are negative, including level III clearance. Locally, we recommend assessment of at least 10 lymph nodes to ensure level II clearance.

5. Sentinel Lymph Node Biopsy

This technology is currently not available in country

6. Consent and Patience Choice

Patients suitable for BCS should be fully informed about their persistent life time risk of local recurrence vs. cosmetic outcomes associated with mastectomy, and should be able to weight risk and benefits in order to reach an informed decision. All those who get adequate lumpectomy with good clear surgical margins should proceed to radiotherapy postoperatively.

Complications including seroma, anterior chest wall tightness, shoulder dysfunction, lymphoedema, injury or thrombosis of the axillary vein (unlikely in level II dissection) and sensory loss should be discussed as part of the consent process.

RADIOTHERAPY OPTIONS

1. Mastectomy

One feature: Any T4 breast cancer, T3 node positive breast cancer, Positive margin (Margin at ink); T1-T2 and ≥4 nodes positive; extracapsular extension (ECE) of positive node; all patients who received neoadjuvant chemotherapy and are node positive after chemotherapy

Two or more features: T3 N0 or 1-3 positive nodes + any additional risk factor: LVI positive, Grade 3, ER neg or triple receptor negative, HER2+3 not receiving anti-HER2 therapy, or age <40

Include supraclavicular fossa (SCF) if ≥4 nodes, 1-3 positive nodes and a high node positive ratio >20%, extracapsular extension in **any** positive node, or if axilla is not adequately assessed.

Include axilla if:
1. ECE in **any** positive node particularly if limited nodal clearance
2. If patient did not undergo complete axillary clearance or Grade 3, or LVI, or ER negative, or Multifocal

Simulated

42.72Gy/16#/5# per week to chest wall, and SCF and axilla if included or 50Gy/25#/5# per week

Bolus to chest wall (C/W) every other day. Scar boost if skin involvement or positive margins only

1. Breast conserving surgery

All patients to have post-operative radiotherapy to the breast

Boost tumor bed in patients <50 years or margin<2mm after re-excision (or if re-excision not possible)

Include SCF if ≥4 nodes, 1-3 positive nodes and a high node positive ratio > 20%, extracapsular extension in **any** positive node, or if axilla is not adequately assessed by sentinel node biopsy or axillary dissection.

Include axilla if:
1. ECE in **any** positive node particularly if limited nodal clearance,
2. If a patient did not undergo complete axillary clearance after a positive sentinel node biopsy with 3 or more nodes positive or no sentinel node biopsy or axillary clearance done.

CT planned

42.72Gy/16#/5# per week to breast, and if included, supraclavicular fossa (SCF) and axilla. 10.5Gy/3# boost to tumor bed.

3. Palliative breast RT

36Gy/6#/1# per week over 6 weeks. Or 20Gy in 5 # over one week if can't attend as OP.

4. Bone Metastases/Skin metastases

8Gy/1# to single site

5. Cord compression

20Gy/5# if good PS and some residual power

8Gy/1# if poor PS and/or no power

30Gy/10#/4# per week for patients with good performance status and those with prior spinal stabilization

6. Brain metastases

Single lesion, good PS, no other disease discuss with neurosurgery, or radiosurgery if small lesion. Follow with WBRT 30GY/10#.

If hydrocephalus or threatening hydrocephalus e.g. lesion abutting/ compressing 4th ventricle, refer for consideration of stenting/ resection

Good PS, multiple mets 20Gy/5#

Poor PS 12Gy/2# over 3 days

DOSE MODIFICATIONS & TOXICITY

1. Delay one week if Neutrophil count below 1.0 in adjuvant patients and below 1.5 in metastatic patients.
2. Delay one week in platelets <75
3. Transfuse the same week as adjuvant chemotherapy if Hb drops below 8g/dl. Delay one week if Hb below 8g/dl in metastatic patients rechecks and if still below 8g/dl then transfuse.
4. Do not reduce dose in adjuvant setting unless persistent neutropaenia, thrombocytopaenia is leading to prolonged treatment delays, or associated with sepsis

5. If severe neutropenia, offer filgrastim (neupogen) which is available

Special considerations

1. Cap the BSA for all patients at 2 m2

2. Avoid Methotrexate in patients with ascites or pleural effusions

3. Instruct patients the importance of high fluid intake during Cyclophosphamide therapy. Discontinue Cyclophosphamide if haemorrhagic cystitis occurs in spite of adequate hydration.

4. Severe gastro-intestinal side effects (anorexia, nausea and vomiting, diarrhea, stomatitis, dry mouth, epigastric pain) - postpone therapy until symptoms subside.

Cardiac dysfunction

All patients for anthracycline or transtuzumab require left ventricular ejection fraction (LVEF) assessment.

a. Obtain baseline LVEF, and if EF <40% do not administer anthracycline based chemotherapy. There is <1% cardiotoxicity risk with cumulative dose of doxorubicin 240mg/m² (based on ACX4 regimen (Shulman et al. JCO 2012;30:4071-4076). If clinical congestive cardiac failure (CCF), unstable angina do not give anthracycline
b. Transtuzumab as follows: Baseline LVEF before cycle 1. If EF <40% do not give transtuzumab. If EF drop by >10% + symptoms; hold transtuzumab dose and reassess

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American Joint Committee on Cancer (AJCC), 8th edition Breast Cancer Staging (2017)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease (Paget disease) of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic skin nodules); invasion of the dermis does not qualify as T4
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	

Clinical	
NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s) Micrometastases (larger than 0.2 mm, but none larger than 2.0 mm)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected‡ ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected‡ ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
pN0(i-)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including isolated tumor cell clusters (ITC))
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)••

pN0(mol+)	Positive molecular findings (RT-PCR)••, but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected (pN1a and pN1b combined)
pN2	Metastases in 4-9 axillary lymph nodes; or in clinically detected positive internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Anatomic stage/prognostic groups			
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Breast carcinoma TNM clinical prognostic stage groups AJCC UICC 8th edition

When TNM is…	And grade is…	And HER2 status is…	And ER status is…	And PR status is…	Then the clinical prognostic stage group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IB

T0 N1¶ M0 T1* N1¶ M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
T0 N1¶ M0 T1* N1¶ M0 T2 N0 M0	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
T0 N1¶ M0 T1* N1¶ M0 T2 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1Δ M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB

T2 N1[Δ] M0 T3 N0 M0				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
T2 N1[Δ] M0 T3 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0	G3	Positive	Positive	Positive	IIB
				Negative	IIIA

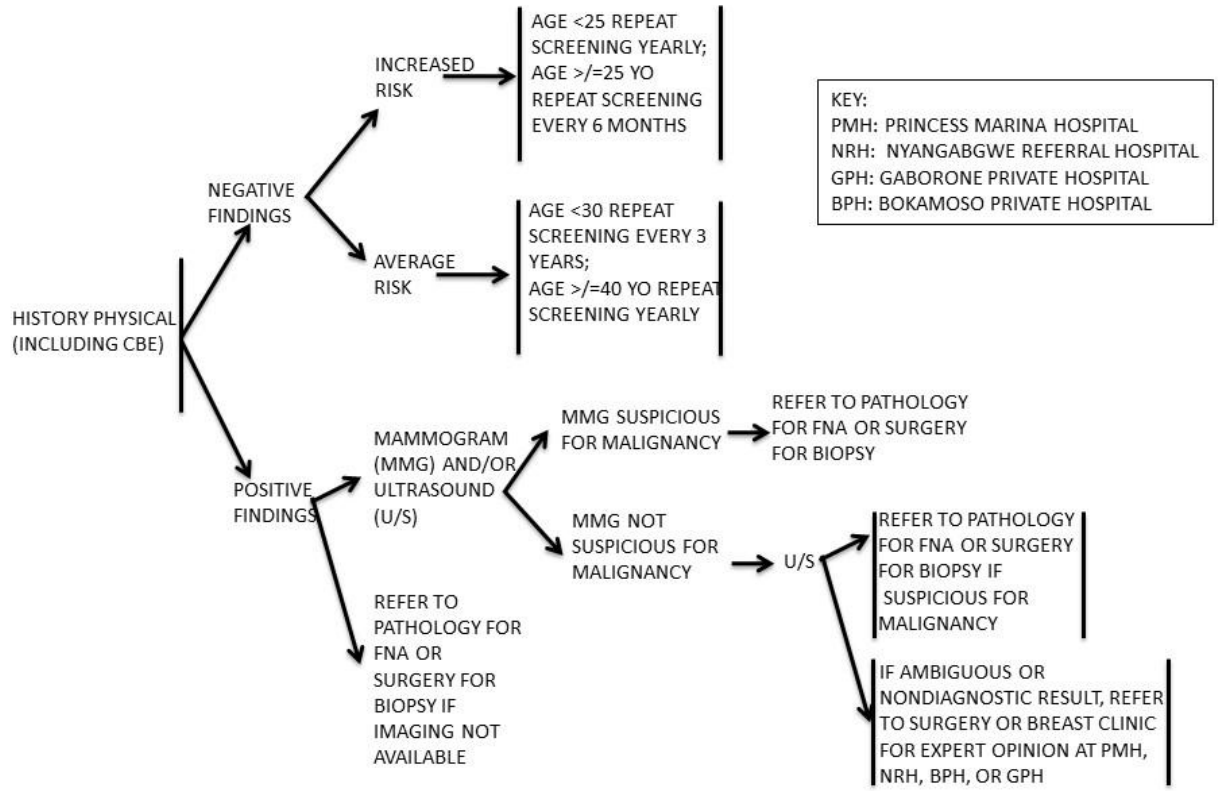
T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC
Any T Any N M1	Any	Any	Any	Any	IV

APPENDIX B:

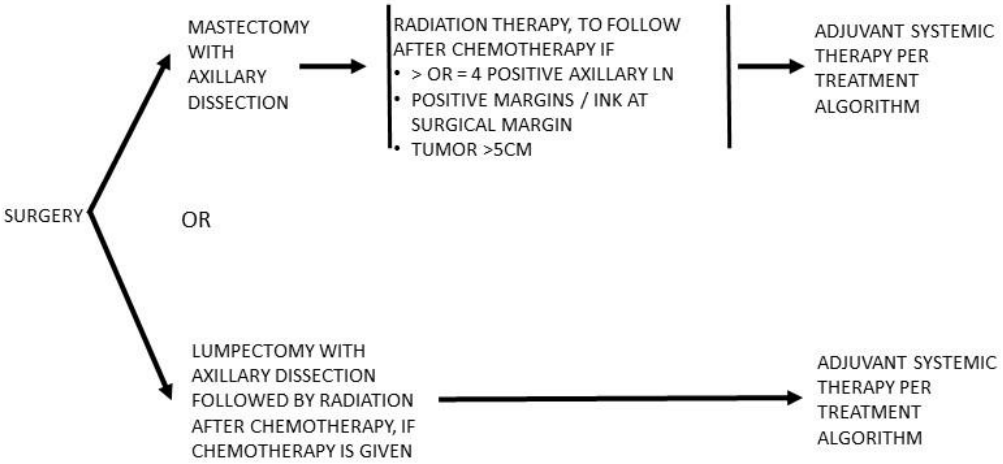
Eastern Cooperative Oncology Group (ECOG, Zubrod, WHO) performance scale

Performance status	Definition
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all selfcare but unable to carry out any work activities. Up and about >50 percent of waking hours.
3	Capable of only limited selfcare; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair

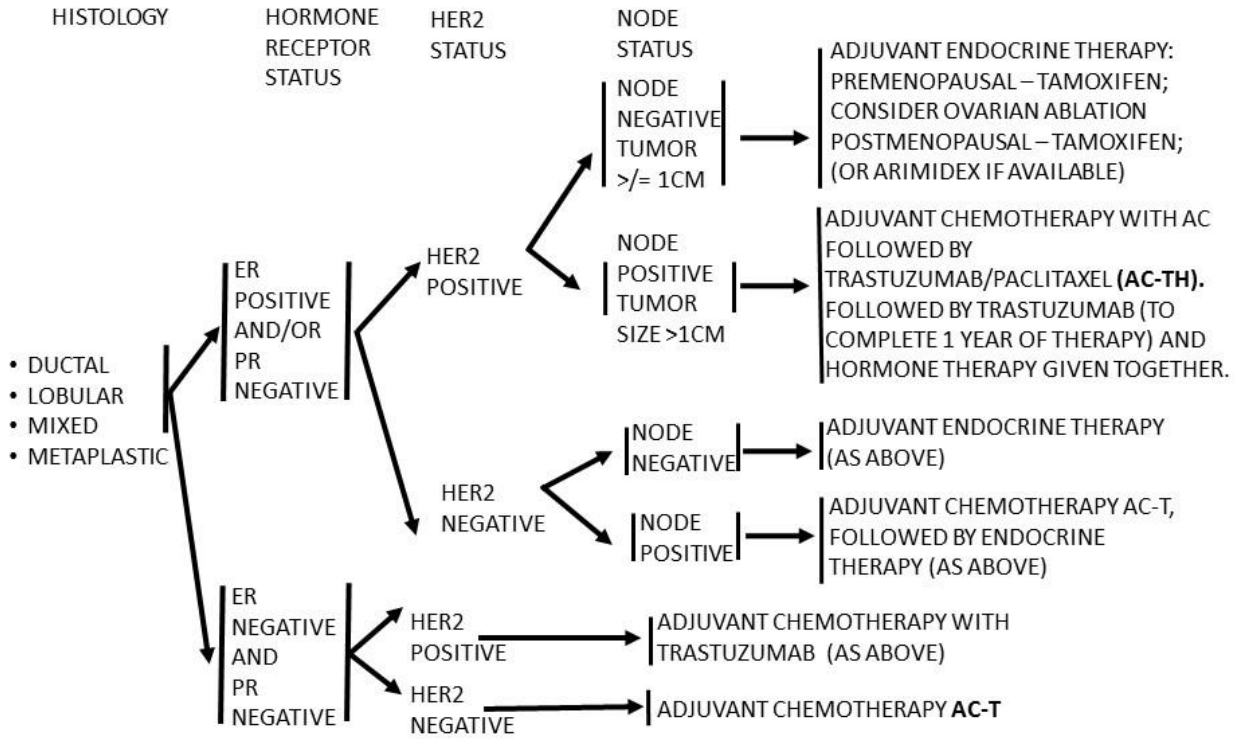
BOTSWANA BREAST CANCER SCREENING AND DIAGNOSIS



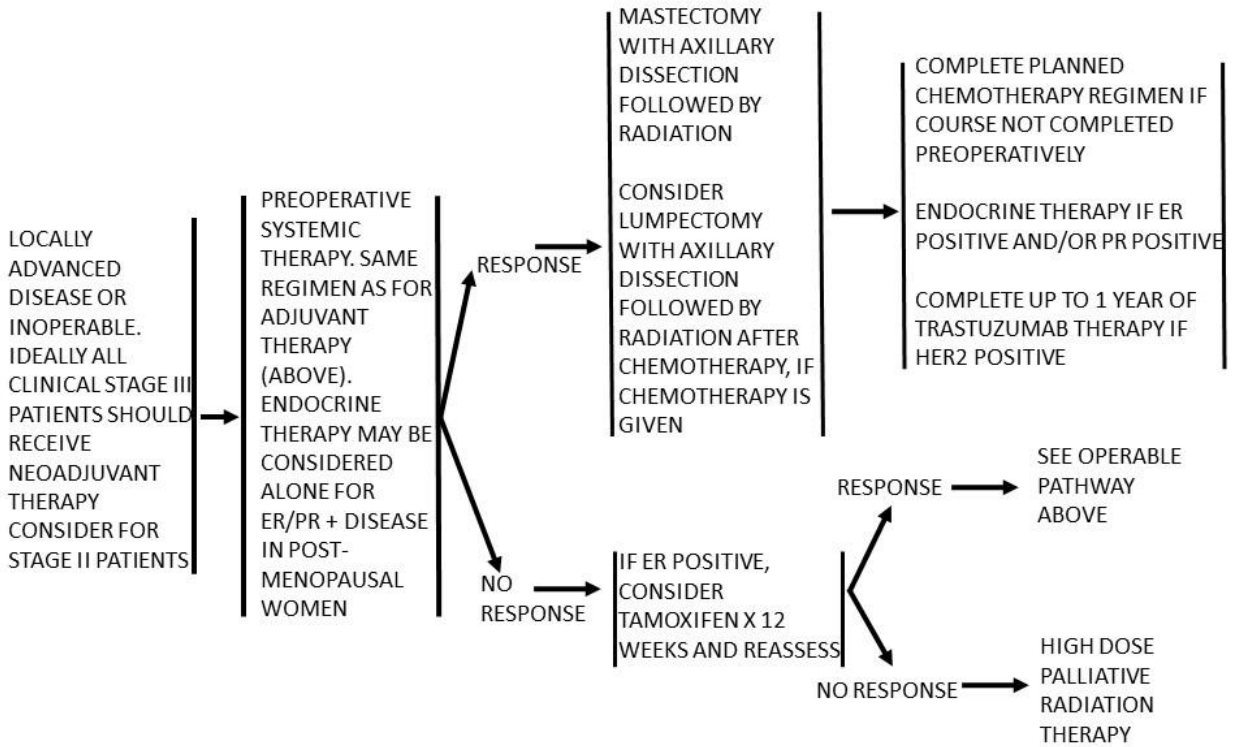
Locoregional treatment of clinical Stage I, IIA, OR IIB disease, or T3, N1, M0

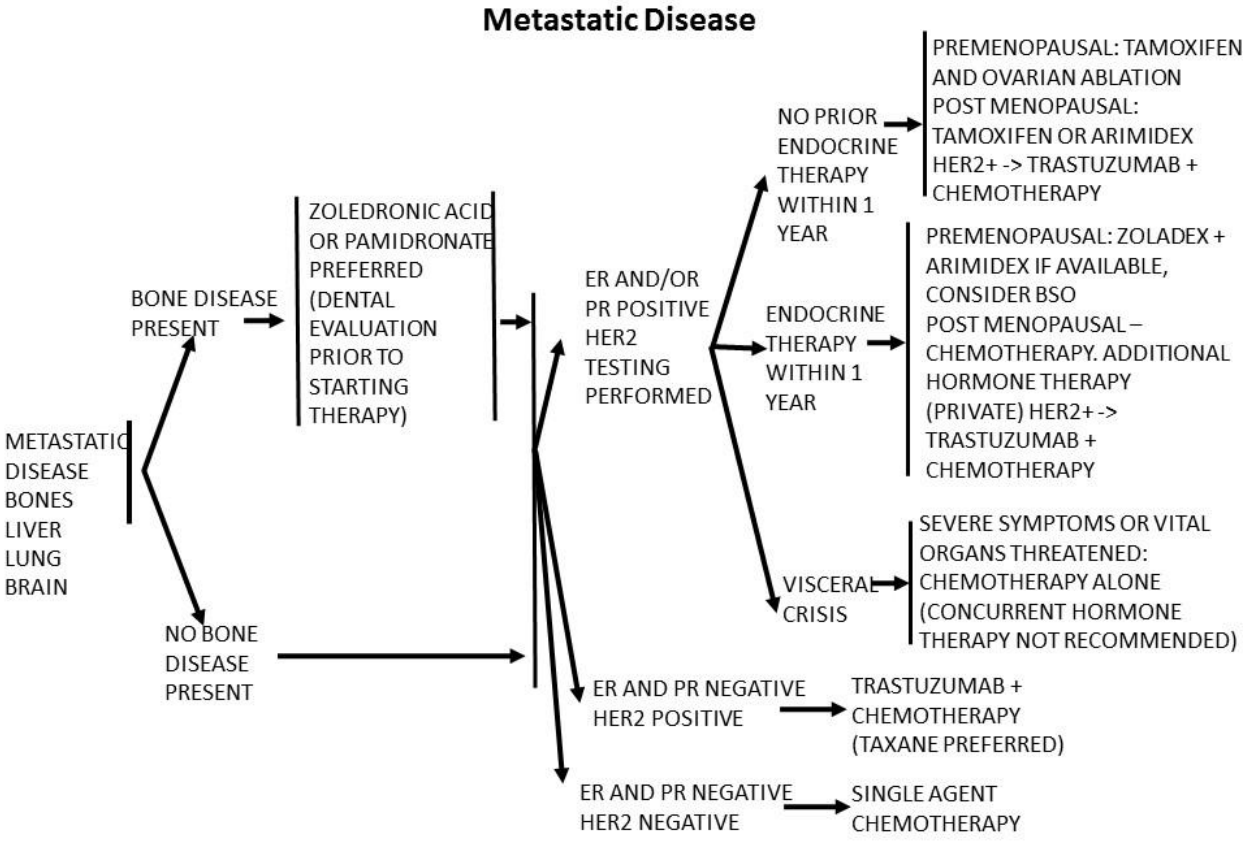


Systemic adjuvant treatment for early stage disease



Locally advanced or inoperable disease / Preoperative Systemic Therapy




Metastatic Disease
METASTATIC DISEASE
BONES
LIVER
LUNG
BRAIN
BONE DISEASE PRESENT
ZOLEDRONIC ACID OR PAMIDRONATE PREFERRED (DENTAL EVALUATION PRIOR TO STARTING THERAPY)
NO BONE DISEASE PRESENT
ER AND/OR PR POSITIVE HER2 TESTING PERFORMED
NO PRIOR ENDOCRINE THERAPY WITHIN 1 YEAR
PREMENOPAUSAL: TAMOXIFEN AND OVARIAN ABLATION
POST MENOPAUSAL: TAMOXIFEN OR ARIMIDEX
HER2+ -> TRASTUZUMAB + CHEMOTHERAPY
ENDOCRINE THERAPY WITHIN 1 YEAR
PREMENOPAUSAL: ZOLADEX + ARIMIDEX IF AVAILABLE, CONSIDER BSO
POST MENOPAUSAL – CHEMOTHERAPY. ADDITIONAL HORMONE THERAPY
(PRIVATE) HER2+ -> TRASTUZUMAB + CHEMOTHERAPY
VISCERAL CRISIS
SEVERE SYMPTOMS OR VITAL ORGANS THREATENED: CHEMOTHERAPY ALONE
(CONCURRENT HORMONE THERAPY NOT RECOMMENDED)
ER AND PR NEGATIVE HER2 POSITIVE
TRASTUZUMAB + CHEMOTHERAPY
(TAXANE PREFERRED)
ER AND PR NEGATIVE HER2 NEGATIVE
SINGLE AGENT CHEMOTHERAPY

Booklet 3

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3. **Colon Cancer Management**

COLON CANCER MANAGEMENT

1. Overview

Colorectal cancer is the third most common cancer in men (746,000 cases, 10% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide. Roughly 45% of the cases occur in less developed regions of the world (GLOBOCAN, 2012). There is wide geographical variation in incidence across the world. Genetic susceptibility to colorectal cancer includes acquired or inherited genetic mutations, inherited syndromes such as Lynch Syndrome and familial adenomatous polyposis. Risk factors should include Adenomatous Polyps, (this risk factor is very important) inflammatory bowel disease (ulcerative colitis, Crohn's disease), smoking, consumption of red and processed meats, alcohol consumption, diabetes mellitus, obesity, and metabolic syndrome.

2. Screening

No national screening program exists currently.

Ideal

Recommendations for colorectal cancer screening are listed below:

- Colonoscopy every 10 years starting at the age of 50 if average risk.
- High risk patients should be evaluated as follows:
    - 8 years after diagnosis of inflammatory bowel disease
    - 10 years prior to the age of the youngest first degree relative or age 40, whichever comes first
    - Age 20-25 years for known Lynch syndrome and polyposis syndrome.
- If abnormal polyp found on colonoscopy, repeat colonoscopy in 5 years
- If multiple polyps, adenoma > 1 cm or villous adenoma then repeat in 3 years
- If greater than 10 polyps, consider genetic syndrome and colectomy.
- Colonoscopy every 5 years if one first-degree relative with colorectal cancer diagnosed before age 50 years or two first-degree relatives with colorectal cancer diagnosed at any age

3. Common findings at presentation

- For localized disease - change in bowel habits (quality and caliber of stool), blood in the stools, dark stools (right sided lesions), abdominal discomfort, weight loss signs or symptoms of anemia (fatigue, dizziness, dyspnea on exertion, etc.)
- For metastatic disease – depending on the site of metastasis (liver: RUQ abdominal pain, jaundice; bone: bone pain; lungs: chest pain, shortness of breath)

Investigations

- Rectal Exam: If the patient has bowel obstruction, colonoscopy may be not indicated. For left-sided large bowel obstruction, colonoscopy can be done in 3-6 months post operation to exclude the proximal lesion.
- The inguinal and supraclavicular LNs should be well assessed and documented. Entire colonoscopy should be completed to rule out synchronous lesions, sigmoidoscopy.
- CBC with differential, basic metabolic panel, liver function testing, and carcinoembryonic antigen (CEA) determination for long term monitoring
- The first series of tests to rule out metastatic disease is a chest x-ray and abdominal ultrasound to look for liver metastases
- If the chest x-ray and abdominal ultrasound are negative, the second series of tests to rule out metastatic disease is a Chest/Abdomen/Pelvic CT scan

4. Pathology

Pathology specimens can be obtained from colonoscopy or biopsy of site of metastatic disease. The following parameters should be reported:

- Grade of the cancer
- Depth of penetration (T)
- Number of lymph nodes evaluated and number positive (N)
    - Minimal number of lymph nodes examined is 12. If the N number reported is less than 12, the specimen should be reviewed by the pathologists.
- For polypectomy: Caution to not fragment lesion as margins need to be assessed
    - Positive margin is anything <2 mm from margin or tumor cells within transected margin for removed polyps.
- Surgical specimen - status of proximal, distal, and radial margins
    - Surgical radial margin does not include the serosa (except for mesenteric margin) and should be assessed in all segments with non-peritoneolized surfaces (should be marked intra-operatively as difficult to assess pathologically alone).
- Lymphovascular invasion
- Perineural invasion (PNI)
- Number and size of extranodal tumor deposit (pericolic or perirectal fat deposits separate from the tumor and not in lymphoid tissue, but within lymphatic drainage systems.

5. Staging

Staging is based on the AJCC TNM 2017 classification. See appendix for full staging.

Early stage (Stage I and II):

- No lymph node metastasis and no distant metastases

Locally Advanced (Stage III):

- Lymph node metastasis but no distant metastases

Metastatic (Stage IV):

- Distant metastatic disease (tumor spread to other organs) – liver most common,

6. Treatment

Early stage disease (Stage 1 – 2: No lymph node metastasis and no distant metastases)

- Curative treatment intent
- Surgical resection of tumor by partial colectomy and at least 12 regional lymph nodes must be removed as it is needed for proper staging and also confers survival benefit
- Patients with stage I or low risk stage II disease do not require adjuvant chemotherapy.
- Patients with high risk stage II disease defined as those who have T4 tumors, poorly differentiated histology, LVI, focal perforation or obstruction, <12 nodes examined, and positive margins can be considered for capecitabine or 5FU monotherapy. FOLFOX not required. Exclusive of those that are MSI-H.
- MMR IHC should be done for the stage II cases.
    - Any adjuvant therapy should be started < 6 weeks post-operatively for maximal benefit as each 4-week delay confers a 14% OS decrease.

Locally Advanced Disease (Stage 3: Lymph node metastasis but no distant metastases)

- Curative treatment intent.
- Surgical resection of tumor by radical colectomy, complete mesocolic excision and at least 12 regional lymph nodes.
- Adjuvant chemotherapy with CapeOx or Folfox for 6 months (see appendix for dosing schedule)
- Can consider adjuvant radiation if positive margins and area can be identified via surgical clips or imaging to direct XRT. Can give concurrent chemotherapy.
- If initially unresectable (i.e. T4 disease) can proceed with 2-3 cycles of FOLFOX or CapeOx neoadjuvantly and reassess for surgery

Metastatic Disease (Stage 4: Distant metastases is present)

- Most patients do not require surgery. Surgery is appropriate when the procedure is palliative (for example relieving an obstruction with a diverting colostomy), bleeding or perforation.
- Care providers and patients should discuss palliative care alone or palliative chemotherapy or more aggressive treatment in young and oligometastatic.
- For oligometastatic disease, curative intent can be employed for patients who are young with good performance status in one of the following categories:
- The patient is to be discussed with Hepatobiliary Surgeon first
- Liver metastases – biopsy is not indicated as will render patient palliative. A primavist MRI is to be requested and discussed with HPB surgeon
- Lung Metastases: discuss with Cardiothoracic surgeon
    - If solitary metastasis is resectable.
    - If both lesions are amenable to XRT.
    - If complete response of metastasis to chemotherapy.

- Can give FOLFOX for good performance status patients and those < 70 years
    - Otherwise give capecitabine monotherapy. The capecitabine can be continued until disease progression.

7. Surveillance and Follow up

Stage I Disease Surveillance

- Colonoscopy at 1 year
- Repeat colonoscopy is recommended at 3 years, and then every 5 years thereafter unless advanced adenoma is found

Stage II and Stage II Disease Surveillance

- History and physical examination every 3 to 6 months for 2 years
- CEA test recommended at baseline and every 3 to 6 months for 2 years
- Colonoscopy is recommended at approximately 1 year after resection
- Repeat colonoscopy is recommended at 3 years and then every 5 years thereafter unless follow up colonoscopy indicated advanced adenoma in which case colonoscopy should be repeated in 1 year
- Chest, abdominal, and pelvic CT scan are recommended every 12 months for up to 5 years, if available. If not available, recommend ultrasound of abdomen and chest x-ray.
- Routine CEA monitoring and CT scanning are not recommended after more than 5 years

Metastatic Disease Surveillance

- Chest, abdominal, and pelvic CT scan are recommended according to symptoms, or every 3 to 6 months for up to 5 years. If not available, recommend ultrasound of abdomen and chest x-ray.
- CEA testing is recommended every 3 to 6 months for the first 2 years and then every 6 months for a total of 5 years

8. Gaps

- Colon cancer screening not available to the public sector.
- No available mutation testing and immunotherapy treatment.
- Genetic testing not available.

9. ESSENTIAL PACKAGE OF SERVICES FOR GIVEN CANCER, BY FACILITY LEVEL

Level	Key Personnel	Screening, Diagnosis & Treatment Interventions
Community	Health educators, VDC	• Community members' sensitization regarding colon cancer symptoms by primary level clinicians • Patients self-refer to health posts and primary clinics
Health posts, primary clinics	Nurses, occasionally GP	• Refer patients with concerning history or other findings concerning for cancer to district hospitals
District Hospital (primary and secondary hospitals)	GPs, nurses, in some cases specialists (internists, GI, surgeons)	• Clinical history taken, and physical exam and referral given for colonoscopy by GPs • Investigations: blood studies, CXR and abdominal US • Refer patients with solid or complex mass to cancer specialty center •
Cancer Specialty (Referral) Center – NRH, PMH, Maun, Serowe	Med Oncologist, Rad Oncologists, Pathologists, Radiologists, Internists, General Surgeons,	• Colonoscopic biopsy by general surgeon or gastroenterologist. • If negative pathology, consider repeat biopsy for patients with concerning physical exam or historical features • If positive pathology, determination of treatment plan • Provision of chemotherapy, surgery and radiotherapy • For patients who are on palliation only, referral to local district hospital for long term follow up

10. APPENDICES

APPENDIX 1

RADIOTHERAPY OPTIONS

- Radiation target volume:
    - Tumor bed (seen on preoperative radiologic imaging and/or surgical clips)
    - Dose: 45–50 Gy in 25–28 fractions as normal tissue tolerance allows with boost to gross disease. +/- Capecitabine 825mg/m2 BID daily x 5days/during RT

CHEMOTHERAPY DOSING

FOLXFOX

- Oxaliplatin 85 mg/m2 day 1.
- Leucovorin 400 mg/m2 IV, day 1.
  5FU 400 mg/m2 IV bolus on day 1, then 1200 mg/m2/day for 2 days (total 2400 mg/ m2 over 46–48 hours) continuous infusion.
  Repeat every 2 weeks for 12 cycles.

CapeOx

- Oxaliplatin 130 mg/m ^{2} over 2 h on day 1
- Capecitabine 1000 mg/m ^{2} PO BID on days 1-14 every 3 wk for eight cycles

CONVERSION CHEMOTHERAPY (perioperative)

- CapeOx X 3-4 cycles …Imaging……Surgical intervention if indicated followed by chemotherapy to total 6 cycles/ palliative chemo if non-surgical candidate.
- Capecitabine 1000-1250 mg/m2 BID on days 1-14 q 3 weeks for 24 weeks (8 cycles)

APPENDIX 2

TREATMENT TOXICITIES

Capecitabine

- Increased incidence of hand-foot syndrome.
- Accumulation of the drug in patients with diminished creatinine clearance.

Oxaliplatin

- Peripheral sensory neuropathy.

DOSE REDUCTIONS FOR TOXICITY

Capecitabine and Oxaliplatin

- Capecitabine requires 1-2 dose reductions with concern for hand-foot syndrome.
- Discontinuation of the oxaliplatin should be strongly considered after 3 months of therapy of unacceptable neurotoxicity and should not be reinitiated unless they experience near total resolution of that neurotoxicity.

Instructions to patients on chemotherapy about fevers

Because of the risk of febrile neutropenia in patients treated with chemotherapy, we recommend that patients be given clear instructions about what to do if they develop a fever (≥38 degrees Celsius).

APPENDIX 3:

American Joint Committee on Cancer (AJCC), 8th edition (2017) Colon and Rectum Cancer Staging

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propria with no extension through muscularis mucosa
T1	Tumor invades submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through visceral peritoneum
T4b	Tumor directly invades or is adherent to adjacent organs or structures
Regional lymph nodes (N)	
Clinical	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastases in one regional lymph node
N1b	Metastases in 2-3 regional lymph nodes
N1c	No regional lymph nodes are positive, but there are tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastases in 4 or more regional lymph nodes
N2a	Metastases in 4-6 regional lymph nodes
N2b	Metastases in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastases

M1	Distant detectable metastases as determined by classic clinical and radiographic means
M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b	Metastasis to more than one organ/site or the peritoneum
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Anatomic stage/prognostic groups			
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4	N2a	M0
	T3-4a	N2b	M0
	T4b	N1-2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

APPENDIX 4:

Eastern Cooperative Oncology Group (ECOG, Zubrod, WHO) performance scale

Performance status	Definition
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all selfcare but unable to carry out any work activities. Up and about >50 percent of waking hours.
3	Capable of only limited selfcare; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair

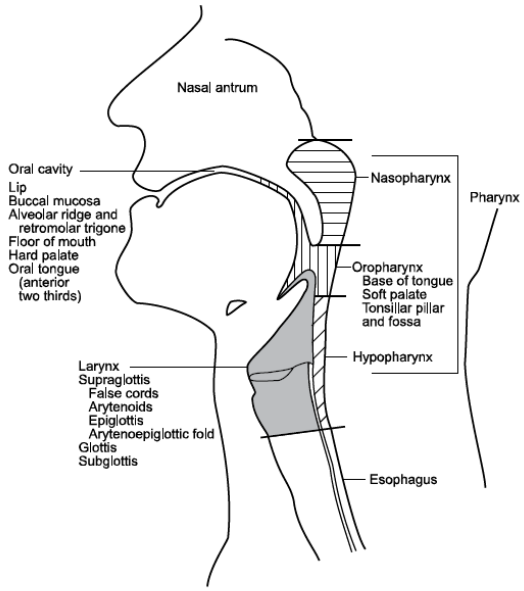
Booklet 4

4. Head and Neck Cancer Management

Head and Neck Cancer Diagnosis and Treatment

1. Overview

It is estimated that head and neck cancers constitute the top ten most common cancers diagnosed among men and women in Botswana (Ferlay et al. 2012). Squamous cell carcinoma accounts for 90% of head and neck cancers and classical risk factors include smoking, alcohol consumption, and viral infections such as HIV, EBV, and HPV (Gillison et al. 2000, Dryden-Peterson et al. 2015, Suneja et al. 2013). In recent years, the incidence of HIV-associated head and neck cancers has risen by 8.8% despite increased use of anti-retroviral therapy in Botswana (Dryden-Peterson et al. 2015). The head and neck guidelines cover the diagnosis and treatment of the following cancers: lip, oral cavity, pharynx, larynx, paranasal sinuses and salivary gland cancers (see image below).

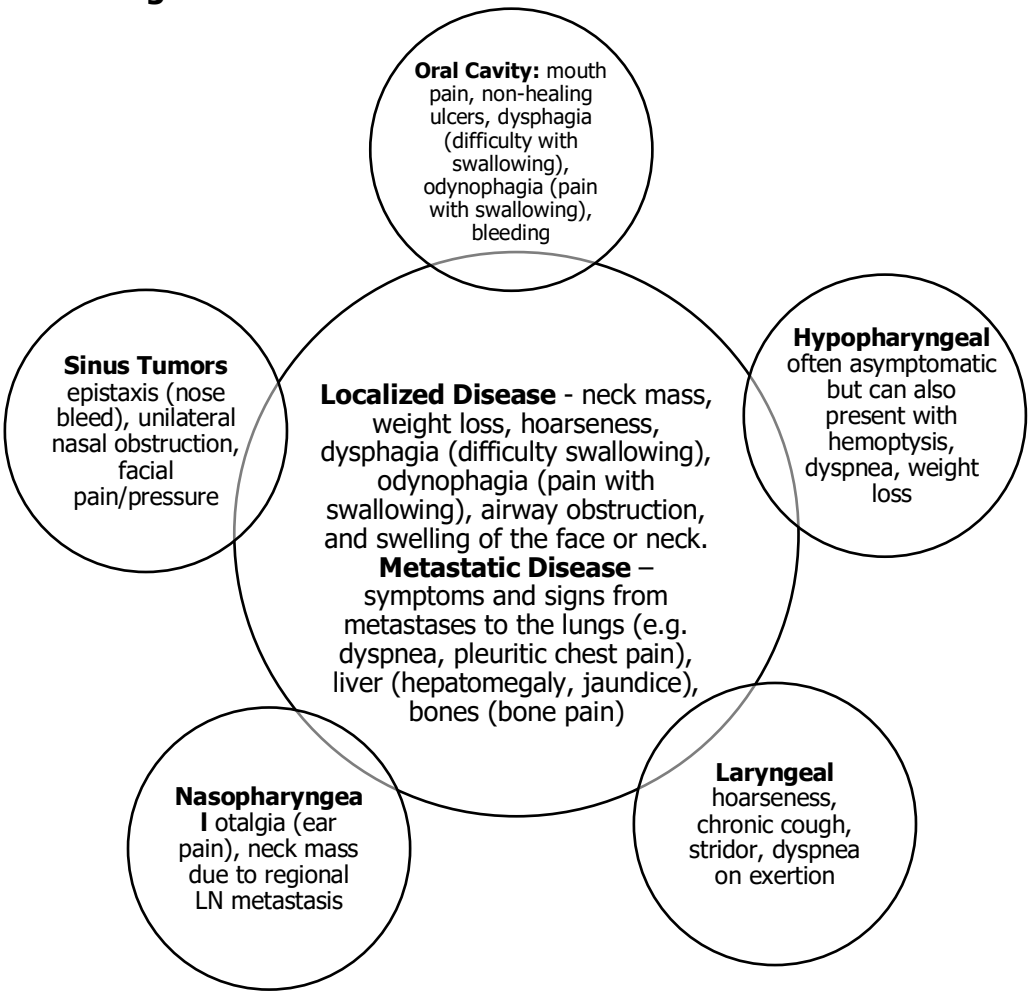


Oral Cavity: Lip mucosa, buccal mucosa, alveolar ridge and retromolar trigone, floor of mouth, hard palate, oral tongue (anterior two thirds)

Oropharynx: base of tongue, soft palate, tonsillar pillar and fossa

(Adapted from NCCN Guidelines Version 2.2017; Head and Neck Cancers)

2. Common Findings at Presentation



3. Investigations

Minimal

- **History:** Assessment for the above symptoms, quantified exposure history (tobacco, alcohol), including HIV status.
- **Physical Exam:** A complete head and neck exam should be performed including assessment for LNs, mirror and/or fiberoptic exam using flexible endoscopy (NPL) as clinically indicated.
- **Labs:** FBC, LFTs, RFTs, TSH, HIV (if unknown or tested negative $\geq$ 6 months ago)
- **Imaging:** CT with contrast of primary site and neck, CXR, Dental evaluation (paronex, occlusal view, and intra-oral x-ray), *Abdominal ultrasound for evaluation of distant metastatic disease if clinically indicated
- **Subspecialty Referral:** ENT, Dental

Ideal

- Magnetic Resonance Imaging (MRI) of primary and of the neck
- Positron Emission Tomography (PET)/Computerized Axial Tomography (CAT/ Computed tomography (CT) for stage III-IV disease
- Multidisciplinary clinic referral for ENT directed flexible endoscopy (NPL) or Exam

- Human Papillomavirus (HPV-)16 and Epstein Barr Virus (EBV) testing are suggested for squamous cell or undifferentiated histology for prognosticating outcome

4. Biopsy

If a tumor is visible (oral cavity and some oropharynx), biopsy should be done at the center where a patient is first seen. If not visible, the patient should be referred to Ear-Nose-Throat specialist (ENT) for flexible endoscopy (NPL) and guided biopsy.

- If presenting with primary tumor: biopsy of the primary mass
- If presenting with LN only: fine needle aspiration (FNA) preferred over open biopsy as an initial step to expedite diagnosis. FNA should always be followed by a biopsy. If FNA is inconclusive, a core or open biopsy may be performed.

*Biopsy needs to be done by ENT or OMFS surgeons and then referred to the Head and Neck Multidisciplinary Team (MDT) when available to discuss treatment plans and complete work up. If MDT is not established yet, patients should be referred to oncology.

5. PATHOLOGY ASSESSMENT

- Document the anatomic components of the larynx, i.e. supraglottic larynx, paraglottic space, glottis region, etc.
- Document surgical procedure, ie. radical neck dissection, modified radical neck dissection, super selective neck dissection, selective neck dissection or extended radical neck dissection
- Report should include accurate T staging of the primary tumor. For oral cavity tumors include tumor thickness and depth of invasion
- Report should include histological subtype, histologic grade, lymphovascular invasion, perineural invasion
- Document the presence of invasive carcinoma or carcinoma in-situ or high-grade dysplasia present at the margins. Report should also include the distance of these lesions from the surgical margin.
- All specimens should be oriented and facilitated by direct communication between the surgeon and pathologist and included in the report. A drawing or photograph is helpful.
- Report the number, level and size of LNs assessed. Extracapsular extension should also be included in the report.
- HPV p16 testing by immunohistochemistry should be reported for carcinoma of the oropharynx
- EBV is associated with the non-keratinizing types of nasopharyngeal carcinomas, including both differentiated and undifferentiated subtypes in practically 100% of cases, and should be reported if ISH testing is performed.

6. STAGING (AJCC 8th Edition); Adapted from NCCN Guidelines Version 3.2019

Stage	Lip and Oral Cavity
0	Tis (Carcinoma in situ), N0*, M0*
I	Tumor ≤ 2cm with DOI* ≤ 5mm **(T1)**, N0, M0
II	Tumor ≤ 2cm with DOI ≥ 5mm and ≤10mm (**T2)** OR > 2cm but ≤ 4cm with DOI ≤ 10mm (**T2**), N0, M0
III	Tumor > 2cm but ≤ 4cm with DOI >10mm OR >4cm with DOI ≤ 10mm (**T3**), N0/N1, M0 OR T1-2 and metastasis to single ipsilateral LN* ≤3cm without ENE* (**N1**), M0
IVA	Tumor >4cm with DOI > 10mm (**T4)**, N0-N2, M0 T1-T4a, and metastases in a single ipsilateral LN, > 3 cm but <6cm; or in multiple ipsilateral LNs, none >6 cm; or in bilateral or contralateral LNs, none >6cm; without ENE **(N2)**, M0 OR Invading adjacent structures: Lip (through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face). Oral cavity (invades through cortical bone, into deep muscle of tongue, maxillary sinus, skin of face) (**T4a**), N0-N2, M0
IVB	*** Any T, and LN mets >6cm without ENE OR mets in any LN >3cm with ENE (**N3**) Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery (**T4b**), any N, M0
IVC	Any T, Any N with distant metastatic disease (**M1**)

***N0** = No lymph node metastasis, **M0**= No distant metastasis, **DOI**= depth of invasion, **ENE** = extranodal extension, **LN** = lymph node

Stage	Nasopharynx
0	Tis (Carcinoma in situ), N0*, M0*
I	Tumor confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement (posterolateral infiltration of tumor) (**T1**), N0, M0
II	No tumor identified but EBV*-positive cervical LN*(s) (**T0**), N1, M0 OR

	T1, and unilateral cervical LN mets or any retropharyngeal LN(s) ≤ 6cm, above the caudal border of cricoid cartilage (**N1**), M0 OR Tumor with parapharyngeal extension and/or adjacent soft tissue involvement (**T2**), N0-1
III	T0-2, bilateral cervical LN met(s) ≤6cm above the caudal border of cricoid cartilage (**N2**), M0 OR Tumor involves bony structures of skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses (**T3**), N0-2, M0
IVA	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or with extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle (**T4**), N0-2, M0 OR Any T, any cervical LN met(s) >6cm and/or extension below caudal border of cricoid cartilage (**N3**), M0
IVB	Any T, Any N, and distant metastatic disease (**M1**)

***N0** = No lymph node mets, **M0**= No distant mets, **EBV**= Epstein Barr Virus, **LN** = lymph node

Stage	**Oropharynx p16- and Hypopharynx Clinical (cN) and Pathologic Staging (pN)**
0	Tis (Carcinoma in situ), N0*, M0*
I	Tumor ≤ 2cm (**T1^{O}**), N0, M0 Tumor limited to one subsite and/or ≤ 2cm (**T1^{H}**), N0, M0
II	Tumor >2cm but ≤ 4cm (**T2^{O}**), N0, M0 Tumor invades > 1 subsite of hypopharynx or adjacent site >2cm but ≤4cm or without fixation of hemilarynx (**T2^{H}**), N0, M0
III	Tumor >4cm or extension to lingual surface of epiglottis (**T3^{O}**), N0, M0 Tumor >4cm with fixation of hemilarynx or extension to esophageal mucosa (**T3^{H}**), N0, M0 OR T1-3^{O,H}, mets to single ipsilateral LN* ≤3cm and ENE*(**c**^{or}**pN1**), M0
IVA	Tumor invading larynx, extrinsic muscle of tongue, medial pterygoid, hard palate or mandible (**T4a^{O}**), **c/p**N0-2, M0 Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle or central compartment of soft tissue (**T4a^{H}**), **c/p**N0-2, M0

	OR T1-T4a^{O,H}, any ipsilateral or bilateral LN(s), >3 cm but ≤ 6cm without ENE (**cN2**), M0 T1-T4a^{O,H}, in single ipsilateral LN≤3cm with ENE or >3 cm but ≤ 6cm without ENE or mets to multiple LNs none > 6cm without ENE (**pN2**), M0
IVB	Any T, LN mets >6cm without ENE or any LN(s) with ENE (**cN3**), M0 Any T, LN mets >6cm without ENE or one ipsilateral LN >3cm with ENE or multiple LN(s) with ENE, or one contralateral LN of any size with ENE (**pN3**), M0 OR Tumor that invades lateral pterygoid muscle, pterygoid pates, lateral nasopharynx, or skull base or encases carotid artery (**T4b^{O}**), any N, M0 Tumor invades paravertebral fascia, encases carotid artery, or involves mediastinal structures (**T4b^{O}**), any N, M0
IVC	Any T^{O,H}, Any N, and distant metastatic disease (**M1**)

***N0** = No lymph node mets, **M0**= No distant mets, ^{O}= oropharynx, ^{H}= hypopharynx, **LN** = lymph node, **ENE**= extranodal extension

Stage	**Oropharynx p16+ Clinical (cTNM) and Pathologic Staging (pTNM)**
cI	cT0-T2 (No primary tumor identified (c**T0**) or Tumor ≤ 2cm (c**T1**), or Tumor > 2cm but ≤4cm **(T2**)), cN0-N1 (No regional mets (**cN0**) or ≥1 ipsilateral LN*(s) ≤6cm (**N1**), M0*
pI	pT0-T2 (No primary tumor identified (p**T0**) or Tumor ≤ 2cm (p**T1**), or Tumor > 2cm but ≤4cm **(pT2**)), pN0-N1 (No regional mets (**pN0**) or Mets in ≤ 4 LNs (**pN1**), M0
cII	cT0-T2, contralateral or bilateral LN ≤ 6cm **(cN2**), M0 OR Tumor > 4cm or extension to lingual surface of epiglottis **(cT3)**, cN0-N2, M0
pII	pT0-T2, pN0 or mets in ≥ 4 LNs **(pN2)**, M0 OR pT3-T4 (Tumor >4cm or extends into lingual surface of epiglottis (**pT3**), tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond **(pT4**)), pN0-N1, M0
cIII	cT0-T3, LN (s) > 6cm (**cN3**), M0 OR Tumor invades larynx extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond (**cT4**), any cN, M0

pIII	pT3-T4, pN2, M0
c/pIV	Any T, Any N, distant metastatic disease (**c/pM1)**

LN = lymph node, **M0**= No distant mets

Stage	**Larynx – Glottis($_{G}$), Supraglottis ($_{Sp}$), Subglottis ($_{Sb}$) Clinical (cTNM) and Pathologic Staging (pTNM)**
0	Tis (Carcinoma in situ), N0*, M0*
I	Tumor limited to one or both vocal cord (may involve anterior or posterior commissure) with normal mobility (**T1$_{G}$**), N0, M0
	Tumor limited to one subsite of supraglottis with normal vocal cord mobility (**T1$_{Sp}$**), N0, M0
	Tumor limited to subglottis (**T1$_{Sb}$**), N0, M0
II	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility (**T2$_{G}$**), N0, M0
	Tumor invades mucosa of >1 adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg. Mucosa of base of tongue, vallecular, medial wall of pyriform sinus) without fixation of the larynx (**T2$_{Sp}$**), N0, M0
	Tumor extends to vocal cord(s) with normal or impaired mobility (**T2$_{Sb}$**), N0, M0
III	Tumor limited to larynx with vocal cor fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage **(T3$_{G}$)**, N0, M0 OR T1-3$_{G}$, mets in ipsilateral LN* $\leq$ 3cm without ENE* (**N1****), M0
	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglotic space, paraglottic space, and or inner cortex of thyroid cartilage (**T3$_{Sp}$**), N0, M0 OR T1-3$_{Sp}$, N1, M0
	Tumor limited to larynx with vocal cord fixation and/or inner cortex of thyroid cartilage (**T3$_{Sb}$**), N0, M0 OR T1-3$_{Sb}$, N1, M0

IVA	Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g. trachea, cricoid, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) (**$T4a_G$**), N0-1, M0 OR T1-T4a, met in one ipsilateral LN > 3 cm $\leq$ 6cm with ENE, or in multiple LNs none > 6cm, without ENE (**cN2**), M0 OR T1-T4a, met in one ipsilateral LN $\leq$ 3cm with ENE, or > 3 cm $\leq$ 6cm without ENE, or in multiple LNs none > 6cm without ENE **(pN2)**, M0
	Tumor invading thyroid cartilage and/or invades beyond the larynx (e.g. Trachea, soft tissues of neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus (**$T4a_{Sp}$**), N0-1 OR $T1\text{-}T4a_{Sp}$, **c/p**N2, M0
	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g. Trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid or esophagus (**$T4a_{Sb}$**), N0-1 OR $T1\text{-}T4a_{Sb}$, **c/p**N2, M0
IVB	Tumor invades prevertebral space, encases carotid artery or invades mediastinal structures (**$T4b_G$)**, Any N, M0 OR Any T_G, any LN > 6cm with ENE or any LN with ENE (**cN3),** M0 OR Any T_G, any LN > 6cm without ENE or met in ipsilateral LN > 3cm with ENE or any LN of any size with ENE (**pN3),** M0
	Tumor invades prevertebral fascia, encases carotid artery or involves mediastinal structures (**$T4b_{Sp}$**), any N, M0 OR Any T_{Sp}, **c/p**N3, M0
	Tumor invades prevertebral fascia, encases carotid artery or involves mediastinal structures (**$T4b_{Sb}$)** with any LN involvement OR Any T_{Sb}, **c/p**N3, M0

IVC	Any $T_{G,Sp,Sb,}$ Any N, Distant metastatic disease (**M1)**

***N0** = No lymph node mets, **M0**= No distant mets, **LN** = lymph node, **ENE**= extranodal extension, **Nodal staging differs based on clinical or pathologic staging but is the same all parts of the larynx

Stage	**Maxillary Sinus ($_{MS}$), Nasal Cavity and Ethmoid Sinuses ($_{NE}$)**
0	Tis (Carcinoma in situ), N0*, M0*
I	Tumor limited to maxillary sinus mucosa without erosion or destruction of bone (**$T1_{MS}$**), N0, M0
	Tumor restricted to any one subsite, with or without bony invasion (**$T1_{NE}$**), N0*, M0*
II	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension into the posterior wall of maxillary sinus and pterygoid plates (**$T2_{MS}$)**, N0, M0
	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion (**$T2_{NE}$),** N0, M0
III	T1-$T2_{MS}$, mets in ipsilateral LN* $\leq$ 3cm without ENE* (**N1****), M0 OR Tumor invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor of medial wall of orbit, pterygoid fossa, ethmoid sinus **($T3_{MS}$**), N0-N1, M0
	T1-$T2_{MS}$, mets in ipsilateral LN* $\leq$ 3cm without ENE* (**N1****), M0 OR Tumor extends to the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate (**$T3_{NE}$**), N0, M0
IVA	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses ($T4a_{MS}$), N0-N2, M0 OR T1-$T3_{MS}$, met in one ipsilateral LN > 3 cm $\leq$ 6cm with ENE, or in multiple LNs none > 6cm, without ENE (**cN2**), M0 OR T1-$T3_{MS,}$ met in one ipsilateral LN $\leq$ 3cm with ENE, or > 3 cm $\leq$ 6cm without ENE, or in multiple LNs none > 6cm without ENE **(pN2)**, M0
	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses (**$T4a_{NE}$**), N0-1, M0 OR

	T1-T3 $_{NE}$, **c/p**N2, M0
IVB	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves except maxillary division of trigeminal nerve (V2), nasopharynx, or clivus (**T4b$_{MS}$)**, Any N, M0 OR Any T_{MS}, any LN > 6cm with ENE or any LN with ENE (**cN3),** M0 OR Any T_{MS}, any LN > 6cm without ENE or met in ipsilateral LN > 3cm with ENE or any LN of any size with ENE (**pN3),** M0
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx or clivus (**T4b$_{NE}$**) OR Any T $_{NE}$, **c/p**N3, M0
IVC	Any $T_{MS, NE,}$ Any N, Distant metastatic disease (**M1)**

***N0** = No lymph node mets, **M0**= No distant mets, **LN** = lymph node, **ENE**= extranodal extension; **Nodal staging differs based on clinical or pathologic evaluation but is the same all parts of the nasal cavity and paranasal sinuses

Stage	**Major Salivary Glands**
0	Tis (Carcinoma in situ), N0*, M0*
I	Tumor $\leq$ 2cm without extraparenchymal extension (clinical evidence of invasion of soft tissues) **(T1)**, N0, M0
II	Tumor >2cm and $\leq$4cm without extraparenchymal extension **(T2)**, N0, M0
III	Tumor >4cm and/or having extraparenchymal extension **(T3),** N0, M0 OR T0-3 mets in ipsilateral LN* $\leq$ 3cm without ENE* (**N1)**, M0
IVA	Tumor invades skin, mandible, ear canal, and/or facial nerve (**T4a**), N0-2, M0 OR T0-T4a, met in one ipsilateral LN > 3 cm $\leq$ 6cm with ENE, or in multiple LNs none > 6cm, without ENE (**cN2**), M0 OR

	T0-T4a, met in one ipsilateral LN ≤ 3cm with ENE, or > 3 cm ≤ 6cm without ENE, or in multiple LNs none > 6cm without ENE **(pN2)**, M0
IVB	Tumor invades skull base and/or pterygoid plates and/or encases carotid (**T4b**), Any N, M0 OR Any T, any LN > 6cm with ENE or any LN with ENE (**cN3),** M0 OR Any T, any LN > 6cm without ENE or met in ipsilateral LN > 3cm with ENE or any LN of any size with ENE (**pN3),** M0
IVC	Any, T, Any N, Distant metastatic disease (**M1)**

***N0** = No lymph node mets, **M0**= No distant mets, **LN** = lymph node, **ENE**= extranodal extension

7. GENERAL TREATMENT PRINCIPLES

Radiation Therapy: A total dose of 70Gy is needed for eradication of gross tumor and either 54-63Gy or 44-60Gy for elective treatment of potential sites.

1. Palliative RT should be considered for symptomatic disease.
    - Palliative radiotherapy:
        - 50Gy in 20 fractions
        - 37.5 Gy in 15 fractions
        - 30 Gy in 10 fractions or in 5 fractions given as 2 fractions/week
        - 20 Gy in 4 fractions
        - 8 Gy in 1 fraction
        - 44.4 Gy in 12 fractions
2. Neoadjvuant chemotherapy may be used when radiation is not readily available or to down stage when tumor cannot be treated within a radiation field without incurring significant risks to adjacent normal tissue.
3. All patients should undergo dental evaluation and extraction as needed, prior to concurrent chemoRT.
4. Preferred interval between resection and post-op RT is $\leq$ 6 weeks

Systemic Therapy: Listed in order of preference, 5FU = Infusional 5FU

- *Non-Nasopharyngeal: Definitive Systemic Therapy*
    1. Primary systemic therapy + concurrent RT
        1. High dose Cisplatin (preferred) or Carboplatin + 5FU
        2. Carboplatin + Paclitaxel or Cisplatin + 5FU or Cisplatin + Paclitaxel or Weekly cisplatin 40mg/m^2 or 5FU + Hydroxyurea
    2. Postoperative ChemoRT
        1. Cisplatin (preferred) for high risk non-oropharyngeal cancers
    3. Induction/Sequential Chemotherapy
        1. Docetaxel + Cisplatin + 5FU (Especially if induction is chosen and patient is PS0 or 1)
        2. Paclitaxel + Cisplatin + 5FU (if patient is PS 0 or 1) otherwise,
        3. Cisplatin/Carboplatin + 5FU or Carboplatin + Paclitaxel
        4. Following induction, agents used with concurrent ChemoRT
            - Weekly carboplatin or cisplatin
- *Non-Nasopharyngeal: Recurrent, Unresectable, or Metastatic (with no surgery or RT option)*
    - Combination Therapy
        1. Carboplatin OR Cisplatin + Docetaxel OR Paclitaxel

2. Cisplatin + 5FU
- Single Agents
  1. Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5FU, Methotrexate, Capecitabine

- *Nasopharynx: Definitive Systemic Therapy*
  - Chemoradiation followed by adjuvant chemotherapy
    1. Cisplatin + RT ☐cisplatin + 5FU
    2. Cisplatin + RT ☐carboplatin + 5FU or Cisplatin + RT followed by no further chemotherapy
  - Induction/Sequential Chemotherapy (Majority of our patients will receive this. Please discuss with RT specialists first)
    1. Cisplatin + 5FU or Cisplatin + Epirubicin + Paclitaxel
       - Docetaxel + Cisplatin + 5FU (for EBV associated)
    2. Docetaxel + Cisplatin
    3. Following induction, agents used with concurrent chemoRT
       - Weekly cisplatin or carboplatin
- *Nasopharynx: Recurrent, Unresectable, or Metastatic (with no surgery or RT option)*
  - Combination Therapy
    1. Cisplatin + Gemcitabine
    2. Cisplatin or Carboplatin + Paclitaxel OR Docetaxel
  - Single Agents
    1. Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5FU, Methotrexate, Capecitabine

- *High Grade Ethmoid/Maxillary Sinus: Definitive Systemic Therapy*
  - Carboplatin + Etoposide ± concurrent RT or cisplatin + etoposide + concurrent RT
  - Cyclophosphamide + Doxorubicin + Vincristine (without concurrent RT)

- *High Grade Ethmoid/Maxillary Sinus: Recurrent, Unresectable, or Metastatic (no surgery or RT option)*
  1. Cisplatin or carboplatin + etoposide
  2. Cyclophosphamide + Doxorubicin + Vincristine

Surgery:

- For T3-T4 primaries of the oropharynx, tonsillar lesions require radical tonsillectomy often with partial mandibulectomy. Base of tongue lesions require partial or total glossectomy and myocutaneous flap reconstruction.

- Laryngectomy: The decision to perform either total laryngectomy or conservation laryngeal surgery will be decided by the surgeon but should adhere to the principles of complete tumor extirpation with curative intent and function preservation. Patients who require removal of greater than half of the tongue or elderly patients with poor pulmonary function often require total laryngectomy to prevent subsequent aspiration. Therefore, for locally advanced oropharyngeal primary, organ preservation with concurrent chemoradiotherapy is preferred.

- Selective neck dissection:
    - N0
        - Oral cavity at least levels I-III
        - Oropharynx at least levels II-IV
        - Larynx at least levels II-IV and level VI when appropriate
        - Hypopharynx at least levels II-IV and level VI when appropriate

    - N1-N2a-c:
        - Selective or comprehensive neck dissection

    - N3
        - comprehensive neck dissection vs. radiation

2. Radical neck dissection: Removes levels I-V LNs, SCM, omohyoid, internal and external jugular veins, CN XI and submandibular gland

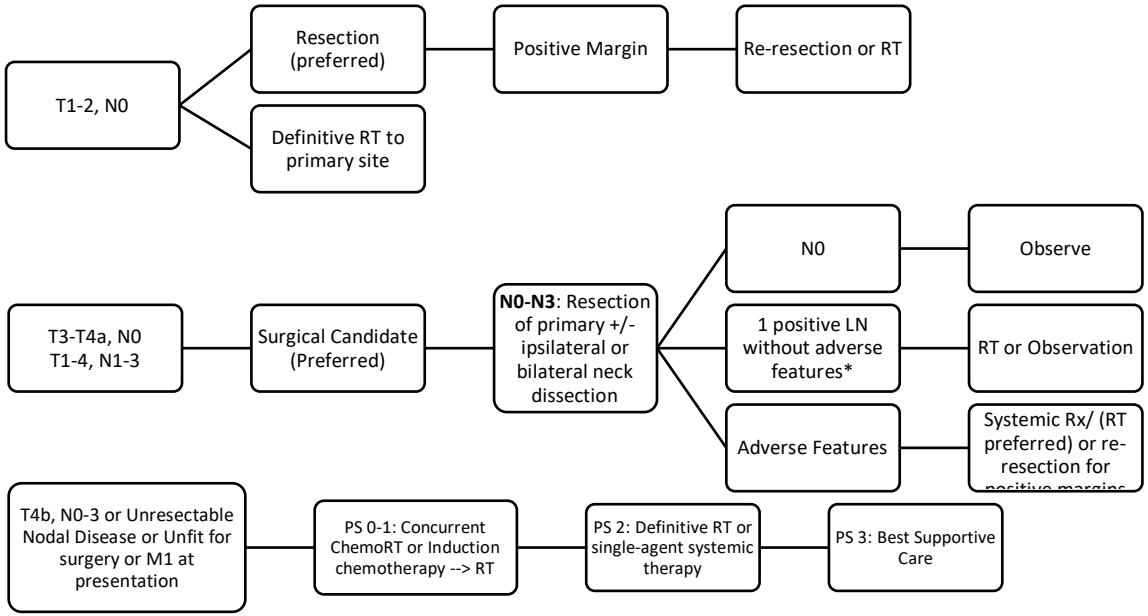
3. Modified radical neck dissection: Leaves more than one of SCM, internal jugular vein or CN XI

4. Supraomohyoid neck dissection: Removes levels I-III

5. Lateral neck dissection: Removes levels II-IV disease

- Surgical Management of Cranial Nerves VII, X (including the recurrent laryngeal nerve), XI, and XII:
    - Operative management of the facial nerve and other major cranial nerves during primary or regional node resection is influenced by the preoperative clinical function of the nerve.
    - When the nerve is functioning, thorough efforts should be made to preserve the structure and function of the nerve (main trunk and/or branches) --even if otherwise adequate tumor margins are not achieved--recognizing that the surgeon should leave no gross residual disease.

- Adjuvant postoperative radiation or chemoradiation is generally prescribed when a microscopic residual or gross residual tumor is suspected.
- Direct nerve invasion by a tumor and/or preoperative paralysis of the nerve may warrant segmental resection (and sometimes nerve grafting) at the discretion of the surgeon if tumor-free margins are assured throughout the remainder of the procedure.

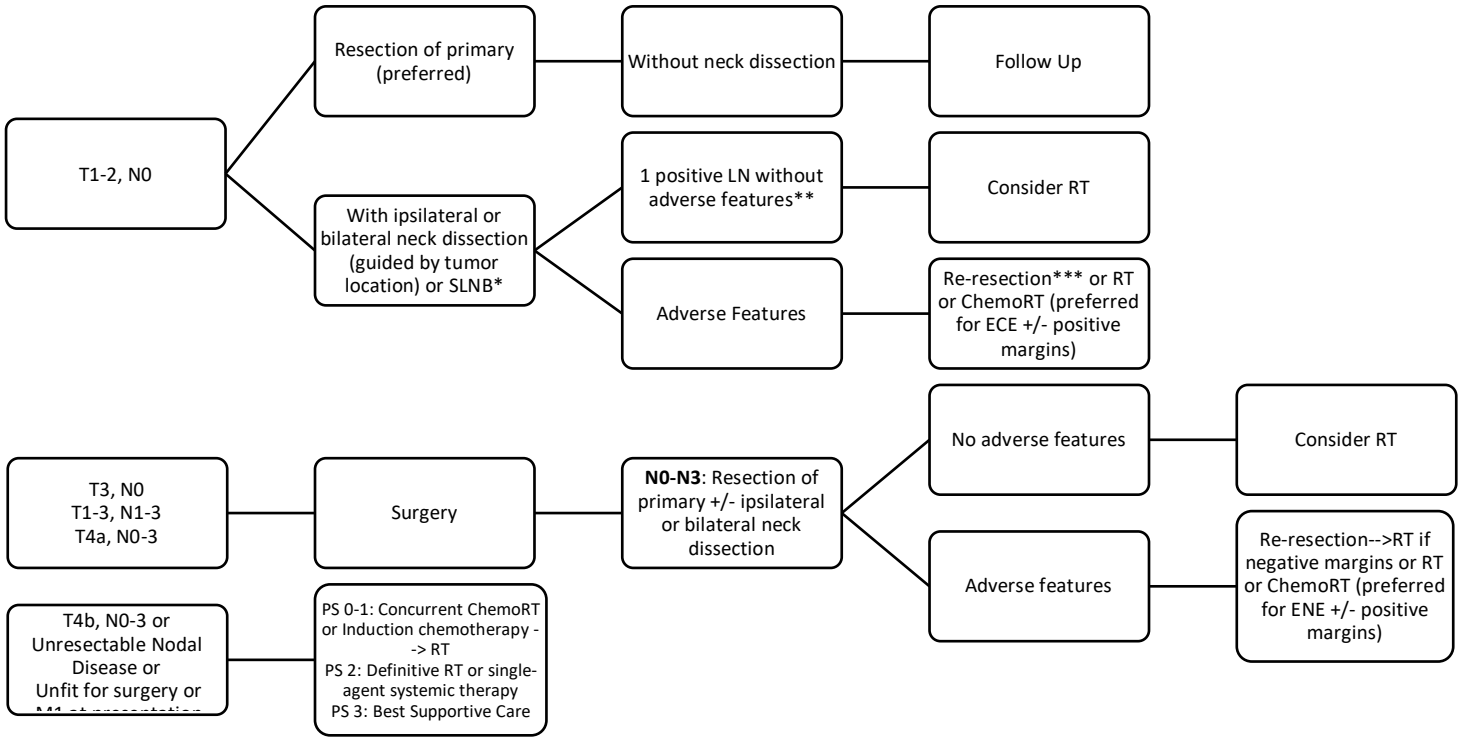


Cancer of Lip Mucosa

*Adverse features: positive margins, extracapsular extension, lymphovascular invasion, perineural invasion

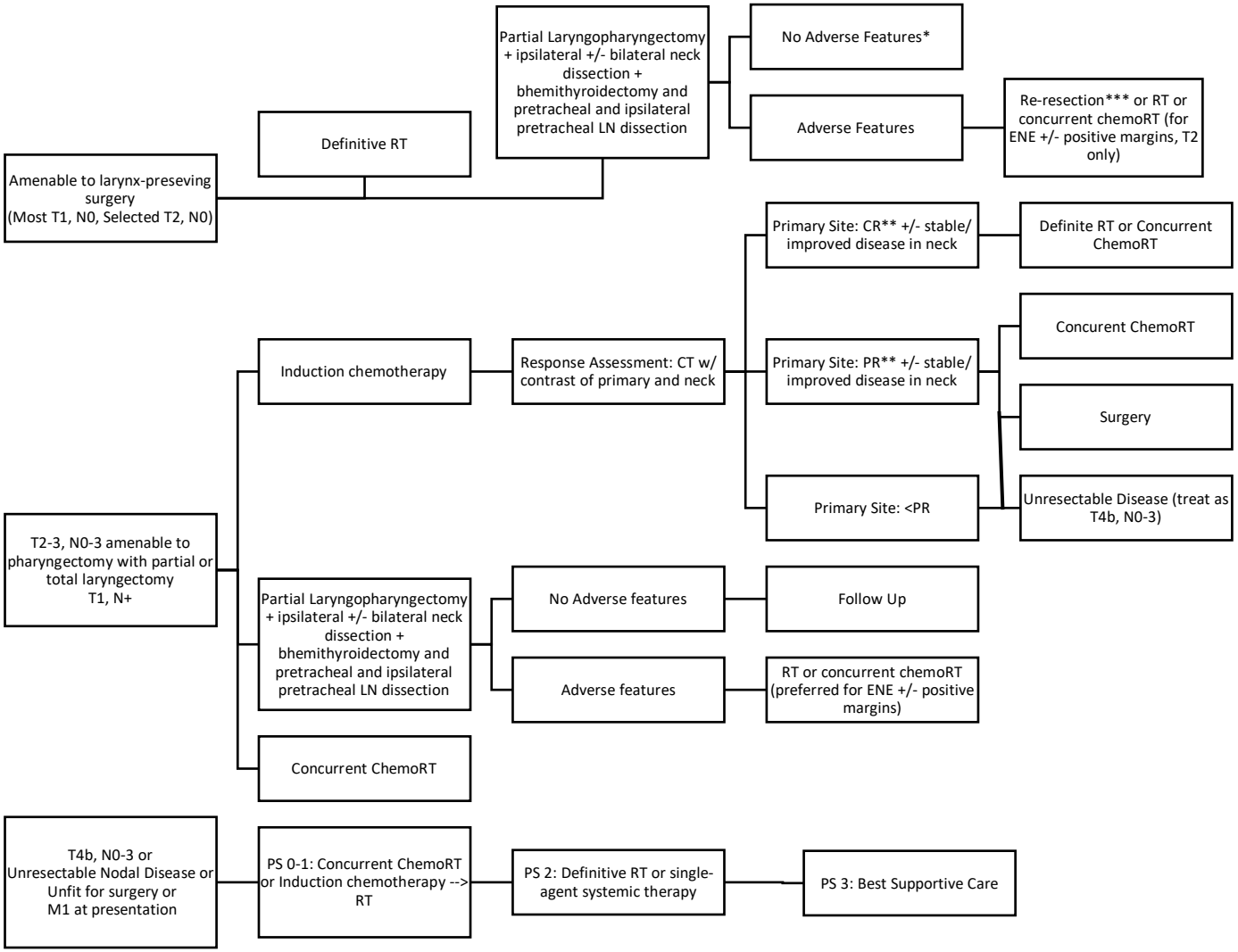
**PS: ECOG performance status

Cancer of Oral Cavity



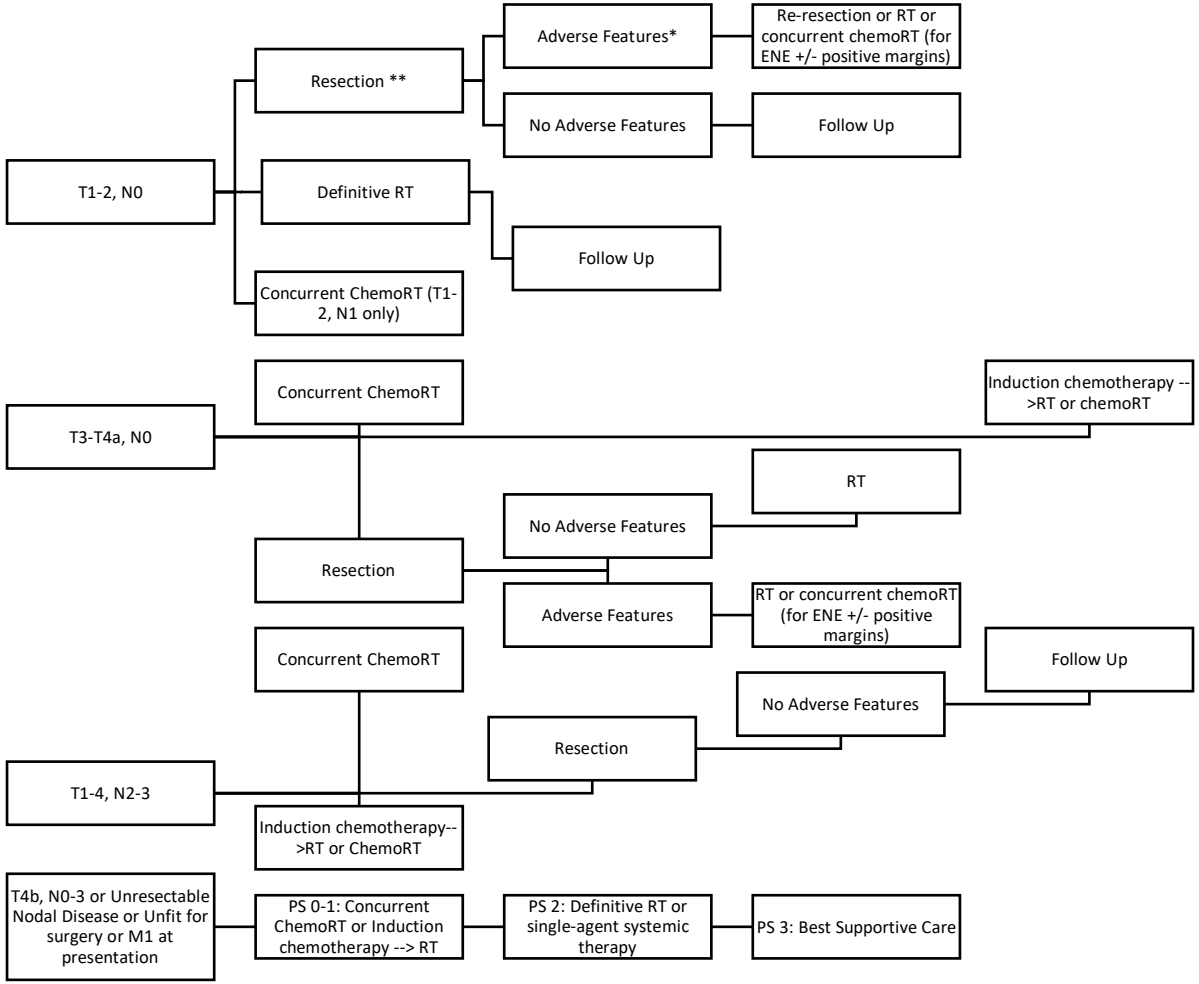
*SLNB: Sentinel Lymph Node Biopsy
**Adverse features: positive margins, extracapsular extension (ECE), lymphovascular invasion, perineural invasion
***Re-Resection: Can be considered for positive margins only
PS: ECOG performance status

Cancer of Hypopharynx



*Adverse features: extranodal extension, positive margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, perineural, vascular, or lymphatic invasion
** CR: Complete response, PR: partial response

***Re-Resection: Can be considered for positive margins only
PS: ECOG performance status

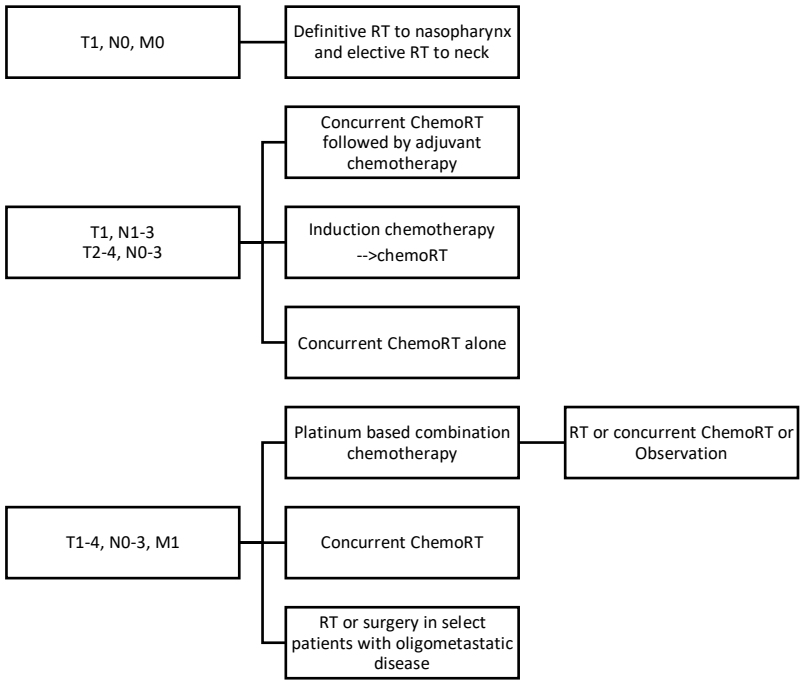


OROPHARYNX

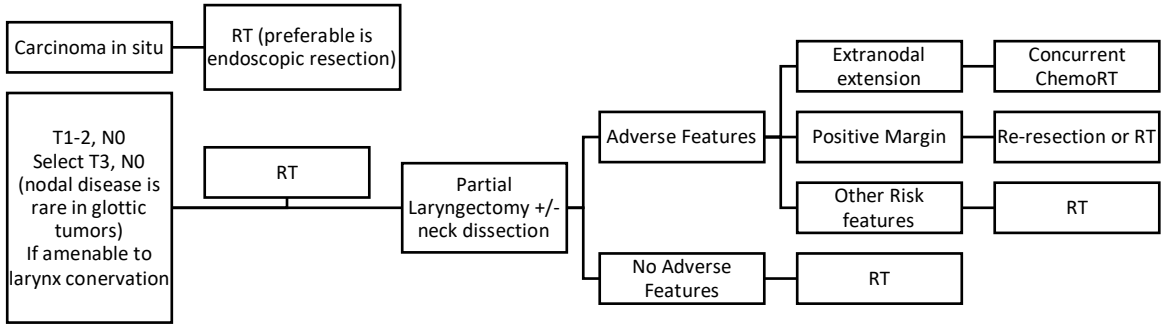
Adverse features: extranodal extension (ENE), positive margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, perineural, vascular, or lymphatic invasion
**Resection: Primary and ipsilateral or bilateral neck dissection
PS: ECOG performance status

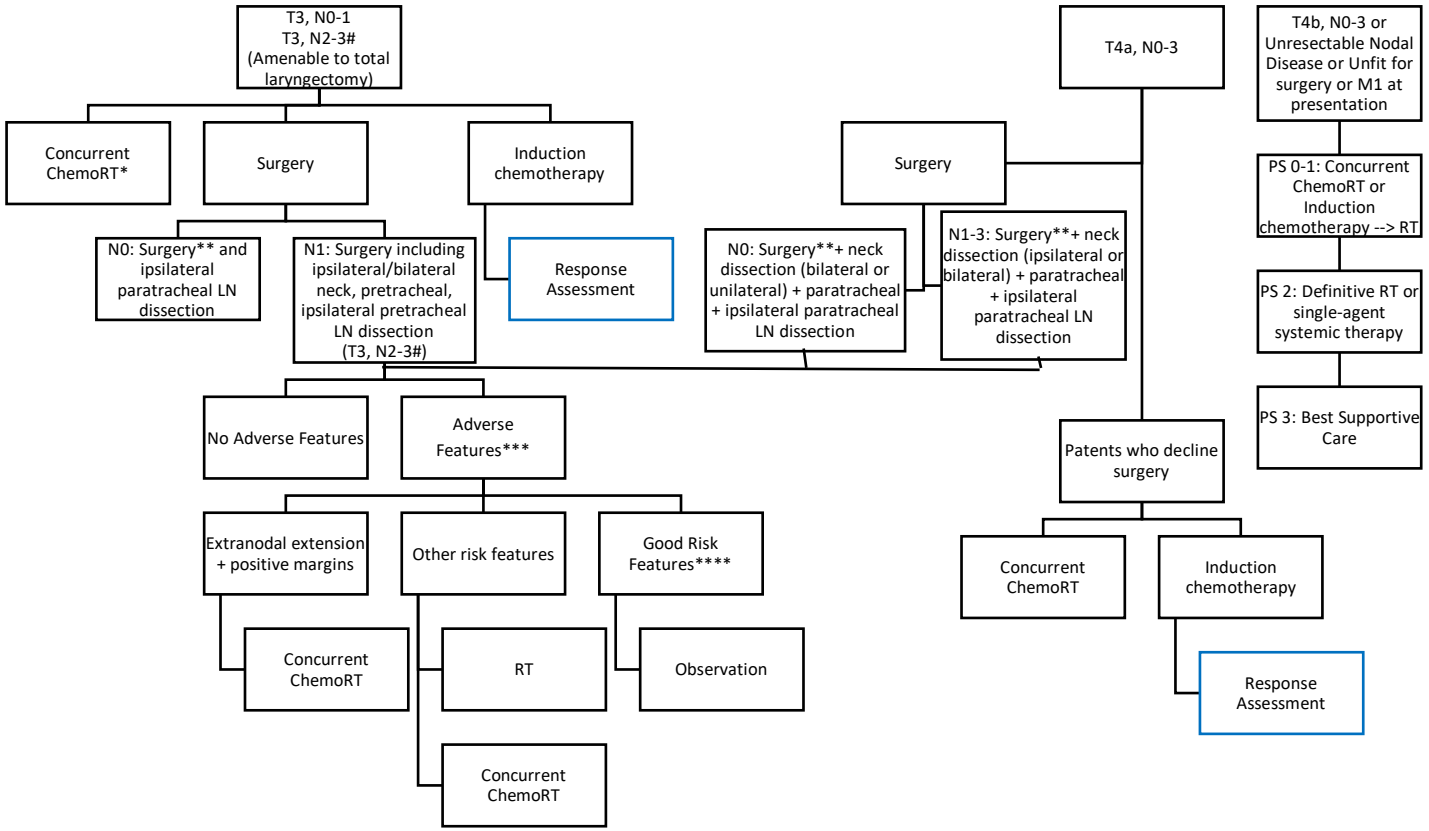
NASOPHARYNX CANCER (NPC)

The World Health Organization (WHO) III subtype is the most common form of NPC in endemic areas and differs from the squamous type of NPC in its association with the Epstein Barr virus (EBV) and sensitivity to chemotherapy and radiotherapy (RT). Subtyping is not yet available in Botswana.



LARYNX


Carcinoma in situ
RT (preferable is endoscopic resection)
T1-2, N0
Select T3, N0
(nodal disease is rare in glottic tumors)
If amenable to larynx conervation
RT
Partial Laryngectomy +/- neck dissection
Adverse Features
Extranodal extension
Concurrent ChemoRT
Positive Margin
Re-resection or RT
Other Risk features
RT
No Adverse Features
RT



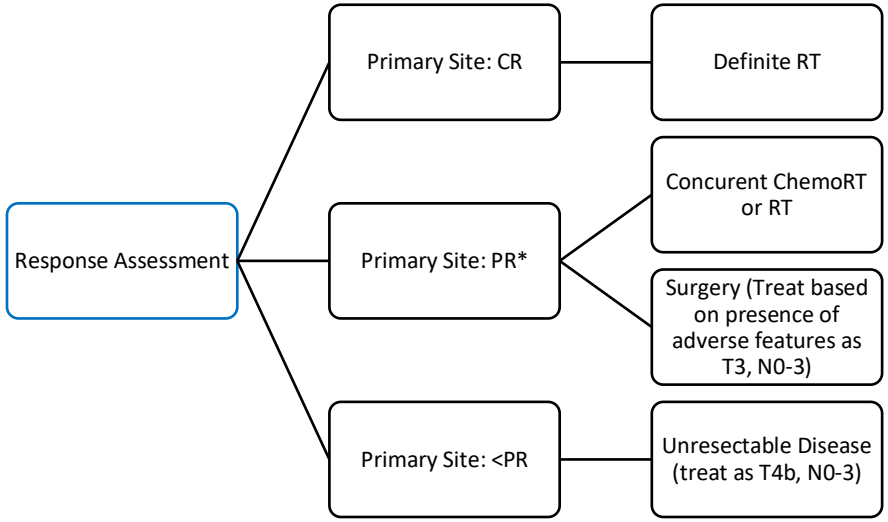
*Cisplatin is the preferred agent for concurrent ChemoRT

*Surgery includes laryngectomy with ipsilateral thyroidectomy

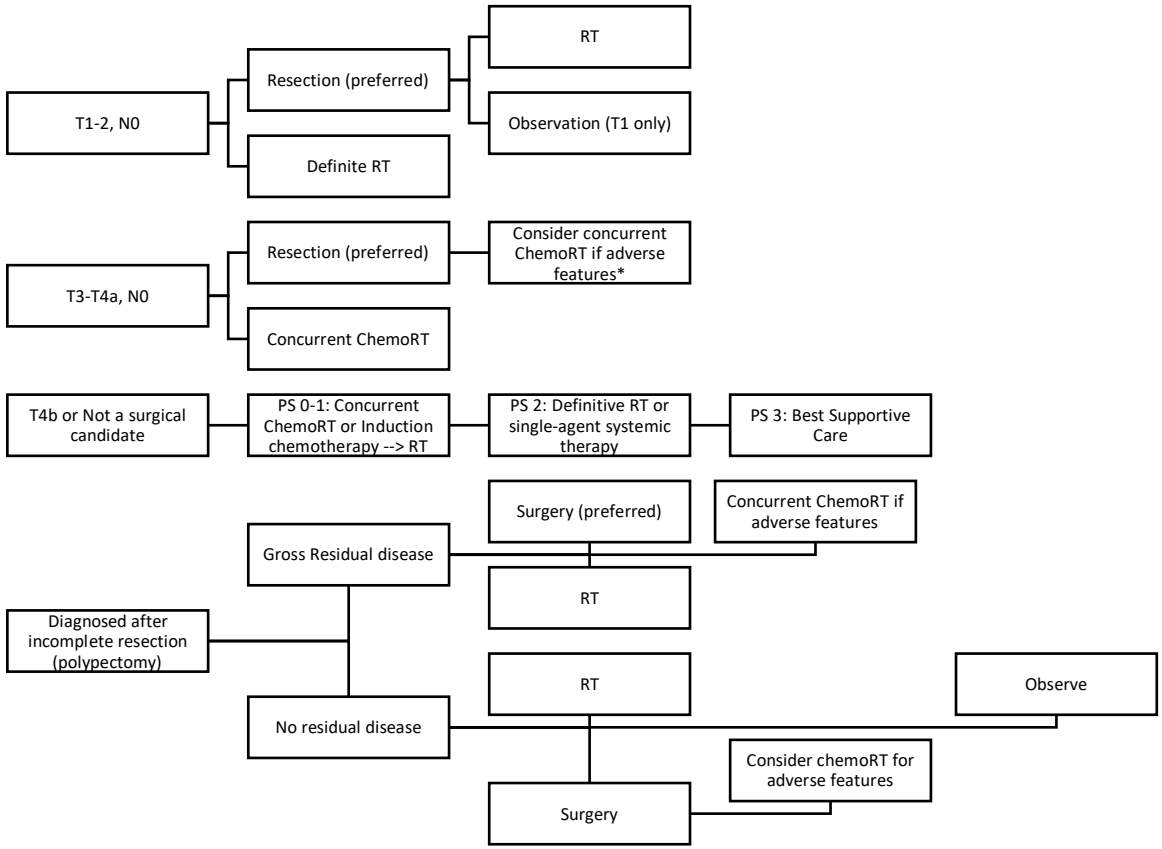
***Adverse Features: extranodal extension, positive margins, pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion

****Favorable T4a patients who can be observed after surgery: indolent histopathology (papillary variant of squamous cell carcinoma, verrucous carcinoma); widely negative margins, pN0 neck—especially level V without perineural or lymphovascular invasion; low volume disease with microscopic extranodal extension beyond the laryngeal skeleton, and widely negative margins; pN0, GradeI-II, subglottic extension <1cm

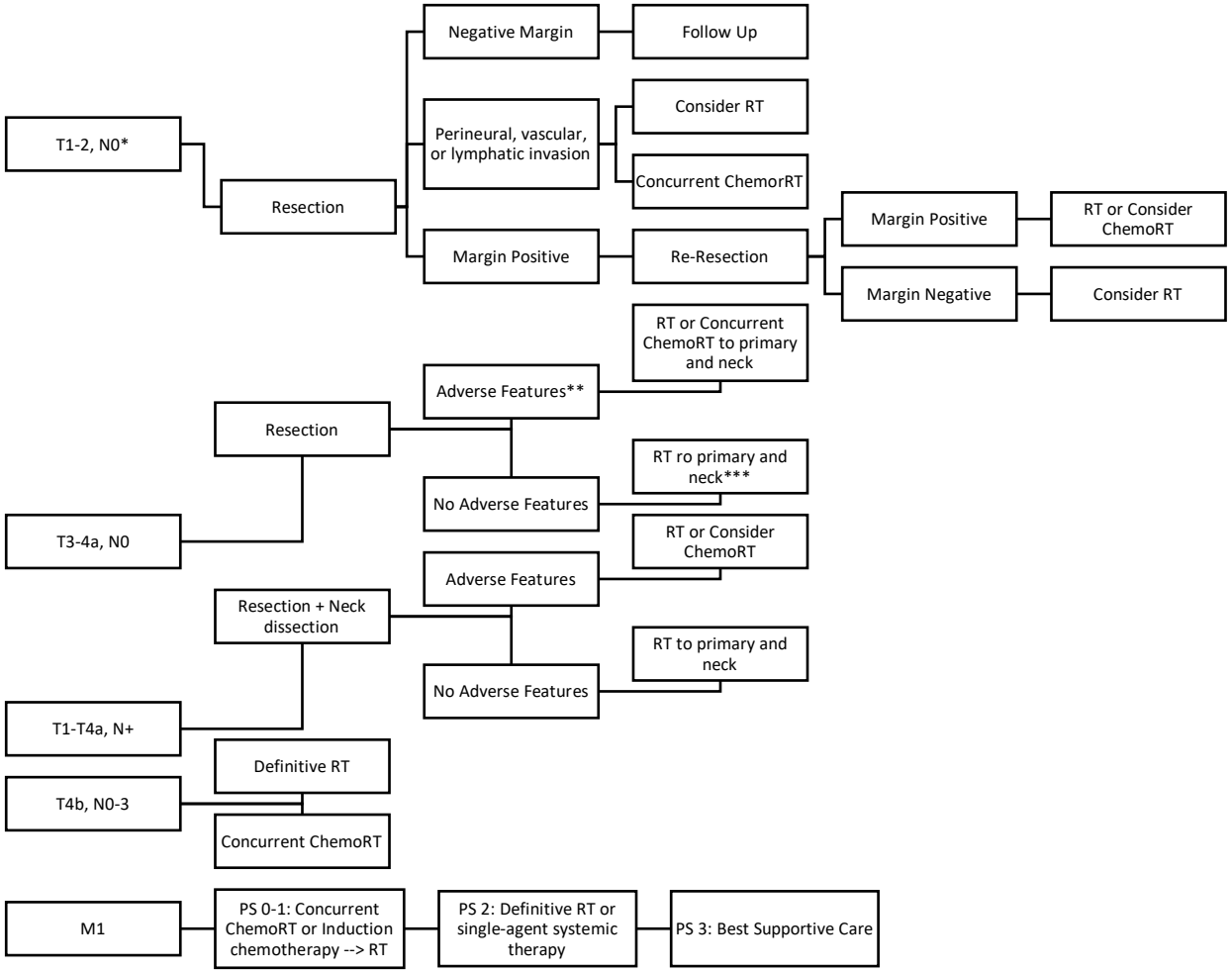
PS: ECOG performance status


Response Assessment
Primary Site: CR
Definite RT
Primary Site: PR*
Concurent ChemoRT or RT
Surgery (Treat based on presence of adverse features as T3, N0-3)
Primary Site: <PR
Unresectable Disease (treat as T4b, N0-3)

ETHMOID SINUS TUMORS

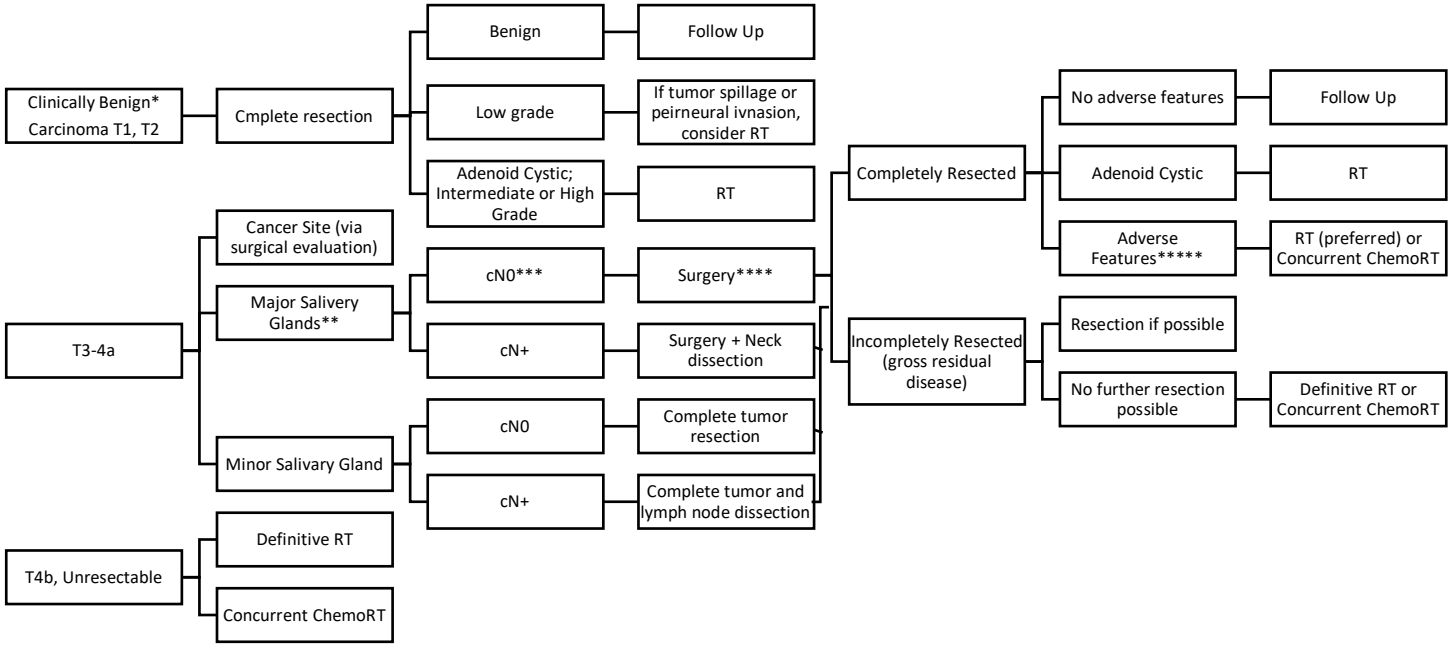


*Adverse Features: neuroendocrine features, small cell, high-grade olfactory esthesioneuroblastoma or neuroendocrine histologies.



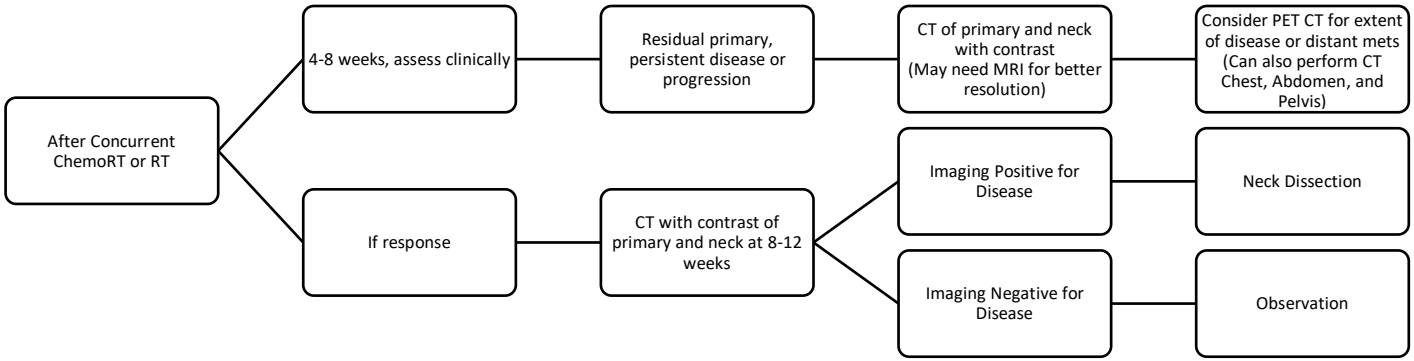
*Except for adenoid cystic histology; T1-1, N0 should be resected followed by adjuvant RT or observation for margin negative and no perineural spread.
**Adverse Features: neuroendocrine features, small cell, high-grade olfactory esthesioneuroblastoma or neuroendocrine histologies.
***For squamous cell carcinoma and undifferentiated tumors

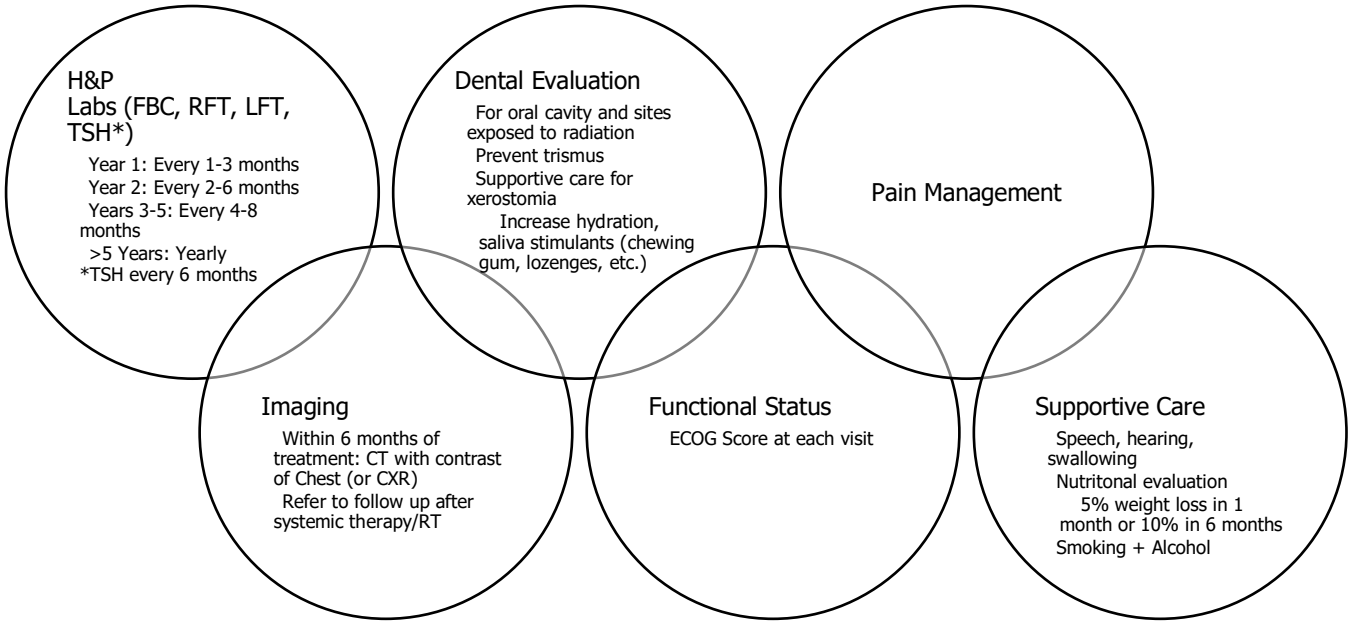
SALIVARY GLAND TUMORS



*Benign tumor: mobile superficial lobe, slow growth, painless, CN V and VII intact, no neck nodes
**Major Salivary Glands: Parotid, submandibular sublingual
***cN: Clinical nodal status
****Surgery: With complete resection of tumor +/- neck dissection for high grade and/or T3-4 tumors
*****Intermediate or high grade, close or positive margins, neural/perineural invasion, lymph node metastases, lymphatic/vascular invasion, T3-4 tumors

8. FOLLOW UP


After Concurrent ChemoRT or RT
4-8 weeks, assess clinically
Residual primary, persistent disease or progression
CT of primary and neck with contrast (May need MRI for better resolution)
Consider PET CT for extent of disease or distant mets (Can also perform CT Chest, Abdomen, and Pelvis)
If response
CT with contrast of primary and neck at 8-12 weeks
Imaging Positive for Disease
Neck Dissection
Imaging Negative for Disease
Observation



9. SPECIAL CONSIDERATIONS FOR NUTRITION

1. Obtain Dietician Evaluation
2. Feeding gastrostomy tube is essential prior to initiating cancer treatment if the patient has significant weight loss or dysphagia and final decision for feeding tube placement should be made in a multi-disciplinary clinic (MDT).

10. CHEMOTHERAPY DOSING

Ideally patients should be evaluated by an HIV provider to review possible drug-drug interactions with cisplatin prior to initiation of therapy.

Concurrent Chemoradiotherapy (for non-metastatic disease)

- Cisplatin (high dose)
  100mg/m2 IV on days 1, 22, 43

Palliative chemotherapy (or neoadjuvant chemotherapy)

- Gemcitabine/Cisplatin (neoadjuvant for nasopharyngeal only)
  Cisplatin 80mg/m2 d1
  Gemcitabine 1000mg/m2 d1,d8
  21d cycles

- TPX (neoadjuvant chemotherapy for other H&N with good functional status)
  Cisplatin is 75 mg/m2 D1
  Docetaxel is also 65 mg/m2 D1
  Capecitabine 2000mg/(m2) (days 1–14)
  Every 21 days, x 2 cycles and reassess clinically or with scans
  ***Support with ciprofloxacin 500 BID starting on day 2 or 3

- Carboplatin/Taxol (for unfit patients)
  Carboplatin AUC 5 D1 or carboplatin AUC2 q weekly
  Paclitaxel 80-100mg/m2 weekly
  Q21 – q28d

11. DOSE MODIFICATION AND TOXICITY

- If renal toxicity is noted, a repeat course of Cisplatin Injection should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the BUN is below 25 mg/100 mL.

- Dose adjustments for renal dysfunction:
  CrCl 10 to 50 mL/minute: Administer 75% of dose
  CrCl <10 mL/minute: Administer 50% of dose

- Encourage patients to maintain adequate hydration in the following 24 hours.

- Delay 1 week if platelet <100,000/mm3 and ANC <1500/mm3

- Audiometric testing is not available in the public sector and is not routinely done before cisplatin. If there is a clinical change in hearing is noted, cisplatin should be dose reduced or discontinued.

- If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do NOT flush the line); initiate sodium thiosulfate antidote; elevate extremity.

Appendix

HEAD and NECK CANCER HISTOLOGICAL SUBTYPES

Nasopharynx

- Squamous (>90%)
- Lymphoepithelioma = WHO III with high lymphoid component.
- Other: lymphoma, plasmacytoma, melanoma, chordoma, rhabdomyosarcoma, minor salivary gland

Oropharynx

- Squamous (95%); NHL (5%)
- Others: adenocarcinoma, mucoepidermoid, adenoid cystic, melanoma, small cell carcinoma.

Ethmoid and Maxillary sinus tumors
- Squamous cell carcinoma
- Adenocarcinoma
- Minor salivary gland
- Esthesioneuroblastoma
- Undifferentiated carcinoma (sinonasal undifferentiated carcinoma, small cell or sinonasal neuroendocrine carcinoma

Eastern Cooperative Oncology Group (ECOG, Zubrod, World Health Organization) performance scale

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

References:

1. Ferlay, Jacques, et al. "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012." *International Journal of cancer, 136.5* (2015): E359-E386.
2. Dryden-Peterson, Scott, et al. "Cancer incidence following expansion of HIV treatment in Botswana." *PLoS One* 10.8 (2015): e0135602.
3. Gillison, Maura L., et al. "Evidence for a causal association between human papillomavirus and a subset of head and neck cancers." *Journal of the National Cancer Institute* 92.9 (2000): 709-720.
4. Suneja, G., et al. "Cancer in Botswana: A prospective cohort study of cancer type, treatment, and outcomes." *International Journal of Radiation Oncology• Biology• Physics* 87.2 (2013): S492-S493.