# Gulf Federation For Cancer Control (GFFCC)

# PART (2)

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| **GULF FEDERATION FOR CANCER CONTROL (GFFCC)**<br><br>**GUIDELINES** | *September*<br><br>**2016** |

# Table of Contents

# GROUP (B)

1. **Breast Cancer**
2. **Colorectal cancer**
3. **Anal canal Cancer**

# B.1-BREAST CANCER CLINICAL MANAGEMENT GUIDELINES

## 1. Epidemiology

Breast cancer is the first cancer site in Kuwait accounting to about 20% of all cancers and 38% of cancers among females. The mean age at diagnosis was 52.3 (51.7-52.9) years for Kuwaiti females. The age-standardized incidence rate (ASR) in 2012 was 48.7 cases /100,000 for Kuwaiti patients compared to 43 cases /100,000 for the Middle East and North Africa (MENA) and 43.3 cases /100,000 for the world.

The etiology of the vast majority of breast cancer cases is unknown. However, numerous risk factors have been established including: increasing age, family history of breast cancer at young age, early menarche, late menopause, older age at the first live childbirth, prolonged hormone replacement therapy, previous exposure to therapeutic chest irradiation, benign proliferative breast disease, increased mammographic breast density, genetic mutations such as BRCA1/2 genes.

## 2. Clinical presentation

Most common presentations are

**2.1 Palpable mass**

The distribution of breast cancer by its location in the breast is UOQ, ~50%; UIQ, ~15%; LOQ, ~11%; LIQ, ~6%; and central; ~18%. Approximately 3% of breast cancers are multicentric.

**2.2 Nipple discharge,**

**2.3 Skin changes,**

**2.4 Nipple areola changes (Paget's disease),**

**2.5 Erythema with classical inflammatory changes with or without palpable mass (inflammatory breast cancer) or,**

**2.6 Abnormal mammographic findings.**

## *3.* Screening and Diagnostic Work-up

### 3.1 *Screening for Average risk population*

*3.1.1* Age 20-40 years: Clinical breast exam and directed imaging for palpable Abnormality

*3.1.2* >40: Annual mammogram and clinical breast exam

**3.2 *Screening for High-risk patients***

*3.2.1* Age 20–35 years: Clinical breast exam and directed imaging, i.e., MRI or sonography for palpable abnormality.

*3.2.2* ≥ 35 Annual mammogram/MRI and annual physical exam.

**3.3 *Work-up for established diagnosis***

*3.3.1* History and physical examination.

*3.3.2* CBC, Liver functions, Renal functions.

*3.3.3* Bilateral mammography ± ultrasound ± MRI.

*3.3.4* Pathology review, ER, PR and HER2 status determination.

*3.3.5* Bone scan is indicated in case of bone pain, elevated alkaline phosphatase or locally advanced presentation.

*3.3.6* Abdomino-pelvic CT is indicated in case of abdominal symptoms, abnormal examination or elevated liver enzymes, or locally advanced presentation.

*3.3.7* Chest CT if symptoms present or locally advanced presentation.

**3.4 *Assessment of pathology***

*3.4.1* Breast carcinomas can be divided into two major groups, *in situ carcinoma* and *invasive (infiltrating) carcinoma.* The in situ subtypes are *primarily ductal* carcinoma in situ (DCIS) and *lobular* carcinoma in situ. The distribution of the invasive subtypes includes 70–80% infiltrating duct cell cancers, approximately 10% infiltrating lobular, and the remaining infiltrating subtypes are mucinous, tubular, papillary, and medullary.

*3.4.2* Further, estrogen-receptor (ER), progesterone-receptor (PR), and human epidermal growth factor receptor HER2 status, Ki67 proliferation index are identified as important molecular features.

## 4. Staging

4.1 Clinical staging depends on findings from history and physical examination and imaging.

4.2 Pathological staging depends on findings during surgical resection and pathological examination. The 7$^{th}$ edition of the tumor, node, and metastasis (TNM) staging system of American Joint committee on cancer (AJCC, 2010) is used.

## 5. Prognostic Factors

The most significant prognostic factor is the axillary lymph node status, followed by tumor size, histologic grade, and age of the patient. Other prognostic factors include biologic subtypes as defined by ER and PR and/or amplified HER2. Based on these molecular markers, four prognostic subtypes of breast have been identified.

5.1 Luminal A
5.2 Luminal B
5.3 HER2 enriched
5.4 Basal like

# 6. Treatment

## 6.1 Non Invasive breast cancer

### 6.1.1 Lobular carcinoma in situ (LCIS)

Work-up includes history and physical examination, bilateral mammography and pathology review.

#### 6.1.1.1 Primary treatment

- If diagnosed by core biopsy, perform surgical excision.
- History and physical examination every 6-12 months for 5 years then annually. Mammography every 12 months.
- Consider tamoxifen as chemoprevention.

### 6.1.2 Ductal carcinoma in situ (DCIS)

Work-up includes history and physical examination, bilateral mammography and pathology review and ER determination.

#### 6.1.2.1 Primary treatment

- Lumpectomy without LN surgery + whole breast irradiation OR.
- Total mastectomy with or without SLN biopsy ± reconstruction OR.
- Lumpectomy without RT in some low risk disease (size, grade, margin, age).
- Re-excision to obtain negative margin may be performed. Patient not amenable for margin free lumpectomy should have total mastectomy. Margins less than 1 mm are considered inadequate. Wider margins (between 1-10 mm) are generally associated with lower recurrence rates.
- Consider tamoxifen for 5 years for ER +ve DCIS.

## 6.2 Invasive breast cancer

### 6.2.1 Early breast cancer (T1N0, T1N1, T2N0, T2N1, T3N0, T3N1& M0)

#### 6.2.1.1 Loco-regional therapy

- Lumpectomy with axillary staging + radiation therapy OR
- Mastectomy + axillary staging ± reconstruction and radiotherapy if indicated

#### 6.2.1.2 Systemic treatment

##### 6.2.1.2.1 Hormone receptor Positive and HER2 Positive

###### 6.2.1.2.1.1 Node negative

- Tumor ≤ 0.5 cm or microinvasive, N0 → adjuvant endocrine therapy
- Tumor ≤ 0.5 cm or microinvasive, N1mi → adjuvant endocrine therapy ± adjuvant chemotherapy and trastuzumab
- Tumor 0.6 -1 cm → adjuvant endocrine therapy ± adjuvant chemotherapy and trastuzumab
- Tumor > 1 cm →adjuvant endocrine therapy + adjuvant chemotherapy and trastuzumab

###### 6.2.1.2.1.2 Node positive

- Adjuvant endocrine therapy + adjuvant chemotherapy and trastuzumab

#### *6.2.1.2.2 Hormone receptor Positive and HER2 negative*

##### *6.2.1.2.2.1 Node negative*

- Tumor ≤ 0.5 cm or microinvasive, N0 → adjuvant endocrine therapy
- Tumor ≤ 0.5 cm or microinvasive, N1mi → adjuvant endocrine therapy ± adjuvant chemotherapy
- Tumor > 0.5 cm → consider 21-gene RT-PCR assay → adjuvant endocrine therapy ± adjuvant chemotherapy

##### *6.2.1.2.2.2 Node positive*

- Adjuvant endocrine therapy + adjuvant chemotherapy.

#### *6.2.1.2.3 Hormone receptor negative and HER2 positive*

##### *6.2.1.2.3.1 Node negative*

- Tumor ≤ 0.5 cm or microinvasive, N0 → No adjuvant therapy
- Tumor ≤ 0.5 cm or microinvasive, N1mi → consider adjuvant chemotherapy and trastuzumab
- Tumor 0.6 -1 cm → consider adjuvant chemotherapy and trastuzumab
- Tumor > 1 cm → adjuvant chemotherapy and trastuzumab

##### *6.2.1.2.3.2 Node positive*

- Adjuvant chemotherapy and trastuzumab

#### ***6.2.1.2.4 Hormone receptor negative and HER2 negative***

##### **6.2.1.2.4.1 Node negative**

- Tumor ≤ 0.5 cm or microinvasive, N0 → No adjuvant therapy
- Tumor ≤ 0.5 cm or microinvasive, N1mi → consider adjuvant chemotherapy
- Tumor 0.6 -1 cm → consider adjuvant chemotherapy
- Tumor > 1 cm → adjuvant chemotherapy

##### **6.2.1.2.4.2 Node positive**

- Adjuvant chemotherapy

**N.B Preoperative (neoadjuvant) chemotherapy or endocrine therapy,** If breast conservation is desired

### 6.2.2 Locally advanced invasive breast cancer (T0N2M0, T1N2M0, T2N2M0, T3N2M0, T4N0M0, T4N1M0, T4N2M0, Any T, N3&M0)

Neoadjuvant chemotherapy followed by either mastectomy + axillary dissection and postoperative radiotherapy or lumpectomy + axillary dissection and postoperative radiotherapy.

### 6.2.3 Stage IV disease (Any T, any N& M1)

Systemic chemotherapy and/or endocrine therapy ± radiotherapy.

### 6.2.4 Inflammatory breast cancer

- Preoperative chemotherapy and trastuzumab if HER2 is positive.
- If response is seen -→ total mastectomy + LN dissection + RT to chest wall and nodal areas then endocrine and/ or trastuzumab if ER and/ or HER2 are positive.
- If no response is seen -→ consider 2nd line systemic therapy and/or preoperative RT then Surgery + RT if not given +----etc.

## 7. Radiotherapy Protocol

***Indications for Post-operative radiation therapy in breast cancer:***

- As a part of conservative breast management of invasive breast cancer i.e. indicated in all patients underwent conservative surgery for invasive breast cancer. Boost is considered in all cases with invasive carcinoma
- Post-mastectomy if:
  - ≥ 4 positive nodes: Postoperative radiotherapy to chest wall and SC ± axilla ± IMC
  - 1- 3 positive nodes: Strongly consider RT to chest wall and SC ± IMC if adverse features present (high grade, young age, ENE ≥ 2 mm, primary ≥ 4 cm, surgical margins < 2 mm, lympho-vascular space invasion, or invasion of the skin, nipple or chest wall, high LN ratio).
  - Negative nodes: No routine adjuvant RT. Consider chest wall RT if adverse features present (positive margins, extensive lympho-vascular invasion, high grade, large primary). Consider additional SC RT if large primary (≥ 5 cm), inadequate axillary dissection (< 10).

### *7.1 External beam: Planning technique*

#### 7.1.1 Patient preparation:

No special preparation

#### 7.1.2 Immobilization:

The patient is positioned supine on the Chest Board. Wedge under knees. The arm on the affected side should be raised on the arm support so that it is at an angle of more than 90 degrees to the patients' body. The opposite arm should rest at the patients' side.

#### 7.1.3 Orientation, set-up, marking and reference points:

**7.1.3.1** Pre-scanning

7.1.3.1.1 Lumpectomy – wires to be placed around the breast and along the primary scar.

7.1.3.1.2 Mastectomy – wires to be placed along the length of the mastectomy scar and on the chest where the breast would have been (use the contra-lateral breast as a guide)

7.1.3.1.3 BBs to be placed on where the tattoos are going to be.

7.1.3.1.3.1 Medial setup point at midline – through the transverse section encompassing the maximum volume of breast tissue.

7.1.3.1.3.2 Lateral TTH 1.5cm post to mammary tissue - through the transverse section encompassing the maximum volume of breast tissue.

7.1.3.1.3.3 Sagittal at superior border (midway between medial and lateral tattoos).

7.1.3.1.3.4 Sagittal at inferior border (midway between medial and lateral tattoos

### 7.1.4 Image Acquisition:

**7.1.4.1** Superior border at level of angle of mandible

**7.1.4.2** Inferior border at a horizontal line 1.5 cm below the infra-mammary crease or the lower part of the breast (whichever is more inferior).

**7.1.4.3** Medial border at midline (ensure coverage of breast tissue or surgical scar)

**7.1.4.4** Lateral border at 1.5 cm posterior to the wire around the breast.

### 7.1.5 Target definition (RTOG Planning Atlas):

#### *7.1.5.1 CTV-reconstructed breast or chest wall (post mastectomy)*

The target volume is the skin flaps and scar and any subcutaneous tissues down to the deep fascia overlying muscles. In locally advanced breast cancer with skin infiltration, skin is included in the target volume.

#### *7.1.5.2 For post-lumpectomy radiotherapy*

For adjuvant radiotherapy after surgical excision of tumor, there is no GTV and the whole breast is the CTV 5mm below the skin. The aim is to treat all the glandular breast tissue down to deep fascia, but not the underlying muscle, rib cage, overlying skin or excision scar.

#### 7.1.5.3 Boost to Tumor Bed

Using CT data, the tumour bed can be visualized using clips placed at surgery around the wall of the surgical cavity to mark its posterior, lateral, medial, superior and inferior borders. The boost-CTV (tumour bed) includes the tumour bed and any seroma. In case of the absence of the surgical clips, seroma, post-operative fibrosis and scaring, pre-surgical images should be used as guidance to localize tumor bed.

The CTV-PTV margin is chosen as 5 mm for tumor bed boost irradiation.

### 7.1.6 The Technique

Three dimentional conformal technique is used for breast/chest wall and nodal irradiation.

### 7.1.7 Beam Arrangement

#### *7.1.7.1 Breast or chest wall*

Conformal two tangential open beams labeled as the medial and lateral tangs 6 MV photon with additional segmented fields according to the plan.

##### *7.1.7.1.1 Field Size*

- Anterior border is 2 cm anterior to the maximal breast tissue (the flash).
- Posterior border covers both medial and lateral BB.
- Superior border placed at the Superior BB.
- Inferior border placed at the Inferior BB on the sagittal cut.
- Check that the field size is compatible with the machine limits.

##### *7.1.7.1.2 Segmentation*

Compute the dose, evaluate the plan, adjust the beam weighting to improve the homogeneity and add segments as appropriate.

#### *7.1.7.2 Nodal Fields*

- An anterior field or anterior-posterior field are used to include level III axillary and supraclavicular nodes in the target volume.
- The medial border is placed at midline with a 10° gantry angle away from the larynx and spinal cord.
- The lateral border lies at the inner edge of the head of the humerus or at the surgical neck of humerus if the axilla is to be irradiated.
- The superior border extends at least 3 cm above the middle half of the clavicle, but laterally leaves a 1–2 cm margin of skin clear superiorly to avoid excessive skin reaction.
- Using a mono-isocentric technique to treat breast and lymph nodes, the inferior border is on line with the superior border of the tangential fields through the match line with the isocentre at depth.
- Shielding of the acromioclavicular joint and humeral head is important to avoid fibrosis and maintain shoulder mobility.

### *7.1.8 Beam Energies*

#### *7.1.8.1 Breast and reconstructed breast*

For most patients, 6 MV photons are chosen as optimal. However, with increased breast volume and separation, higher energies (commonly 15 or 18 MV) may produce better homogeneity. However, care should be taken to check that superficial cavity wall margins and scars of reconstructed breasts receive adequate dose.

#### *7.1.8.2 Chest wall*

- Conventional planning uses opposing tangential fields but dosimetry is rarely optimal because of the thin target volume of the chest wall surrounded by air and lung. Skin doses cannot be calculated or measured accurately and the use of bolus to the skin remains selective in high risk disease (after excision of local recurrence or extensive lymph-vascular invasion or skin infiltration).

- Electron fields have the advantage of avoiding the lung and heart, but CT should be used as the thickness of the chest wall which may vary throughout its volume, making choice of electron energy difficult, for most patients 6-12 MEV are chosen.
- Electrons to the chest wall may be combined with photons to the axilla and supraclavicular nodes.

#### *7.1.8.3 Tumour bed*

- Electron beams are used for tumor bed boost irradiation, target volume should be encompassed by the 90% iso-dose.
- For larger volumes, small tangential photon beams with CT planning may be preferable or mixed tangential + electron fields.

#### 7.1.8.4 Axillary and supraclavicular lymph node irradiation

- For advanced palpable axillary disease, extensive or residual axillary disease, an additional posterior opposing beam (18 MV) is used to give adequate dose with the anterior field (6MV).

#### 7.1.8.5 Internal mammary node irradiation

- Tangential fields are moved further across the midline on to the contralateral side to treat internal mammary nodes.

#### 7.1.8.6 Bilateral breast irradiation

- When bilateral breast irradiation is indicated, both arms are immobilized above the head. An appropriate gap of 1.5-2 cm should be left in the midline between the tangential fields to avoid overlap.

### *7.1.9 Dose prescription and fractionation*

#### *7.1.9.1 Adjuvant Radiotherapy*

##### *7.1.9.1.1 Breast, reconstructed breast and chest wall*

- 42.5 Gy in 16 daily fractions of 2.66 Gy given in 22 days (selected small well-formed breasts unlikely to suffer from acute skin reactions). OR
- 50 Gy in 25 daily fractions given in 5 weeks (large, pendulous breasts or post mastectomy or DCIS).

##### *7.1.9.1.2 Tumour bed*

- 10 Gy in 5 daily fractions given in 1 week
- 16–20 Gy in 8–10 daily fractions given in 2 weeks in case of incomplete excision or residual primary tumour.

##### *7.1.9.1.3 Lymph node irradiation*

- 50 Gy in 25 daily fractions given in 5 weeks.
- Doses are prescribed at depth of supraclavicular area (e.g. at 2.5-3 cm).

#### *7.1.9.2 Palliative Radiotherapy*

Dose of palliative breast irradiation is variable according to the general condition of the patients and expected survival. The dose might be:

- 8 Gy single fraction,
- 20 Gy over 5 fractions,
- 30 Gy over 10 fractions,
- 40 Gy over 15 fractions or
- 50Gy over 25 fractions.

### *7.1.10 Dose limitations to Organs at risk*

**7.1.10.1** The heart, especially the left anterior descending artery, should be excluded. Where this is impossible, maximum heart distance (MHD) must be kept to less than 1 cm, mean dose should be less than 5%.

**7.1.10.2** Lung V20 should be less than 30-35%

**7.1.10.3** Contra-lateral breast should be excluded

### *7.1.11 Verification*

**7.1.11.1** Plan is reviewed by the radiation oncologist and once accepted, secondary calculation using RadCalc by the physicist is done. Then, the patient setup done on the machine using the initial positioning and immobilization data as well as plan data.

**7.1.11.2** Portal images are taken and are compared to the DRR. Oncologist reviews the offline portal images within one working day. Marks are placed on the patient's skin. Treatment starts after portal approval.

**7.1.11.3** Weakly portal images are taken to verify the patient position which will be reviewed by the oncologist during the weekly follow-up of the patient.

## 7.2 Brachytherapy

Not used in referral center for breast RT.

## 7.3 Sequelae of treatment

To be included in pre-treatment discussion with patient and consent form.

### 7.3.1 Acute Radiation Sequelae

**7.3.1.1** Redness and skin irritation in the treatment area

**7.3.1.2** Loss of axillary hair in the treated area, usually temporary

**7.3.1.3** Tiredness, nausea and/or vomiting.

### 7.3.2 Chronic Radiation Sequelae

**7.3.2.1** After nodal radiotherapy, there is a risk of arm lymphedema,

**7.3.2.2** Breast edema, shrinkage, pain and tenderness,

**7.3.2.3** Skin telangiectasia,

**7.3.2.4** Shoulder stiffness after nodal irradiation

**7.3.2.5** Rib fracture,

**7.3.2.6** Symptomatic lung fibrosis,

**7.3.2.7** Cardiac morbidity

**7.3.2.8** Second malignancy when radiotherapy is combined with chemotherapy
**7.3.2.9** Nerve injury after nodal irradiation (very rare).

# 8 Principles of hormonal therapy

**8.1 In premenopausal patients** at diagnosis, either Tamoxifen (Tam) 20 mg daily for 5 years ± ovarian function suppression or aromatase inhibitors (AIs) + ovarian suppression (OFS). After 5 years, extended hormonal treatment may be considered according to the menopausal status of the patient.

**8.2 In postmenopausal patients**, 5 years of AIs or 5 years Tamoxifen or 5 years sequential AIs/Tam, after the 5 years extended hormonal treatment may be considered according to the risk category of the patient.

# 9 Principles of chemotherapy

## 9.1 Regimens for neoadjuvant/adjuvant chemotherapy in HER2 negative:

**9.1.1** Dose dense AC (Adriamycin+ Cyclophosphamide) followed by weekly Paclitaxel
**9.1.2** Dose dense AC (Adriamycin+ Cyclophosphamide) followed by Paclitaxel every 2 weeks
**9.1.3** Dose dense AC (Adriamycin+ Cyclophosphamide)
**9.1.4** CMF (Cyclophosphamide+ Methotrexate + 5-Flurouracil)
**9.1.5** AC followed by Docetaxel every 3 weeks
**9.1.6** AC (Adriamycin+ Cyclophosphamide) followed by weekly Paclitaxel
**9.1.7** EC (Epirubicin+ Cyclophosphamide)
**9.1.8** FEC (5-Flurouracil+ Epirubicin+ Cyclophosphamide) followed by T
**9.1.9** TAC (Docetaxel+ Adriamycin+ Cyclophosphamide)

## 9.2 Regimens for neoadjuvant/adjuvant chemotherapy in HER2 positive:

**9.2.1** AC (Adriamycin+ Cyclophosphamide) followed by T (Docetaxel or Paclitaxel) + Trastuzumab ± pertuzumab

**9.2.2** TCH (Docetaxel + Carboplatin+ Trastuzumab)

# 1. Management of Recurrence

- First, any recurrence should be biopsied.
- Determination of the ER/PR and HER2 status if originally unknown, negative, or not over expressed.

## *1.1 Treatment*

### *1.1.1 Local recurrence only*

1.1.1.1 If initially treated with lumpectomy-→ Total mastectomy -→then consider systemic therapy.
1.1.1.2 If initially treated with mastectomy + prior RT-→ Surgical resection if possible-→ then consider systemic therapy.

1.1.1.3 If initially treated with mastectomy + no prior RT-→ Surgical resection if possible + RT to chest wall and nodal areas-→ then consider systemic therapy.

### *1.1.2 Regional or loco- regional recurrence:*

1.1.2.1 Axillary recurrence →surgical resection if possible + RT to the chest and nodal areas.

1.1.2.2 Supraclavicular (S.C) recurrence → RT to the chest and nodal areas versus S.C alone.

1.1.2.3 Internal mammary (IMC) recurrence-→ RT to the chest and nodal areas and internal mammary areas versus IMC only.

### *1.1.3 Systemic recurrence*

According to the ER, PR, and HER2 status (chemotherapy, hormonal therapy and targeted therapy) + Denosumab or Zoledronic acid in case of bone metastasis

## 11 Follow up:

11.1 History and physical examination is considered every 4 months for the first 2 years then every 6 months for the subsequent 3 years then yearly thereafter.

11.2 Mammography is considered on yearly basis for all patients.

11.3 Bone mineral density (BMD) is considered for patients receiving aromatase inhibitors and bone modifying agents are given accordingly. BMD is repeated every 2 years or otherwise according to the previous result.

11.4 Gynecological follow-up is recommended for patients receiving tamoxifen.

## 12 Ongoing departmental studies

12.1 Retrospective study on outcome for breast cancer patients less than 35years at time of diagnosis treated in referral center.

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# B.2- RECTAL CANCER CLINICAL MANAGEMENT GUIDELINES

## 1. Epidemiology

The estimated age-standardized incidence rate of colo-rectal cancer for Kuwait in 2012, is 16.7 new cases per 100,000 population. The rate is lower than that estimated for the world (17.2 new cases per 100,000 population); yet Kuwait had the highest estimated rate compared to other Gulf countries. It is the second cancer site in Kuwait if female related malignancies are excluded, accounting to about 9.0% from all cancers in Kuwait. The disease is equally distributed to both sexes in Kuwaiti population. Mean age at diagnosis was 55 years for Kuwaitis.

The majority of newly diagnosed colorectal cancers are sporadic (75%). Genetic disorders that carry a predisposition for colorectal cancers include hereditary non-polyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP). Patients who have a higher probability of HNPCC should be tested for microsatellite instability or immunohistochemistry to identify protein expression for the mismatch genes.

## 2. Clinical Presentation

Common presenting symptoms of rectal cancer include

2.1. Frank rectal bleeding,
2.2. Constipation, diarrhea (particularly for obstructive lesions),
2.3. Narrowing of stool caliber,
2.4. Tenesmus,
2.5. Rectal urgency,
2.6. Urinary symptoms, or
2.7. Sciatic pain, suggestive of locally advanced disease.

## 3. Diagnosic work up

3.1. Complete history and physical examination including digital rectal examination (DRE) and rigid sigmoidoscopy with biopsy
3.2. Complete blood count, liver and renal function tests
3.3. CEA and CA 19.9
3.4. Chest X-ray (alternatively CT scan), and CT of liver and abdomen (PET-CT indicated if equivocal finding on CT scan should be done)
3.5. MRI pelvis is recommended in order to select patients for preoperative staging and Extent of the tumor prior to external beam radiation or upfront surgery
3.6 Complete colonoscopy preoperatively is required
3.7 Histo-pathological examination should include :
  3.7.1 Surgical specimen with proximal, distal and circumferential margins
  3.7.2 Regional lymph nodes (at least 12 nodes are recommended to be examined)
  3.7.3 The circumferential resection margin (CRM) status is very important.
  3.6.4 Vascular and nerve invasion should be evaluated.
  3.6.5 K-ras mutation tested (especially in cases presented with metastatic disease)
3.8 PET-CT scan for initial staging and as guidance for planning of radiotherapy if possible

3.9 Assessment of response after pre-operative chemo-radiation is done by MRI pelvis and PET/CT if done before treatment

## 4. Staging

4.1. Clinical staging depends on findings from history and physical examination and imaging.

4.2. Pathological staging depends on findings during surgical resection and pathological examination. The 7th edition of the tumor, node, and metastasis (TNM) staging system of American Joint committee on cancer (AJCC, 2010) is used.

## 5. Prognostic Factors

Stage at presentation is the most important prognostic factor for rectal cancer. Other adverse prognostic factors include serum carcinoembryonic antigen (CEA) level, and presence of obstructive or perforated lesions

## 6. Treatment

### 6.1 Aims of treatment

**6.1.1** To reduce risk of residual disease in the pelvis, and thus will reduce the risk of local recurrence

**6.1.2** To preserve good sphincter function if possible.

### 6.2 Treatment according to stage

#### 6.2.1 cT 1-2, N0

***6.2.1.1*** Trans-abdominal resection, low anterior resection (LAR) or abdomino-perineal resection (APR). Further management will be planned according to pathological staging.

***6.2.1.2 Post-operative management:***

- pT1-2, N0, M0: observation only.
- pT3, N0, M0 / pT1-3, N1-2, M0: Adjuvant chemo-radiation followed by adjuvant chemotherapy.

#### 6.2.2 cT3, N0 / any T, N1-2

***6.2.2.1*** Pre-operative chemo-radiotherapy followed by trans-abdominal resection followed by Adjuvant chemotherapy.

***6.2.2.2*** If patient has medical comorbidities contraindicating multimodality treatment, upfront trans-abdominal resection and further adjuvant treatment planned according to pathological staging. This will help some patients to avoid overtreatment. However, pT3N0M0 or pT1-3 N1-2 should be treated as mentioned above (if tolerable).

#### 6.2.3 cT4 unresectable

***6.2.3.1*** Pre-operative chemo-radiotherapy followed by

***6.2.3.2*** Trans-abdominal resection (if possible)

***6.2.3.3*** Adjuvant chemotherapy

#### 6.2.4 Any T, any N& M1 with resectable metastasis:

All options are available and can be applied depending on each individual case after multidisciplinary discussion.

##### *6.2.4.1 Palliative chemotherapy +/- targeted therapy followed by*

- Primary resection with metastatectomy followed by chemo-radiation.
- Concomitant chemo-radiation followed by resection of primary and metastasis.
- Trans-abdominal resection of the primary and synchronous metastatectomy
  - Proven pT1-2 N0: chemotherapy only
  - Proven pT3-4 N0 or any T N1-2: concomitant chemo-radiation.
- Concomitant chemo-radiation followed by resection of primary and metastasis followed by chemotherapy. Restaging after initial treatment should be done and monitoring of response is mandatory

#### 6.2.5 Any T, any N& M1 with un-resectable metastasis OR inoperable:

If patient presented with obstruction or bleeding, palliative chemo-radiation or diverting colostomy may be intended first. Palliative chemotherapy should follow.

In selected cases that turn to be resectable and have stable disease for 4-6 months, radical resection of primary and metastatectomy (or radical chemo-radiation if not given before) may be considered.

## 7 Radiotherapy Protocol

The following process is to provide current clinical treatment regimens for the radiotherapy of rectal cancer whether preoperative or post-operative (with concomitant chemotherapy) or on palliative bases.

### 7.1 External beam: planning technique

#### 7.1.1 Patient preparation (rectal and bladder status)

##### *7.1.1.1 The day before simulation*

- Patient should avoid eating large amount of fruits and vegetables, beans and dairy products

##### *7.1.1.2 The evening before simulation*

- Patient should take two table spoons of laxative. This will help in bowel movements.

##### *7.1.1.3 The day of simulation*

- Patient should eat light meals before simulation. Avoid large amount of fresh fruits and vegetables, beans and dairy products. If patient have not had a bowel movement in the past 16 hours, then patient should take another two table spoons of laxative.

##### *7.1.1.4 One hour before simulation*

- Patient should evacuate the bladder and drink 500 cc of water before simulation to make bladder full (at least 70%)

- Repeat this bladder filling process before each of daily radiation treatments.

### 7.1.2 Immobilization

Belly board devices improve immobilization and reduce set-up errors in the prone position.

### 7.1.3 Orientation, set-up, marking and reference points

*7.1.3.1* Patients lie in the prone position.

*7.1.3.2* The small bowel can be displaced anteriorly by the use of the belly board, which allows it to fall forwards into its aperture.

*7.1.3.3* A radio-opaque marker is placed on the anal verge and a DRE performed to determine the distance from the anal verge marker to the inferior edge of the tumor.

*7.1.3.4* For patients with colostomy or ileostomy, place CT wire around tape on skin.

*7.1.3.5* Ostomy bags should be emptied prior to CT.

*7.1.3.6* Patient aligned with 3 laser beams. Set 3 marks on the patient skin. The middle one in the midline, 2 cm superior to the anal cleft and the two lateral marks at 7 cm PA depth.

*7.1.3.7* Permanent ink (or tattoo) is applied to the lateral and midline reference points

*7.1.3.8* In case of PET/CT planning, the radiographer is responsible to ensure patient positioning in the same imaging position with the belly board in the Gama camera. PET/CT diagnostic study, if performed, should be done before the planning study to avoid wash out of radio nucleotide material. The PET scan usually is done after the acquisition of the CT images. This may cause some hallo of FDG in bladder as it will be more distended with urine. Also some intestinal movement may alter the normal bowel uptake.

### 7.1.4 Image acquisition

*7.1.4.1* CT examination will be performed on a four-detector spiral CT scanner using a slice thickness of 3 mm. Slices are acquired from L3-4 to 4cm below the anal marker.

*7.1.4.2* In case of PET/CT simulation, Images are printed and transferred to viewing station on CD.

### 7.1.5 Target definition

*For pre-operative radiotherapy (phase I, II)*

Clinical indications and eligibility for preoperative XRT:

- Eligible histologies: adenocarcinoma, undifferentiated carcinoma
- Inferior border of tumor within 15 cm of anal verge.
- Clinical Stage T1-2 N1-2, T3-4 N0-2

#### *7.1.5.1* GTV:

Is defined as the gross tumor as evident by initial imaging and investigations. All the data obtained from DRE, colonoscopy, CT and MRI scans, and PET/CT should be correlated carefully. This should include the primary tumor and the gross nodal metastasis.

#### *7.1.5.2* CTV:

CTV: It includes the GTV and potential microscopic spread to adjacent tissues including the mesorectum and pre-sacral space, perirectal and presacral nodes including nodes close to the obturator foramen (include lateral pelvic nodes). The distal internal iliac nodes will be treated.

- **CTV Phase I**
  - **For low rectal tumors:**

The caudal extent of this elective target volume should be a minimum of 2 cm caudal to gross disease, including coverage of the entire mesorectum to the pelvic floor even for upper rectal cancers. Unless there is radiographic evidence of extension into the ischio-rectal fossa, extension of CTV does not need to go more than a few millimeters beyond the levator muscles. For very advanced ano-rectal cancers, extending through the mesorectum or the levators, add ~1-2 cm margin up to bone wherever the cancer extends beyond the usual compartments.

- **For mid-rectal tumors:**

The posterior and lateral margins of CTV should extend to lateral pelvic sidewall musculature or, where absent, the bone. Anteriorly, CTV is extended to ~1 cm into the posterior bladder, to account for day-to-day variation in bladder position. Also in the mid pelvis, include at least the posterior portion of the internal obturator vessels (which lie between the external and internal iliacs in the mid pelvis) with CTV.

- **For upper rectal tumors*:***

The recommended superior extent of the peri-rectal component of CTV was at whichever is more cephalad: the recto-sigmoid junction or 2 cm proximal to the superior extent of macroscopic disease in the rectum/peri-rectal nodes. The most cephalad extent of CTV will be higher than the peri-rectal component, in order to properly cover the internal iliac and pre-sacral regions. The most cephalad aspect of CTV should be where the common iliac vessels bifurcate into external/internal iliacs (approximate boney landmark: sacral promontory).

***N.B.*** For rectal carcinomas extending into gynecologic or genitourinary structures, the external iliac region should be added (i.e. elective nodal coverage for these cases). Inguinal nodes may be included if the distal vagina or anus is involved by direct extension of primary or recurrent tumor.

➢ **CTV Phase II**

Boost clinical target volumes extend to entire mesorectum and presacral region at involved levels, including ~2 cm cephalad and caudal in the mesorectum and ~2 cm on gross tumor within the anorectum.

#### *7.1.5.3* PTV

PTV margin should be 0.7 cm around the CTV, except at skin.

**For post-operative radiotherapy**

- It is indicated only if there is a residual local disease or T3, T4 lesions and/or positive lymph nodes
- No GTV is delineated
- Same CTV and PTV applied for phase I in pre-operative treatment (see before) are considered CTV and PTV for post-operative treatment
- Direct contact with the operating surgeon is mandatory for more details regarding the localization of the tumor, any residue left and any clips positioned in surgical field.

#### *7.1.5.4* For palliative radiotherapy

- If patient has not received irradiation before, CTV and PTV will be the same as in pre-operative treatment section.
- If patient received radiation before to the same area of interest i.e. pelvis, re-irradiation target should be individualized according to site of recurrence and related symptoms.

7.1.5.5 OAR include Lung, heart and contralateral breast

### 7.1.6 The Technique

Three dimentional conformal technique is used.

### 7.1.7 Beam Arrangement

*7.1.7.1* For pre-and post-operative radiotherapy, three-field technique is preferred i.e. posterior open field and two later wedged fields.

*7.1.7.2* For palliative irradiation, beam arrangement depends on the gross recurrence site with special attention to the previously irradiated OAR.

### 7.1.8 Beam energies

(6-18 MV) photon beams are used.

### 7.1.9 Dose prescription and fractionation (e.g. long vs. short course)

*7.1.9.1 For preoperative irradiation:*

- *Long (standard) radiation course()*:
- Phase I: 45 Gy in 25 fractions
- Phase II: 5.4Gy in 3 fractions
- Concomitant with capcitabine

- *Short radiation course:*
- May be used in proximal tumors, early stage (Stage II and III mid rectal cancers who do not have threatened circumferential radial margins) and/or metastatic disease to liver only with potential respectability of both primary and liver metastasis.
- 25 Gy in 5 fractions without chemotherapy.

#### *7.1.9.2 For postoperative irradiation*

- 50.4Gy in 28 fractions to the pelvis
- Concomitant with capcitabine

#### *7.1.9.3 For un-resectable cancer*

- Doses higher than 54 Gy may be required if technically possible (45 Gy/5weeks + tumor boost up to 60 Gy) for palliation.

#### *7.1.9.4 For palliative irradiation*

- Dose varies from single fraction of 8 Gy to 30 Gy in 10 fractions according to the symptom and site to be treated.

### 7.1.10 Dose limitation to Organs at risk

*7.1.10.1* ***Small bowel:*** 45-50Gy max point dose; V30 <200cc

*7.1.10.2* ***Femoral heads:*** 45Gy max point dose; V30 <50%

*7.1.10.3* ***External genitalia:*** 25Gy max point dose; V20 <50%

*7.1.10.4* ***Bladder:*** 65Gy max point dose; V35 <50%

*7.1.10.5* ***Large bowel:*** 45-50Gy max point dose; V30 <200cc

Bowel should be contoured up to ~ 1 cm above the PTV. This, in turn, implies that absolute volume of bowel (in cc) is more important than relative volume (in %). The bowel should be contoured tightly, rather than with a broad, ill-defined margin. It is recognized that the location of bowel could vary from one day to the next, but the DVH from the simulation should remain representative.

With regard to large bowel, it is very important to recognize that all of the rectum and much of the recto-sigmoid will be part of CTV and, therefore, should NOT be treated as an avoidance structure. Therefore, it is recommended that "uninvolved colon", defined to be that part of the large bowel that lies outside the CTVs, be contoured separately from the rectum.

### 7.1.11 Verification:

*7.1.11.1* Normalization to a prescription point: Review prescription point position and ensure it is 1.5cm away from air bone and field borders

*7.1.11.2* Editing Isodose Lines:

- Show relevant isodose lines in values (105, 100, 95, 90, 80, 70, 60, 50, 40%)
- Ensure the target volume is homogeneously covered (- 5%/ +7%) of the prescription dose.

- Identify point of maximum dose and make sure that it is <10%. Plans with hotspots of 10% or more to an area greater than 2 $cm^2$ (1.6cm diameter point) in any plane shall be improved.
- D100 GTV = 100% prescribed dose (4500cGy in Ph1) & (540cGy in Ph2)
- D100 PTV = 95% prescribed dose (4275cGy in Ph1)
- Non-PTV volume cannot receive more than 97% prescribed dose.

## 7.2 Brachytherapy

Not Applicable.

## 7.3 Sequelae of treatment

To be included in pre-treatment discussion with patient and consent form.

### 7.3.1 Acute Radiation Sequalae: (Table B.2.a)

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Redness and skin irritation in the treatment area<br>- Loss of pubic hair in the treated area, usually temporary<br>- Tiredness<br>- Nausea and/or vomiting | - Diarrhea<br>- Sores and bleeding from the bowel | - Narrowing or blockage of the bowel (these side effects may occur as well after treatment and be serious enough to require surgery) |

### 7.3.2 Late Radiation Sequalae: (Table B.2.b)

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Loss of pubic hair in the treated area, usually temporary<br>- Sterility in fertile women and men | - Sores and bleeding from the bowel<br>- Narrowing and dryness of the vagina and genital area with dyspareunia and possibly bleeding<br>- Inability to have or keep an erection (impotence)<br>- Hip fracture | - Narrowing or blockage of the bowel (these side effects may occur as well after treatment and be serious enough to require surgery)<br>- Fibrosis of the urinary tubes<br>- Development of an abnormal path or connection between organs (fistulae) |

### 7.3.3 Chemotherapy (Capcitabine) Expected Toxicity: (Table B.2.c)

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Diarrhea with cramping, indigestion<br>- Loss of appetite<br>- Dry skin with rash, cracking, and/or peeling<br>- Hair fall<br>- Redness, tenderness, peeling, and/or tingling of the palms and soles of the feet<br>- Puffiness of the hands and feet<br>- Mouth sores and sore throat<br>- Low white blood cell count, which may increase the risk of infection<br>- Low red blood cell count, which may result in anemia, tiredness, and/or shortness of breath<br>- Low platelet count, which may result in increased bruising and bleeding | - Nausea and or vomiting<br>- Eye irritation, watery eyes, and/or runny nose<br>- Blurred vision<br>- Darkening and thinning of the skin<br>- Darkening, dryness, and marking of the nails<br>- Increased sensitivity to sunlight<br>- Headaches, which may continue<br>- Light-headedness<br>- For women, missed menstrual periods | - Confusion<br>- Unsteadiness, loss of coordination<br>- Temporary loss of consciousness<br>- Slurred speech<br>- Dry cough and shortness of breath<br>- Vomiting blood from the digestive tract<br>- Serious infection, which may be life threatening<br>- Allergic reactions, which can involve flushing, difficulty breathing, and low blood pressure and which can be life threatening<br>- Change in heart rhythm<br>- Damage to the heart or spasm of the heart's blood vessels that can cause chest pain<br>- Heart attack<br>- Kidney damage<br>- Inflammation of the liver, which may result in yellowing of the skin and eyes, tiredness, and/or pain on the upper right of the stomach area |

## 8 Principles of hormonal treatment

Not applicable

## 9 Principels of chemotherapy

9.1 Radiation therapy is delivered with concomitant Capcitabine 825 mg/m2 twice daily during radiotherapy days. It should be taken 30 minutes after meals

9.2 On treatment investigations includes CBC weekly for patients receiving Capcitabine.

## 10 Management of Recurrence

### 10.1 Diagnosis of recurrence

**10.1.1** Rising tumor markers: imaging should be done to confirm site and extent of recurrence.

**10.1.2** CT showing isolated pelvic recurrence.

### 10.2 Treatment options

**10.2.1** Resection of isolated pelvic recurrence if available followed by systemic treatment.

**10.2.2** Palliative chemo-radiation if no radiotherapy given before.

**10.2.3** Palliative chemotherapy in cases of distant metastasis or local un- resectable recurrence previously received radiation.

# 11 Follow up

## 11.1 For patients receiving pre-operative chemo-radiotherapy:

**11.1.1** **For patients received Long course of radiotherapy:**

***11.1.1.1*** MRI for assessment of response 6-8 weeks after finishing radiotherapy

***11.1.1.2*** Referral for surgical intervention thereafter to be done before 8 weeks post-radiotherapy.

***11.1.1.3*** Adjuvant chemotherapy, if indicated.

***11.1.1.4*** Long-term follow up as in post-operative context

**11.1.2** **Patients received short course of pre-operative radiotherapy:**

***11.1.2.1*** should undergo surgery within 7 days of the last fraction of preoperative RT

## 11.2 For patients receiving post-operative radiotherapy:

**11.2.1** Complete history and clinical examinations including digital rectal examination should be done at every 4 months for 1st 2 years, every 6 months for next 3 years, then annually thereafter.

**11.2.2** Tumor markers (CEA and CA 19.9): Every visit.

**11.2.3** CT of abdomen and pelvis +/- MRI pelvis annually for 3 years.

**11.2.4** Colonoscopy should be done at 1 year then 3-5 years as clinically indicated.

## 11.3 For patients receiving palliative radiotherapy:

**11.3.1** Follow up individualized according to general status and further management.

# 12 Ongoing departmental studies

**Not Applicable.**

## 13 References:


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6. ICRU 83 Volume 10 No1 2010.
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# B.3- ANAL CANAL SQUAMOUS CELL CARCINOMA CLINICAL MANAGEMENT GUIDELINES

## 1. Epidemiology

Carcinoma of the anal canal is a rare disease, accounts for 1–2% of all gastrointestinal malignancies and 4% of anal–rectal cancers. The age-standardized incidence rate (ASR) in 2012 was 0.1 cases /100,000 for Kuwaiti male patients and 0.3 cases /100,000 for Kuwaiti female patients, compared to 0.3 cases /100,000 for gulf male patients and 0.2 cases /100,000 for female gulf patients. And for the world, the ASR was 0.3 cases /100,000 for male patients and 0.6 cases /100,000 for female patients.

The etiology of disease has not been clearly identified; however, a number of risk factors have been identified for anal carcinoma. The most significant risk factors include human papilloma virus (HPV) infection, immunosuppression, and smoking.

## 2. Clinical presentation

Commonly observed signs and symptoms of anal cancer include

**2.1** Bleeding (45% cases at presentation),

**2.2** Anal pain/mass.

**2.3** Anal incontinence is associated with tumor invasion into anal sphincter (5% cases).

**2.4** Change in bowel habit,

**2.5** Tenesmus and

**2.6** Pruritus.

## 3. Diagnostic work-up

Diagnosis and clinical staging depends on findings from history and physical examination.

**3.1** Digital rectal examination (DRE). Examination of inguinal lymph nodes (LN) and FNA of suspicious LN

**3.2** Routine laboratory tests including HIV test, CD4 counts

**3.3** Recommended: chest, abdomen CT, pelvic MRI

**3.4** Optional: FDG/PET-CT

**3.5** Anoscopy/ proctoscopy and biopsy

## 4. Staging

The staging is typically based on clinical findings with biopsies of the primary tumor and regional lymph node. The 7th edition of the TNM staging system of American Joint Committee on Cancer (AJCC, 2010) is used.

## 5. Prognostic Factors

**5.1** Staging at diagnosis is the most important prognostic factor of anal cancer.

**5.2** Adverse prognostic factors include male gender, age ≥ 65 years, haemoglobin levels ≤ 10 g/l at presentation, nodal metastasis at presentation, poor performance status, and the presence of HIV infection or AIDS, especially if CD4 counts are less than 200 µl.

The 5-year overall survival rates of patients with well or poorly differentiated disease are roughly 75 and 25%, respectively.

## 6. Treatment

Radical chemo-radiation is established as the primary treatment for squamous cell carcinoma of the anus. Level IA evidence has shown comparable 5 year survival and local control rates to the radical surgery, with the benefit of preservation of sphincter function. The UKCCCR trial of radiotherapy versus chemo-radiation showed a 46% improvement in local control by the addition of concomitant chemotherapy.

Surgical excision may be considered for:

- Small low grade tumours of the anal margin, where sphincter preservation is possible and risk of lymphatic invasion is low.
- Persistent or recurrent tumours.
- May be considered for tumours that have destroyed the anal sphincters.

**Aim of treatment, (**except in metastatic cases), is radical elimination of the tumor from the primary site and regional lymphatics with functional preservation of the anal canal.

### 6.1 Treatment of anal canal squamous carcinoma

#### 6.1.1 cT 1-2, N0

Radical concomitant chemo-radiation

#### 6.1.2 cT3-4, N0 / any T, N1-3

Radical concomitant chemo-radiation

#### 6.1.3 Metastatic disease

Palliative Chemotherapy, Radiation may be considered to relief local symptoms of advanced disease e.g. bleeding or severe pain

### 6.2 Treatment of anal margin carcinoma

#### 6.2.1 T 1, N0, low grade

Local wide excision: according to surgical margin:

Adequate margin: just observation

Inadequate margin: re-excision with wider margin is advised. If not possible, radical chemo-radiation is considered

### 6.2.2 T2-4, N0 / any T, N1-3

Radical concomitant chemo-radiation

### 6.2.3 Metastatic disease

Palliative chemotherapy, Radiation may be considered to relief local symptoms of advanced disease e.g. bleeding or severe pain

## 6.3 Assessment of response after chemoradiation:

Evaluation after 8-12 weeks of radiation must be done to assess response and plan further management. Assessment includes:

**6.3.1** Clinical examination and DRE.

**6.3.2** Biopsy of any suspicious lesion at primary site.

**6.3.3** If inguinal LN were initially infiltrated, reassessment by examination, US and Biopsy if needed.

**6.3.4** If PET/CT was initially done for staging or planning, repeat PET/CT

## 6.4 Treatment after reassessment 8 weeks post-chemoradiation

### 6.4.1 In case of Complete Remission

Keep under follow up

### *6.4.2* In case of Stable Disease

6.4.2.1 Re-evaluate after 4 weeks. If:

- Regression: continue observation and follow up in 3 months. Once progressed, treat with surgery
- Progression: treat with surgery.

### 6.4.3 In case of progressive disease

6.4.3.1 Re-biopsy and re-stage. If:

- Local disease only: abdomino-perineal resection + inguinal LN dissection (if proved positive; on affected side only)
- If re-staging proved metastasis treat with palliative chemotherapy

# 7. Radiotherapy protocol

The following process is to provide current clinical treatment regimens for the radiotherapy of anal cancer whether with radical intent or on palliative bases.

## 7.1 External beam planning techniques

### 7.1.1 Patient preparation

#### *7.1.1.1 The day before simulation*

Patient should avoid eating large amount of fruits and vegetables, beans and dairy products

#### *7.1.1.2 The evening before simulation*

Patient should take two table spoons of laxative. This will help in bowel movements.

#### *7.1.1.3 The day of simulation*

Patient should eat light meals before simulation. Avoid large amount of fresh fruits and vegetables, beans and dairy products. If patient has not had a bowel movement in the past 16 hours, then patient should take another two tablespoons of laxative.

#### *7.1.1.4 One hour before simulation*

Patient should evacuate the bladder, and then drink 500 cc of plan water before simulation

Repeat this bladder filling process before each of daily radiation treatments.

### 7.1.2 Immobilization

Patient is in supine position, no immobilization devices needed.

### 7.1.3 Orientation, set-up, marking and reference points

7.1.3.1 It is preferred to treat the patient in supine position for better matching of the inguinal fields. However, prone position may be used in individualized cases with or without belly-board if inguinal nodes are not to be treated

7.1.3.2 A marker is placed on anal verge (anal canal tumour), marker on inferior extent of tumour (anal margin tumour).

7.1.3.3 Patient aligned with 3-plans laser beams.

7.1.3.4 Permanent ink (or tattoo) is applied to the lateral and midline reference points

7.1.3.5 In case of PET/CT planning, the radiographer is responsible to ensure patient positioning in the same imaging position

7.1.3.6 PET/CT diagnostic study, if performed, should be done before the planning study to avoid wash out of radio-nucleotide material.

7.1.3.7 The PET scan usually is done after the acquisition of the CT images. This may cause some hallo of FDG in bladder as it will be more distended with urine. Also some intestinal movement may alter the normal bowel uptake.

### 7.1.4 Image acquisition

#### *7.1.4.1 CT simulation*

- CT examination will be performed on a four-detector spiral CT scanner using a slice thickness of 3 mm. Slices are acquired from L5 to 4cm below the anal marker.

#### *7.1.4.2 PET/CT simulation*

- Images acquisition is done as per PET/CT department protocol.
- Images are printed and transferred to viewing station.

### 7.1.5 Target definition

#### *7.1.5.1 GTV:*

Defined as all known gross disease determined from CT (and MRI or PET if performed), clinical information, digital exam, endoscopic findings and biopsy. There are three GTVs:

- GTVA includes the gross primary anal tumor volume (as documented by digital exam, and as seen on CT, and PET or MRI).
- GTVN50, including all involved nodal regions (as documented by biopsy or radiological findings) containing macroscopic disease < 3 cm in greatest dimension (which will receive 50.4 Gy).
- GTVN54, including all nodal regions (as documented by biopsy or radiological findings) containing macroscopic disease > 3 cm in greatest dimension (which will receive 54 Gy).

#### *7.1.5.2 CTV:*

CTV is defined as the GTV plus areas considered to contain potential microscopic disease. Four different CTVs are to be defined, namely

- CTVA: for the primary anal tumor volume; includes the gross primary anal tumor volume, the anal canal + a 2.5 cm expansion craniocaudal and 1.5 cm radial (except into bone or air).
- CTV45 or CTV36: for the elective nodal regions (nodal regions receive 36-41.4 Gy for T2N0 cases and 45 Gy for all others);
- CTV50: for nodal regions containing macroscopic disease < 3cm in greatest dimension;
- CTV54: for nodal regions containing macroscopic disease > 3cm in greatest dimension.

CTV for lymph nodes + a 1.0 cm expansion (except into uninvolved bone, genitourinary structures, muscles, or bowel).

*Nodal regions include:*
a) Mesorectal (including peri-rectal and presacral)
b) Right and left inguinal
c) Right and left external iliac
d) Right and left internal iliac

#### *7.1.5.3 PTV*

- PTV provides a margin around the CTV to compensate for the variables of treatment set-up and internal organ motion.
- A minimum of 0.8-1 cm around the CTV is required in all directions to define each respective PTV.
- A nodal PTV should not be allowed to overlap with the primary PTVA, provided that their dose objectives are different, so that the maximum dose to the nodal PTV can be controlled in the optimization.
- The PTVs should spare non-target skin surfaces (manually or automatically trimmed to 3-5 mm within the skin surface).

7.1.5.4 OAR include the small bowel, femoral heads, bladder and vagina.
Transplanted kidneys may lie in the pelvis and should be excluded from the treatment volume or repositioned.

### 7.1.6 The technique:

Three dimentional conformal technique is used

### 7.1.7 Beam arrangement:

4 fields Box technique with supplementary electron beams to inguinal areas

**7.1.8 Beam energies:** (6-18 MV) photon beams are chosen and regarding the electron energy will be depending on the depth of the inguinal lymph nodes

### 7.1.9 Dose prescription and fractionation

#### *7.1.9.1 For radical irradiation:*

**For T2N0 disease:**

- The primary tumor (PTVA) should receive 50.4 Gy in 28 fractions at 1.8 Gy per fraction.
- The nodal PTVs (PTV36) should receive 36-41.4 Gy in 20-23 fractions electively at 1.8 Gy per fraction and include all nodal regions

**For T3N0 or T4N0 disease**:

- The primary tumor (PTVA) should receive 54-59 Gy in 30-33 fractions at 1.80 Gy per fraction.
- The nodal PTVs (PTV45) should receive 45 Gy in 25 fractions electively at 1.8 Gy per fraction and include all nodal regions

**For N+ disease:**

- The primary tumor PTV (PTV54) should receive 54 Gy in 30 fractions at 1.8 Gy per fraction.
- Clinically negative nodal PTV (PTV45) should receive 45 Gy in 25 fractions electively at 1.8 Gy per fraction and should include all uninvolved nodal regions.

- Involved nodes ≤ 3 cm in maximum dimension PTV (PTV50) should receive 50.4 Gy in 28 fractions at 1.8 Gy per fraction
- Involved nodes > 3 cm in maximum dimension PTV (PTV54) should receive 54 Gy in 30 fractions at 1.8 Gy per fraction

#### *7.1.9.2 For palliation*

Dose varies according to the symptom and site to be treated

### *7.1.10 Dose limitation to Organs at risk*

Surrounding critical normal structures, including the femoral heads (right and left), bladder, external genitalia, small bowel and large bowel outside the CTVs,

7.1.10.1 Small bowel: 45-50Gy max point dose; V30 <200cc

7.1.10.2 Femoral heads: 45Gy max point dose; V30 <50%

7.1.10.3 External genitalia: 25Gy max point dose; V20 <50%

7.1.10.4 Bladder: 65Gy max point dose; V35 <50%

7.1.10.5 Large bowel: 45-50Gy max point dose; V30 <200cc

Bowel should be contoured up to ~ 1 cm above the PTV. This, in turn, implies that absolute volume of bowel (in cc) is more important than relative volume (in %). The bowel should be contoured tightly, rather than with a broad, ill-defined margin. It is recognized that the location of bowel could vary from one day to the next, but the DVH from the simulation should remain representative.

### 7.1.11 Plan verification and execution

7.1.11.1 The plan will approved by the treating consultant and any modification in trade off of doses may be informed to the physicist.

7.1.11.2 The prescription sheet will be signed. Name, file number, civil ID, region, site to be treated and dose prescribed are cross checked.

7.1.11.3 Treatment instructions need to be written on the therapy sheet so as not to confuse the therapist.

7.1.11.4 The Therapist /Radiographer will be informed on scheduling the patient

7.1.11.5 On the day execution, the first portal is taken. Any modification or shifts showed be approved by the treating physician. Treatment takes place the next day after the first portal.

## 7.2 Brachytherapy

Not used in referral center

## 7.3 Sequelae of treatment

To be included in pre-treatment discussion with patient and consent form.

### 7.3.1 Early Radiation Sequalae: (Table B.3.a)

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Redness and skin irritation in the treatment area that may result in bleeding and/or infection, which may require hospitalization<br>- Loss of pubic hair in the treated area, usually temporary<br>- Tiredness<br>- Nausea and/or vomiting | - Diarrhea<br>- Sores and bleeding from the bowel (these side effects may occur well after treatment and be serious enough to require surgery) | - Narrowing or blockage of the bowel (these side effects may occur well after treatment and be serious enough to require surgery) |

### 7.3.2 Late Radiation Sequalae: (Table B.3.b)

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Loss of pubic hair in the treated area, usually temporary<br>- Sterility in fertile women<br>- Sterility in men | -Sores and bleeding from the bowel (these side effects may occur as well after treatment and be serious enough to require surgery)<br>- Narrowing and dryness of the vagina and genital area with dyspareunia and possibly bleeding<br>- Development of fibrosis in the anal canal, which may result in decreased function<br>- Long-term dryness of the skin<br>- Inability to have or keep an erection (impotency)<br>- Hip fracture<br>- Edema of ankles, feet, and/or legs | - Narrowing or blockage of the bowel (these side effects may occur as well after treatment and be serious enough to require surgery)<br>- Fibrosis of the urinary tubes<br>- Development of an abnormal path or connection between organs (fistulae)<br>- Skin damage, which may result in surgery<br>- Narrowing of or persistent bleeding in the vagina, which may result in surgery |

### 7.3.3 Chemotherapy (MMC/5-FU) Expected Toxicity: (Table B.3.c)

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Diarrhea with cramping or bleeding<br>- Nausea and or vomiting<br>- Change in taste, particularly a metallic taste<br>- Loss of appetite<br>- Dry skin with rash, cracking, and/or peeling<br>- Mouth sores and sore throat<br>- Temporary thinning or loss of hair<br>- Low white blood cell count, which may increase the risk of infection<br>- Low red blood cell count, which may result in anemia, tiredness, and/or shortness of breath<br>- Low platelet count, which may result in increased bruising and bleeding | - Eye irritation, watery eyes, and/or runny nose<br>- A blocked tear duct, which may require treatment<br>- Blurred vision<br>- Darkening and thinning of the skin<br>- Darkening, dryness, and marking of the nails<br>- Increased sensitivity to sunlight<br>- Headaches, which may continue<br>- Light-headedness<br>- Fever<br>- Puffiness of the hands and feet<br>- For women, missed menstrual periods<br>- Redness, tenderness, peeling, and/or tingling of the palms and soles of the feet | - Confusion<br>- Unsteadiness, loss of coordination<br>- Temporary loss of consciousness<br>- Slurred speech<br>- Dry cough and shortness of breath<br>- Tissue damage from leakage of mitomycin from a vein, which may require surgery<br>- Vomiting blood from the digestive tract<br>- Serious infection, which may be life threatening<br>- Irritation of a vein due to a blood clot, which may result in tenderness over the vein and pain in the part of the body affected and which may require treatment<br>- Allergic reactions, which can involve flushing, difficulty breathing, and low blood pressure and which can be life threatening<br>- Change in heart rhythm<br>- Damage to the heart or spasm of the heart's blood vessels that can cause chest pain<br>- Heart attack<br>- Kidney damage<br>- Inflammation of the liver, which may result in yellowing of the skin and eyes, tiredness, and/or pain on the upper right of the stomach area |

## 8. Principles of hormonal therapy

Not applicable.

## 9. Principles of chemotherapy

Mitomycin/ 5- Fluorouracil (MMC/5-FU) as per squamous cell carcinoma of the anal canal chemotherapy protocol given concomitant with radiation therapy.

## 10. Management of recurrent disease

### 10.1 Local recurrence

Abdominoperineal resection + inguinal LN dissection (if proved positive; on affected side only)

### 10.2 Nodal recurrence

Inguinal LN dissection (if proved positive; on affected side only)

Radiation of inguinal LN can be done if previously not irradiated, with or without concomitant chemotherapy

**10.3 Metastatic disease**

Palliative chemotherapy

## 11. Follow Up

**11.1** History, clinical examination (including DRE and inguinal LN examination) Every 6 weeks until CR, then every 3 months for first year, every 4 months for second year, every 6 months for third year, then annually.

**11.2** CT chest, abdomen and pelvis and/or PET-CT, if initially done and with locally advanced disease (T3-4) or positive LN.

**11.3** Consider vaginal dilator in women who are treated and do not regulary engage in intercourse to help prevent stenosis/ narrowing.

## 12. Ongoing departmental studies

Not applicable.

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4. Paulino. PET-CT in Radiotherapy Treatment Planning, (1st ed.): Rectal and Anal Cancers.
5. ACT II Trial Protocol, Anal Cancer Working Party, 2002
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9. James R et al. ACT II: the second UK phase III anal cancer trial. Clin Oncol (R Coll Radiol) 17(5): 364-6, 2005
10. The R.C.R. Board of Faculty of Clinical Oncology 'Radiotherapy Dose - Fractionation' 2006ICRU 83 Volume 10 No1 2010.
11. A Review of the Clinical Evidence for Intensity-modulated Radiotherapy: J. Staffurth; Clinical Oncology 22 (2010) 643-657.

# GROUP (C)

1. Head &Neck malignancies
2. Thyroid cancer
3. Lung cancer
4. GIT malignancies
5. Skin cancer

# C.1- HEAD & NECK CANCER CLINICAL MANAGEMENT GUIDELINES

## 1. Epidemiology:

Head & neck cancers comprise of malignant tumors of upper aero digestive tract. Head and Neck Cancer is a major health problems worldwide. It is a major global health issue with about half million new cases diagnose per year and their incidence appears to be increasing in the developing countries, as with many types of cancer the risk of developing of H&N cancer increasing with age and in proportion to the intensity and duration of the exposure of smoking in different form. Smokeless tobacco like Shamma, Khat and Pan plays an important role in H&N cancer particularly oral cavity.

In 2012 the Aged Standardized Rate (ASR) for male Kuwaiti 8.3 and female Kuwaiti 3.4, ASR for Non-Kuwait for male 3.3 and for female 3.6. Predisposing factors are tobacco abuse in various forms, alchol abuse or combination of tobacco and alcohol. Virus infection plays an important role in Head and Neck cancer (Nasopharynx and EBV, Oropharynx and HPV). The major anatomical sites are oral cavity, nasal cavity, paranasal sinuses, pharynx, larynx & salivary glands.

In GCC, 71,882 new cases were newly diagnosed between 1998-2005 as per data from six cancer registries of GCC region. Head and neck cancers comprised 11.5% of all cancers, out of which 7.3% were males and 4.2% were females.

## 2. Clinical Presentation:

Some common head and neck cancer symptoms include:

- 2.1 A lump in the nose, neck, mouth or throat
- 2.2 (obstacles) Bleeding per nose or ulcer in the mouth
- 2.3 A persistent sore throat
- 2.4 Trouble swallowing (dysphagia)
- 2.5 Unexplained weight loss
- 2.6 Frequent coughing
- 2.7 Change in voice or hoarseness
- 2.8 Ear pain or trouble hearing
- 2.9 Headaches

## 3. Diagnosis Work up:

- 3.1 Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.
- 3.2 Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.
- 3.3 Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.

3.4 Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.
3.5 Radiologic investigation CT scan of whole body and MRI face neck for cancer nasopharynx and as per discretion of clinician.
3.6 PET scan for staging and RT planning.
3.7. Biopsy of primary and FNAC of neck nodes. Immuno histochemistry for better pathological assessment.
3.8 Excision biopsy of node with tumor markers if the primary is not assesible.
3.9 Ebstein barr virus quantitative assessment for nasopharyngeal cancers and HPV type 16 /18 assessment for oropharyngeal cancers.
3.10 Nutritional assement and swallowing status prior to radical radiotherapy.
3.11 Review of pathology at referral center.

#### 3.11.1 Assessment of pathology for in operable cases

3.11.1.1 Histological type
3.11.1.2 Grading

#### 3.11.2 Histopathological examination for post-operative cases

3.11.2.1 Size of primary and gross nodes.
3.11.2.2 Status and measurement of margins with proper orientation of directions.
3.11.2.3 Regional lymph nodes numbers removed and from which stations. Evidence of any ECE.
3.11.2.4 Vascular and nerve invasion should be evaluated.

## 4. Staging

As per the TNM/AJCC staging 7$^{th}$ edition, 2010.

## 5. Treatment- as per sub sites.

# SUBSITES OF HEAD AND NECK CANCERS-

## ORAL CAVITY CANCERS

### 1. Epidemiology:

According to the data available from Kuwait cancer registry 2012, the incidence rate in Kuwait (ASR) was 3.1 per 100000 population in comparison to the worldwide incidence of 5 per 100000 population. The ASR for GCC according to GCC registry 2011 was 3.2.

**Sub-sites include**

**1.1** Lip (some classify this area as skin); more than 90% of cases occur on the lower lip.
**1.2** Floor of mouth.
**1.3** Anterior two-thirds of tongue.
**1.4** Buccal mucosa.
**1.5** Hard palate.
**1.6** Upper and lower alveolus and gingiva.
**1.7** Retro molar trigon.

## 2. Clinical Presentation

**2.1** A lump in the neck or mouth .
**2.2** A red lesion (erythroplakia) or white lesion (leukoplakia)
**2.3** A non-healing extraction socket or non-healing ulcer
**2.4** A lesion fixed to deeper tissues or to overlying skin or mucosa

## 3. Diagnosis Work up

**3.1** Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.
**3.2** Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.
**3.3** Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.
**3.4** Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.
**3.5** Radiologic investigation CT scan of whole body and MRI face neck as per discretion of clinician.
**3.6** PET scan for staging and RT planning.
**3.7** Biopsy of primary and FNAC of neck nodes. Immunohistochemistry for better pathological assessment.
**3.8** Excision biopsy of node if the primary is not assessable.
**3.9** HPV type 16 /18 assessment.
**3.10** Nutritional assessment and swallowing status prior to radical radiotherapy.
**3.11** Review of pathology at Referral center.

**3.11.1 Assessment of cytology**

3.11.1.1 Histological type
3.11.1.2 Grading

**3.11.2 Histopathological examination for post-operative cases**

3.11.2.1 Histological type
3.11.2.2 Grading
3.11.2.3 Size of primary and gross nodes.
3.11.2.4 Status and measurement of margins with proper orientation of directions.
3.11.2.5 Regional lymph nodes numbers removed and from which stations.
3.11.2.6 Evidence of any ECE.
3.11.2.7 Vascular and nerve invasion should be evaluated.

## 4. Staging

As per the TNM/AJCC staging 7$^{th}$ edition, 2010.

## 5. Prognostic Factors

5.1 tumour-related prognostic factors : the primary tumour (T) size and its depth of invasion, the Grade of tumor, and the presence or absence of vascular invasion.

5.2 The presence of lymph node metastasis(N), and their size, number, and position (level), as well as signs of extracapsular tumourspread (ECS)

5.3 The incidence of distant metastatic disease increases with rising tumour stage and nodal metastasis.

5.4 HPV +ve malignancies are common in young non-smoker, non- alcohol consumers and has good prognosis.

## 6. Treatment

Often multimodal approach is needed for treatment. Primary treatment modalities are surgery, radiotherapy and chemotherapy. General principle of management for early stage disease is surgery and for locally advanced disease or irresectable, non metastatic disease can be treated by induction chemotherapy or concomitant chemo-radiotherapy. Surgical salvage may be warranted if radiotherapy fails. Metastatic disease is mainly treated by palliative chemotherapy.

### 6.1.1 T1,2 N0 M0 –Stage I

Wide local excision primary with aim of achieving free margins + Unilateral neck dissection (SOHD) with or without sampling from contralateral neck. This will include wide excision, hemi glosectomy, partial mandibulectomy as per site of primary.Reconstruction with flap as per individual case. Neck dissection depends on risk of nodal involvement obtained from clinical, radiological examination & pathology.In absence of nodal disease and favorable postoperative pathology these patient are subjected for follow up.

Positive margins, nodal disease inadequate nodal clearance, and depth of tumor more than 4 mm are advised for post op adjuvant concomitant chemotherapy with EBRT.The dose of radiation is 60 Gy in 30 Fr@ 2Gy /Fr.Weekly cisplatinum is indicated with RT. Involved positive margins are boosted to cumulative dose to 66 Gy.

### 6.1.2 T1-3N1M0 (Resectable)- Stage III

Wide local excision and ipsilateral or bilateral comprehensive neck dissection.Adjuvant EBRT with chemotherapy is indicated in all node positive cases with adverse pathology factors. Planned dose as above.

### 6.1.3 Unresectable – Stage IV

Induction chemotherapy followed by Radical EBRT with concomitant chemotherapy. Prescribed RT dose is 70 Gy/35 Fr@2Gy/Fr. All cases with CR are kept under close follow up.

Residual disease post CT/RT or recurrent disease are salvaged by surgery.

### 6.1.4 Metastatic cancers (M1)-

These are managed by palliative/salvage chemotherapy, palliative RT or best supportive care.

## 7. Radiotherapy Treatment

### 7.1 External Beam:

**7.1.1 Patient Preparation:** Patients can have light breakfast or drinks this will not hamper the process of simulation, any history of allergy should be noted. Contrast should be used with caution in such cases. History of asthma, allergic

disorders, angioedema & individuals with food allergy are addressed with caution.

7.1.2 **Immobilization:** Patient is immobilized in supine position by use of head rest, base plate and orfit cast. The entire head neck and shoulders are immobilized by 5 point fixation areas. The aim of positioning is to elevate chin, depress shoulder to desirable position as per patient comfort. Aim here is to have spine as straight as possible. A custom-made mouth bite may help to push the tongue inferiorly when irradiating the hard palate or upper alveolus or to separate the roof of the mouth from the inferior oral cavity when irradiating the tongue.

7.1.3 **Orientation, set-up, marking and reference points:** Patient lie in supine position, the customized orfit is fixed with base plate and head rest. Use of traction is optional depending on patient comfort and clinical situation.Three reference radiopaque markers are placed over the orfit in same plane orthogonally with help of lasers. This may or may not be over the centre of tumor. At least one of the axial cut should have two of the reference markers. This is not only for patient set up but also for the planning purpose and execution of plan.

7.1.4 **Image acquisition:** CT simulation is performed on spiral CT scanner with slice thickness of 2 millimetres from vertex to carina.Contrast will help in better delineation of the vessels this in turn will help for contouring nodal stations.

7.1.5 **Target definition:** GTV- Is defined as the gross tumor as evident by initial examination, imaging studies and endoscopy examinations. This will include gross tumours and nodes.PET is valuable in precise delineation of gross tumors. All cases treated by radical radiation as primary treatment modality will have GTV p for the primary tumor and GTV n for nodal component depending on its presence or absence.CTV-growing GTV isotropically by 10 mm to produce a CTV-P 70. The CTV70 is edited to take account of local patterns of tumour spread and natural tissue barriers, CTV_N 70 includes positive LNS with 5 mm expansion. CTV_60 includes high risk nodal volumes. CTV_50 includes low risk lower neck nodes. This field is planned with following borders- Upper border – usually at lower border of cricoid, ( aim is to keep beams away from shoulders). Here aim is to cover entire supraclavicular fossa. Lower border- The lower border is placed under the head of clavicle with half centimeter margin. PTV: CTV is expanded isotropically 5 mm to get the PTV , however the skin interface with PTV is to be avoided and PTV at such places is tailored.

7.1.6 **Technique:** Three –D or IMRT are both practiced.

7.1.7 **Beam arrangement:**

***7.1.7.1 For phase 1:***

Conformal 3D plan with combination of 7 or more beams. The beams are differentially weighted with or without wedges and can have different energies. Field in field or segmental fields are also added to achieve adequate coverage. Sparing of the parotids of non involved site not at cost of PTV coverage is the primary aim.

Low anterior neck with photons prescribed at depth is used in conjunction with phase 1. A midline PTV may still need to be treated with lateral opposed beams but MLC shielding will help to spare normal tissues, and wedges can be used to compensate for the change in neck contour and produce a more even dose distribution. When only one side of the neck is treated, an arrangement of three coplanar beams can usually provide good tumour coverage while sparing the contralateral mucosa and parotid gland. At least one of the beams must have no exit dose through the spinal cord for this organ to remain within tolerance. In practice this means the angle of the posterior oblique beam is chosen to provide best coverage of the PTV while avoiding the cord.
There are no fixed landmarks in conformal radiotherapy plans for beam arrangements.

#### *7.1.7.2 For phase 2:*

Usually 2 parallel opposed fields are used for adequate coverage of GTV & CTV. Spine is blocked and nodal stations in this area are treated by electrons.

#### *7.1.7.3 For Phase 3:*

Opposed lateral, oblique or combination of electrons are added to cover gross disease.
Concomitant chemotherapy with cisplatinum is used in almost all cases. Cisplatinum in dose of 40 mg/m2 or carboplatin in AUC of 2 are used.
Concomitant weekly targeted therapy with cetuximab in selected cases. A loading dose of 450 mg/m2 is administered week before planned date of RT later this is followed with weekly dose of 250 mg/m2 till the duration of radiotherapy.

### 7.1.8 Beam Energy: is adjusted individually according to plan of each case.

### 7.1.9 Dose prescription and fractionation:

#### *7.1.9.1 Adjuvant radiotherapy:*

For larger T2 (3 cm), T3 and T4 tumours, local control is best achieved by surgery and adjuvant radiotherapy. Adjuvant local radiotherapy is also indicated where a smaller primary tumour is excised with positive margins and the preferred option of further excision is not possible. Where a small primary tumour has been excised with close (5 mm) margins, concomitant 60 Gy of normal fractionation with weekly chemotherapy with cisplatinum is used in almost all cases. Cisplatinum in a dose of 40 mg/m2 or carboplatin in AUC of 2 are used. Concomitant weekly targeted therapy with cetuximab is used in selected cases. A loading dose of 450 mg/m2 is administered week before planned date of RT later this is followed with weekly dose of 250 mg/m2 till the duration of radiotherapy.

#### *7.1.9.2 Radical Radiotherapy:*

##### *7.1.9.2.1 Phase 1 – Planned Dose 40 GY/20 FR @2 Gy/Fr /5 days a week*

All radical cases are planned by 3 D conformal radiotherapy. The aim of planning here is to spare the parotids as much as possible but not at cost of PTV. Mean dose to at least one of the parotids should be less than 23 Gy.

A low anterior neck portal is also used in conjunction with phase 1 conformal plan in cases with locally advanced disease. Prescribed dose for low anterior neck is **50 Gy in 25 Fr**. A gap of 0.5 mm is used in overlapping fields of lower neck and upper neck fields.

*7.1.9.2.2 For phase 2:*

Planned dose 20 Gy in 10 Fr photons for anterior neck and 20 Gy in 10 Fr electrons (variable energy) for posterior neck to shield the spine. The electron energy depends on depth of area to be treated.

*7.1.9.2.3 Phase 3:*

All gross nodes and gross primary disease are treated in phase 3 up to 70 Gy. Here if the gross disease lies in the territory of or overlapping spinal cord, beam arrangements are made or electrons are used to prescribe the required dose.

Residual nodes and primary can be boosted beyond 70 Gy in selected cases depending on response up to 76 Gy.

### *7.1.9.3 Palliative Radiotherapy:*

Palliative radiotherapy to the primary site can also be useful when metastases are present at diagnosis, or in locally recurrent disease to ameliorate fungating tumour or reduce bleeding GTV, CTV and PTV are defined as for curative treatment either on a planning CT scan or lateral simulator radiograph. To minimise normal tissue toxicity (particularly mucositis), smaller margins can be used than for curative treatment – e.g. 5 mm from GTV to CTV20Gy in 5 fractions or 30 Gy in 10 fractions.

### 7.1.10 Dose limitation to OAR:

QUANTEC recommendations are followed careful assessment of mandible dose is essential to reduce the risk of late osteoradionecrosis. Hot-spots of 107 per cent within the mandible should be avoided.

| Organ | Endpoint | Rate (%) | Dose-volume parameter | $D_{max}$ (Gy) | $D_{mean}$ (Gy) |
|---|---|---|---|---|---|
| Brain | Symptomatic necrosis | <3<br><5 | | <60<br><65 | |
| Brainstem | Necrosis or cranial neuropathy | <5<br><5 | D100 <54 Gy<br>D1–10 cc ≤59 Gy | <64 Point | |
| Spinal cord | Grade ≥2 myelopathy | <1 | | 50 | |
| Optic nerve & chiasm | Optic neuropathy | <3<br>3–7 | | <55<br>55–60 | <50 |
| Retina | Blindness | <1 | | <50 | |
| Cochlea | Hearing loss | <15 | | | ≤45 |
| Parotid 1 | Grade 4 xerostomia | <20 | | | <20 |
| Parotid 2 | | <20 | | | <25 |
| Mandible | ORN | <5 | | <70 Point | |
| Pharyngeal constrictors | PEG tube dependent<br>Aspiration | <5<br><5 | | | <50<br><60 |
| Larynx | Grade ≥2 edema | <20 | V50 <27% | | <44 |
| Brachial plexus | Clinically apparent nerve damage | <5 | | <60 | |
| Lung | Symptomatic pneumonitis | 5 | V5 <42%,<br>V20 <22% | | 7 |

#### 7.1.11 Verification and plan execution:

Weekly review for all patients in the OPD throughout treatment course used protocol is for the treatment isocentre on lateral and anterior DRRs from the CT simulation to be compared with porta; images from the treatment machine taken on days 1–3 and weekly thereafter. An off-line correction is made relative to the isocentre position if the mean error in any one plane is 3 mm.

## 7.2 Brachytherapy:

7.2.1 **Introduction:** Brachytherapy is a promising alternative to surgery for some oral cancer patients. Because there is no incision and no surgical wound to heal, recovery from the procedure is generally rapid. Brachytherapy offers excellent conformal radiotherapy to small tumours of the tongue and buccal mucosa that are well demarcated, not close to bone and accessible for implantation. Brachytherapy is often technically impossible (tumour is close to bone) or the necessary expertise unavailable for tumours of the hard palate, brachytherapy is not technically possible and relative hypoxia in bone may reduce cure rates.

7.2.2 **Methods**

*7.2.2.1* High-dose rate (HDR) brachytherapy offers a fast, precise way to give radiation treatment for some cancer patients. The radiation is deposited inside a tumor, delivering a maximum dose while minimizing exposure to the surrounding healthy tissue. Each HDR brachytherapy treatment takes about 15-20 minutes.

*7.2.2.2* Low-dose rate (LDR) brachytherapy involves placing radioactive seeds directly into the oral cancer tumor. Also sometimes called permanent seed implants, LDR brachytherapy uses radioactive seeds bound together in short rows and permanently implants them into the organ. These pellets emit low levels of radiation for several weeks. When this radiation treatment ends, the harmless seeds are left in place permanently.

Brachytherapy of oral cavity tumours is not practiced.

## 7.3 Sequleae of treatment

7.3.1 **Acute: (Table C.1.a)**

| Likely (more than 10%) | Less Likely (3- 9%) | Rare but serious(less than 2 %) |
|---|---|---|
| Redness and skin pigmentation in radiated area. Loss of hairs in treated zones. | Confluent to grade III mucositis. Secondary infection on top of mucositis | Grade IV mucositis, Skin Necrosis |
| Genralised fatigue, nausea. | Cataract if lens receive more than tolerance dose | Prolong dryness and persistent xerostomia |
| Dry Skin peeling, mucositis patchy to grade II, dysphagia with pain.Change of taste and loss of taste. | | |
| Xerostomia | | |

7.3.2 **Late:**

*7.4.2.1* Some skin pigmentation which is more evident in fair skin individuals.

*7.4.2.2* Dryness of mouth and chronic xerostomia this depends on the dose received by parotids. In cases where both parotids receive a good amount of dose the possibility of xerostomia in long run is emphasized to patients.

7.4.2.3 Apical lung fibrosis evident on chest x ray can cause some symptoms this is due to the area of lung in lower neck portals.

All side effects during the course of EBRT are expected to resolve gradually by 6 weeks post radiation.

## 8. Hormonal Treatment:

Not applicable

## 9. Chemotherapy:

**9.1** Concurrent chemotherapy as mentioned in radiotherapy treatment.

**9.2** Induction or adjuvant chemotherapy is decided in MDT meeting and is applied by medical oncology department. TPF or PF is practiced in referral center.

- TPF chemotherapy (docetaxel 75 mg/m(2), followed by intravenous cisplatin 100 mg/m(2) and fluorouracil 1000 mg/m(2) per day, administered as a continuous 24-h infusion for 4 days) or PF (intravenous cisplatin 100 mg/m(2), followed by fluorouracil 1000 mg/m(2) per day as a continuous 24-h infusion for 5 days)

## 10. Management of Recurrence/Relapse:

It is decided in MDT meeting according to initial treatment, symptoms and patient performance status.

## 11. Follow Up

### 11.1 Follow Up Investigations:

11.1.1 DL scopy and endoscopy once every 3 to 6 months in first 2 years.
11.1.2 CT scan or MRI at least once and twice in a year with residual.
11.1.3 Routine labs and assessment of Thyroid function in post RT cases.
11.1.4 Nutritional and swallowing assessment and also recovery from RT side effects.

### 11.2 Follow Up Visits Schedule

11.2.1 1 YEAR-Every month
11.2.2 2 YEAR-Every 2 months
11.2.3 3 to 5 YEARS- Every 4 to 6 months

## 12.Ongoing Randomized studies:

Phase II-III randomized controlled study of concomitant cetuximab plus hyperfractination radiation therapy versus chemotherapy plus hyperfractination radiation therapy in advanced non metastatic head and neck cancer

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8. Gregoire, Levandang et al CT based delineation of nodal levels and related CTV volumes in node negative neck DAHANCA, RTOG, GORTEC, NCIC consensus guidelines (Radiotherapy Oncology 69)
9. Pignon et all Chemotherapy added to locoregional treatment of head and neck squamous cell cancers(Lancet 355).
10. Practical radiotherapy planning (Ann barrett, Dobbs) IV edition.
11. NCCN guidelines 2016

## OROPHARYNGEAL CANCERS:

### 1. Epidemiology:

Oropharyngeal cancers are not common in Kuwait and according to the data available from cancer registry 2012 giving an annual incidence of 0.4 per 100,000 population in comparison to 0.8 per 100,000 population worldwide. The figures might not represent the true number as many of tongue base cancers are reported as tongue cancers among oral cavity cancers. The ASR for the Gulf region according to GCC registry 2011 was 0.5.

The sub sites include:

1.1 Tonsil fossae and pillars
1.2 Base of tongue and vallecula.
1.3 Inferior surface of soft palate and uvula.
1.4 Posterior pharyngeal wall.

### 2. Clinical Presentation:

2.1 Sore throat. Pain, foreign body sensation.
2.2 Otalgia
2.3 Dysphagia. Weight loss
2.4 Ulcers
2.5 voice changes
2.6 Trismus
1.7 Neck masses

### 2. Diagnosis Work up:

3.1 Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.
3.2 Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.
3.3 Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.
3.4 Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.
3.5 Radiologic investigation CT scan of whole body and MRI face neck for cancer nasopharynx and as per discretion of clinician.
3.6 PET scan for staging and RT planning.
3.7 Biopsy of primary and FNAC of neck nodes. Immuno histochemistry for better pathological assessment.
3.8 Excision biopsy of node with tumor markers if the primary is not assesible.
3.9 HPV type 16 /18 assessment.
3.10 Nutritional assessment and swallowing status prior to radical radiotherapy.
3.11 Review of pathology at referral center.

3.11.1 **Assessment of cytology**

3.11.1.1 Histological type
3.11.1.2 Grading

### 3.11.2 Histopathological examination for post-operative cases

3.11.2.1 Histological type
3.11.2.2 Grading
3.11.2.3 Size of primary and gross nodes.
3.11.2.4 Status and measurement of margins with proper orientation of directions.
3.11.2.5 Regional lymph nodes: the numbers removed and from which stations.
3.11.2.6 Evidence of any ECE.
3.11.2.7 Vascular and nerve invasion should be evaluated.

## 4 Staging

As per the TNM/AJCC staging 7th edition, 2010.

## 5 Prognostic Factors

5.1 Tumour-related prognostic factors: the primary tumour (T) size and its depth of invasion, the Grade of tumor, and the presence or absence of vascular invasion.

5.2 The presence of lymph node metastasis (N), and their size, number, and position (level), as well as signs of extra capsular tumour spread (ECS)

5.3 The incidence of distant metastatic disease increases with rising tumour stage and nodal metastasis.

5.4 HPV positivity is favorable prognostic factor

## 6 Treatment

### 6.1 Management of the primary tumor

#### 6.1.1 Tongue base

- Small tumours. Surgery if lateralized or RT.
- Larger tumours. CCRT.

#### 6.1.2 Tonsillar region

- Small tumors. Surgery or RT.
- Extensive primary tumours- Possible surgery or Radical CCRT.

#### 6.1.3 Soft palate

- Small tumours. Usually RT or surgery if minimal resulting dysfunction.
- Large tumours. CCRT.

#### 6.1.4 Pharyngeal wall

- Small tumours. RT can be effective with minimal morbidity.
- Extensive tumours. Possible surgery or Surgery and CCRT or Radical CCRT.

## 6.2 Management of the neck.

**6.2.1** Neck dissection with primary as per stage and respectability.

**6.2.2** If neck dissection is not feasible or bulky, nodes RT indicated.

**6.2.3** If the primary tumor is extensive, the histology is poorly differentiated, the adenopathy is large (i.e., >3.0 cm), multiple nodes are involved, or extracapsular extension. CCRT is considered.

## 6.3 Management by stage:

### 6.3.1 T1-2N0M0-(Stage I and II)

- Wide local excision of primary with nodal sampling. Aim is to have complete removal with clear margins. Usually adjuvant RT not needed in these patients.
  Or
- External beam radiotherapy with or without concomitant chemotherapy, is an alternative if cosmetic outcome is limiting issue or for other reasons.
- Radiation dose, 70 Gy/35 Fr@2Gy/Fr/7 weeks. Con current chemotherapy is justified with higher grade, nodal metastasis & adverse pathology.

### 6.3.2 T1-3,N1 M0-( Stage III)

- Surgery followed by adjuvant chemoradiotherapy, other option is radical CCRT.

### 6.3.3 Bulky nodes and locally advanced (stage IVA) –

- Option of treatment is either induction chemotherapy WITH PF or TPF followed by EBRT
  Or
- EBRT/CCT as primary treatment modality. The sequencing of these modalities is variable and subjective. If possible, patient should have CCRT as first choice.
- At referral center locally advanced such cases are managed by hyper fractionated radiotherapy with concomitant chemotherapy (cisplatinum or carboplatin).Amifostine is used at doses of 500 Mg s/c before RT.
- Dose for Hyperfractionated EBRT is-
  - Phase 1 for hyperfractionated radiotherapy- 39.6 Gy/33 Fr @ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week.
  - Phase 2 for hyperfractionated radiotherapy-20.40 Gy/17 Fr@ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week.
  - Phase 3 for hyperfractionated radiotherapy- 9.6 Gy/ 8Fr @ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week.
  - Lower neck field and supraclavicular region is treated to dose of 50.4 Gy/42 Fr@ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week. Usually prescribed at Dmax or at depth.

### 6.3.4 Metastatic cases :

Option of treatment are palliative chemotherapy or palliative EBRT or both. Supportive measures for advanced cases.

# 7. Radiotherapy protocol:

## 7.1 External Beam: Planning Technique

*7.1.1* **Patient Preparation:** Patients can have light breakfast or drinks this will not hamper the process of simulation, any history of allergy should be noted. Contrast should be used with caution in such cases. History of asthma, allergic disorders, angioedema & individuals with food allergy are addressed with caution.

*7.1.2* **Immobilization:** Patient is immobilized in supine position by use of head rest, base plate and or fit cast. The entire head neck and shoulders are immobilized by 5-point fixation areas. The aim of positioning is to elevate chin, depress shoulder to desirable position as per patient comfort. Aim here is to have spine as straight as possible. no mouth bite, but any dentures should be left in place.

*7.1.3* **Orientation, set-up, marking and reference points:** Patient lie in supine position, the customized orfit is fixed with base plate and head rest. Use of traction is optional depending on patient comfort and clinical situation. Three reference radiopaque markers are placed over the orfit in same plane orthogonally with help of lasers. This may or may not be over the centre of tumor. At least one of the axial cut should have two of the reference markers. This is not only for patient set up but also for the planning purpose and execution of plan.

*7.1.4* **Image acquisition:** CT simulation- This is performed on spiral CT scanner with slice thickness of 2 millimeters cuts from vertex to carina.Contrast will help in better delineation of the vessels this in turn will help for contouring nodal stations.

*7.1.5* **Target definition:** **GTV-** Is defined as the gross tumor as evident by initial examination, imaging studies and endoscopy examinations. This will include gross tumors and nodes.PET is valuable in precise delineation of gross tumors. All cases treated by radical radiation as primary treatment modality will have GTV p for the primary tumor and GTV n for nodal component depending on its presence or absence.**CTV-** CTV70 includes GTV and the risky area for example: CTV70 for a left base of tongue tumour should include the whole tongue base and left tonsillar fossa The CTV 60 includes nodal stations at risk of microscopic disease. CTV50 includes lower neck fields. **PTV:** CTV is expanded isotropically 5 mm to get the PTV, however the skin interface with PTV is to be avoided and PTV at such places is tailored.

*7.1.6* **Technique:** Three –D or IMRT are both practiced.

*7.1.7* **Beam Arrangement:**

*7.1.7.1 For phase 1:*

- Conformal 3D plan with combination of 7 or more beams. The beams are differentially weighted with or without wedges and can have

different energies. Field in field or segmental fields are also added to achieve adequate coverage. Sparing of the parotids of non-involved site not at cost of PTV coverage is the primary aim.

- Low anterior neck with photons prescribed at depth is used in conjunction with phase 1.
- There are no fixed landmarks in conformal radiotherapy plans for beam arrangements.

***7.1.7.2 For phase 2 –***

- Usually 2 parallel opposed fields are used for adequate coverage of GTV & CTV. Spine is blocked and nodal stations in this area are treated by electrons.

***7.1.7.3 For Phase 3 –***

- Opposed lateral, oblique or combination of electrons are added to cover gross disease.
- Concomitant chemotherapy with cisplatin is used in almost all cases. Cisplatin in dose of 40 mg/m2 or carboplatin in AUC of 2 are used.
- Concomitant weekly targeted therapy with cetuximab in selected cases. A loading dose of 450 mg/m2 is administered week before planned date of RT later this is followed with weekly dose of 250 mg/m2 till the duration of radiotherapy.

***7.1.8*** **Beam Energy:** is adjusted by physicist according to plan of each case.

***7.1.9*** **Dose prescription and fractionation:**

*7.1.9.1* ***Adjuvant Radiotherapy:*** Concomitant 60 Gy of normal fractionation with weekly chemotherapy with cisplatin is used in almost all cases. Cisplatin in dose of 40 mg/m2 or carboplatin in AUC of 2 are used. Concomitant weekly targeted therapy with cetuximab in selected cases. A loading dose of 450 mg/m2 is administered week before planned date of RT later this is followed with weekly dose of 250 mg/m2 till the duration of radiotherapy.

***7.1.9.2 Radical Radiotherapy:***

*7.1.9.2.1 Phase 1 – Planned Dose 40 GY/20 FR @2 Gy/Fr /5days a week*

All radical cases are planned by 3 D conformal radiotherapy. The aim of planning here is to spare the parotids as much as possible but not at cost of PTV. Mean dose to at least one of the parotids should be less than 23 Gy. A low anterior neck portal is also used in conjunction with phase 1 conformal plan in cases with locally advanced disease. Prescribed dose for low anterior neck is **50 Gy in 25 Fr**. A gap of 0.5 mm is used in overlapping fields of lower neck and upper neck fields.

*7.1.9.2.2 For phase 2- Planned dose 20 Gy in 10 Fr photons for anterior neck and 20 Gy in 10 Fr electrons (variable energy) for posterior neck* spine is shielded and the posterior neck is treated with electrons. The electron energy depends on depth of area to be treated.

*7.1.9.2. 3 Phase 3* All gross nodes and gross primary disease are treated in phase 3 up to 70 Gy. Here if the gross disease lies in the territory of or overlapping spinal cord, beam arrangements are made or electrons are used to prescribe the required dose.
Residual nodes and primary can be boosted beyond 70 Gy in selected cases depending on response up to 76 Gy.

***7.1.9.3 Palliative Radiotherapy*:** Palliative radiotherapy to the primary site can also be useful when metastases are present at diagnosis, or in locally recurrent disease to ameliorate fungating tumour or reduce bleeding GTV, CTV and PTV are defined as for curative treatment either on a planning CT scan or lateral simulator radiograph. To minimise normal tissue toxicity (particularly mucositis), smaller margins can be used than for curative treatment – e.g. 5 mm from GTV to CTV20Gy in 5 fractions or 30 Gy in 10 fractions.

### 7.1.10 Dose limitation to OAR: (Table C.1.b)

| Organ | Endpoint | Rate (%) | Dose-volume parameter | $D_{max}$ (Gy) | $D_{mean}$ (Gy) |
|---|---|---|---|---|---|
| Brain | Symptomatic necrosis | <3<br><5 | | <60<br><65 | |
| Brainstem | Necrosis or cranial neuropathy | <5<br><5 | D100 <54 Gy<br>D1–10 cc ≤59 Gy | <64 Point | |
| Spinal cord | Grade ≥2 myelopathy | <1 | | 50 | |
| Optic nerve & chiasm | Optic neuropathy | <3<br>3–7 | | <55<br>55–60 | <50 |
| Retina | Blindness | <1 | | <50 | |
| Cochlea | Hearing loss | <15 | | | ≤45 |
| Parotid 1 | Grade 4 xerostomia | <20 | | | <20 |
| Parotid 2 | | <20 | | | <25 |
| Mandible | ORN | <5 | | <70 Point | |
| Pharyngeal constrictors | PEG tube dependent<br>Aspiration | <5<br><5 | | | <50<br><60 |
| Larynx | Grade ≥2 edema | <20 | V50 <27% | | <44 |
| Brachial plexus | Clinically apparent nerve damage | <5 | | <60 | |
| Lung | Symptomatic pneumonitis | 5 | V5 <42%,<br>V20 <22% | | 7 |

ICRU recommendations are followed.

**7.1.11 Verification:** Weekly review for all patients in the OPD throughout treatment course. used protocol is for the treatment isocentre on lateral and anterior DRRs from the CT simulation to be compared with porta; images from the treatment machine taken on days 1–3 and weekly thereafter. An off-line correction is made relative to the isocentre position if the mean error in any one plane is 3 mm.

## 7.2 Brachytherapy: When Applicable

**7.2.1** Introduction

**7.2.2** Methods

## 7.3 Sequleae of treatment

### 7.3.1 Acute: (Table C.1.c)

| Likely (more than 10%) | Less Likely (3- 9%) | Rare but serious(less than 2 %) |
|---|---|---|
| Redness and skin pigmentation in radiated area. Loss of hairs in treated zones. | Confluent to grade III mucositis. Secondary infection on top of mucositis | Grade IV mucositis, Skin Necrosis |
| Genralised fatigue, nausea. | Cataract if lens receive more than tolerance dose | Prolong dryness and persistent xerostomia |
| Dry Skin peeling, mucositis patchy to grade II, dysphagia with pain. Change of taste and loss of taste. | | |
| Xerostomia | | |

### 7.3.2 Late:

**7.4.2.1** Some skin pigmentation which is more evident in fair skin individuals.

**7.4.2.2** Dryness of mouth and chronic xerostomia this depends on the dose received by parotids. In cases where both parotids receive a good amount of dose the possibility of xerostomia in long run is emphasized to patients.

**7.4.2.3** Apical lung fibrosis evident on chest x ray can cause some symptoms this is due to the area of lung in lower neck portals.

All side effects during the course of EBRT are expected to resolve gradually by 6 weeks post radiation.

# 7 Hormonal Treatment:

Not Applicable

# 8 Chemotherapy:

9.1 Concurrent chemotherapy as mentioned in radiotherapy treatment.

9.2 Induction or adjuvant chemotherapy is decided in MDT meeting and is applied by medical oncology department. TPF or PF is practiced in referral center.

TPF chemotherapy (docetaxel 75 mg/m(2), followed by intravenous cisplatin 100 mg/m(2) and fluorouracil 1000 mg/m(2) per day, administered as a continuous 24-h infusion for 4 days) or PF (intravenous cisplatin 100 mg/m(2), followed by fluorouracil 1000 mg/m(2) per day as a continuous 24-h infusion for 5 days)

## 9 Management of Recurrence/Relapse:

Is decided in MDT meeting according to initial treatment, symptoms and patient performance status.

## 10 Follow Up

### 11.1 Follow Up Investigations:

**11.1.1** DL scopy and endoscopy once every 3 to 6 months in first 2 years.
**11.1.2** CT scan or MRI at least once and twice in a year with residual.
**11.1.3** Routine labs and assessment of Thyroid function in post RT cases.
**11.1.4** Nutritional and swallowing assessment and also recovery from RT side effects.

### 11.2 Follow Up Visits Schedule

**11.2.1** 1 YEAR-Every month
**11.2.2** 2 YEAR-Every 2 months
**11.2.3** 3 to 5 YEARS- Every 4 to 6 months

## 11 Ongoing Randomized studies

Phase II-III randomized controlled study of concomitant cetuximab plus hyperfractination radiation therapy versus chemotherapy plus hyperfractination radiation therapy in advanced non metastatic head and neck cancer

## 12 Reference:


1) Corvo (2007) Evidence based radiation oncology in head and neck squamous cell carcinoma.(Radiotherapy oncology 85).
2) Gregoire, Levandang et al CT based delineation of nodal levels and related CTV volumes in node negative neck DAHANCA, RTOG,
3) GORTEC, NCIC consensus guidelines (Radiotherapy Oncology 69).
4) Pignon et all Chemotherapy added to locoregional treatment of head and neck squamous cell cancers (Lancet 355).
5) Alorabi M, Shonka NA, Ganti AK. EGFR monoclonal antibodies in locally advanced head and neck squamous cell carcinoma: What is their current role?. *Crit Rev Oncol Hematol*. 2015 Dec 19.
6) Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006 Feb 9. 354(6):567-78
7) Practical radiotherapy planning (Ann barrett, Dobbs) IV edition.
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## CANCER HYPOPHARYNX:

### 1. Epidemiology:

Hypopharyngeal carinoma is relatively less common and usually are seen as advanced cases.

According to the data available from Kuwait cancer registry 2012 , the incidence rate in Kuwait ( ASR ) was 0.3 per 100000 population in comparison to the worldwide incidence of 0.5 per 100000 population. The ASR for Gulf region according to GCC registry 2011 was 0.6.

**Subsites include:**

**1.1** Tumors originating from pyriform fossa
**1.2** Post cricoid area
**1.3** Adjoining pharyngeal wall

### 2. Clinical Presentation

**2.1** Chronic sore throat, and foreign body sensation in the throat.
**2.2** Referred otalgia.
**2.3** Neck mass
**2.4** Later, weight loss, hemoptysis, laryngeal stridor, and hoarseness

### 1. Diagnostic Work up

**3.1** Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.
**3.2** Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.
**3.3** Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.
**3.4** Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.
**3.5** Radiologic investigation CT scan of whole body and MRI face neck for cancer nasopharynx and as per discretion of clinician.
**3.6** PET scan for staging and RT planning.
**3.7** Biopsy of primary and FNAC of neck nodes. Immunohistochemistry for better pathological assessment.
**3.8** Excision biopsy of node with tumor markers if the primary is not assesible.
**3.9** Nutritional assement and swallowing status prior to radical radiotherapy.
**3.10** Review of pathology at referral center.

### 2. Staging

As per the TNM/AJCC staging 7$^{th}$ edition, 2010.

### 3. Prognostic Factors

**3.1** Tumour-related prognostic factors: the primary tumour (T) size and its depth of invasion, the Grade of tumor, and the presence or absence of vascular invasion.

**3.2** The presence of lymph node metastasis (N), and their size, number, andposition (level), as well as signs of extracapsular tumourspread (ECS)

**3.3** The incidence of distant metastatic disease increases with rising tumour stage and nodal metastasis.

## 4. Treatment

### 6.1- T1 2 N0 M0 – (Stage I and II)

Radical radiotherapy is indicated in stage I and stage II cancers.

Definitive conventional EBRT with or without weekly CCT, Radiation dose, 70 Gy/35 Fr@2Gy/Fr/7 weeks.

### 6.2 - T3 N0, T1-3 N1 M0 (Stage III)

Stage III cancers are grey zone as either surgery or RT can be given as initial modality.

**6.2.1-** Laryngectomy with cervical neck dissection is treatment option in such cases.

OR

Definitive conventional EBRT with weekly CCT, (Dose EBRT as above). Rigrous follow up is needed in this group of patients as residual and relapses are salvageable by laryngectomy.

### 6.3 T4aN1-2 M0-(Stage IV non-metastasis)

Radical surgery (laryngopharyngectomy) with neck dissection- further adjuvant EBRT/CCT as per pathology.

OR

Radical EBRT/ CCT as above

Radiation dose, 70 Gy/35 Fr@2Gy/Fr/7 weeks.

Stage III and Stage IV non-metastatic case can be treated by hyper fractionation at referral center considering several parameters related with condition of patient.

## 5. Radiotherapy Treatment

### 5.1 External Beam: Planning Technique

#### 7.1.1 Patient preparation

Patients can have light breakfast or drinks this will not hamper the process of simulation; any history of allergy should be noted.Contrast should be used with caution in such cases. History of asthma, allergic disorders, angioedema & individuals with food allergy are addressed with caution.

#### 7.1.1 Immobilization

Patients lie supine on a headrest to keep the spine straight, with a custom-made shell fixed to the couch top in at least five places to reduce movement. The treated volume will usually extend inferior to the level of the shoulders which should be as low as possible to facilitate beam entry. No mouth bite is required.

**7.1.2 Orientation, set-up, marking and reference points:**

Patient lie in supine position, the customized orfitis fixed with base plate and head rest. Use of traction is optional depending on patient comfort and clinical situation.Three reference radiopaque markers are placed over the orfit in same plane orthogonally with help of lasers. This may or may not be over the centre of tumour. At least one of the axial cut should have two of the reference markers. This is not only for patient set up but also for the planning purpose and execution of plan.

**7.1.3 Image Acquisition:**

CT simulation is performed on spiral CT scanner with slice thickness of 2 millimeters cuts from vertex to carina. Contrast will help in better delineation of the vessels this in turn will help for contouring nodal stations.

**7.1.4 Target definition:**

***7.1.5.1 for radical radiotherapy:*** **GTV-** Is defined as the gross tumor as evident by endoscopy, EUA reports and diagrams, and diagnostic imaging. This will include gross tumors and nodes.PET is valuable in precise delineation of gross tumors. All cases treated by radical radiation as primary treatment modality will have GTV p for the primary tumor and GTV n for nodal component depending on its presence or absence.

7.1.5.1 ***CTV- The CTV:*** There is no evidence on which to base GTV-CTV margins at the primary site but submucosal spread is common and can extend at least 10 mm from the GTV. We recommend the GTV is grown by the planning computer by a 10 mm axial margin and a 15 mm longitudinal margin to create a CTV70. This is then edited to take account of patterns of spread and natural barriers to tumour progression (e.g. bone). The CTV70 is also edited to include adjacent lymph nodes (usually level III but occasionally part of levels II and IV) on the same axial slices as the CTV70. For lateral pyriform fossa tumours these high risk nodes will be ipsilateral; for other hypopharyngeal tumours they will be bilateral.

7.1.5.2 **PTV:** CTV is expanded isotopically 5 mm to get the PTV.

**7.1.5.4** For adjuvant radiotherapy after careful discussion with the surgeon and pathologist, the CTV60 is defined as sites of possible residual microscopic disease. If a large resection with reconstruction and flaps has been performed, the anatomy visible on the planning CT will be very different from that on the initial diagnostic images.The CTV60 should include the margins of resection and sites of any dissected nodal levels where there was tumour. Sites of positive resection margins or where there was extracapsular nodal spread should be further defined as CTV66.

**7.1.5 The Technique:** Three–D or IMRT both are practised in referral center.

**7.1.6 Beam Arrangement:** If the high dose PTV extends posterior to the plane of the spinal cord a twophase technique will be needed.

Opposing lateral beams in phase 1 will include the spinal cord. A second phase using smaller lateral photon beams with posterior border anterior to the spinal cord is then matched to electron beams to the posterior neck. The electron energy is chosen to keep within spinal cord tolerance but cover PTV if possible. Alternatively, the opposing photon beams can be angled to treat the PTV while avoiding the cord.

**7.1.7 Beam Energy:** is adjusted individually according to plan of each case.

**7.1.8 Dose prescription and fractionation**

**7.1.8.1 *Adjuvant radiotherapy***

Concomitant 60 Gy of normal fractionation with weekly chemotherapy with cisplatinum is used in almost all cases. Cisplatinum in dose of 40 mg/m2 or carboplatin in AUC of 2 are used. Concomitant weekly targeted therapy with cetuximab in selected cases. A loading dose of 450 mg/m2 is administered week before planned date of RT later this is followed with weekly dose of 250 mg/m2 till the duration of radiotherapy.

***7.1.9.2 Radical Radiotherapy***

*7.1.9.2.1 Phase 1 – Planned Dose 40 GY/20 FR @2 Gy/Fr /5days a week*

All radical cases are planned by 3 D conformal radiotherapy. The aim of planning here is to spare the parotids as much as possible but not at cost of PTV. Mean dose to at least one of the parotids should be less than 23 Gy.

A low anterior neck portal is also used in conjunction with phase 1 conformal plan in cases with locally advanced disease. A gap of 0.5 mm is used in overlapping fields of lower neck and upper neck fields.

**Low anterior neck field- This field is planned with following borders-**

Upper border – usually at lower border of cricoid, (aim is to keep beams away from shoulders).Lateral borders- Placed usually a beam crossing medial two third and lateral one third of clavicle.Here aim is to cover entire supraclavicular fossa. Lower border- The lower border is placed under the head of clavicle with half centimeter margin under the lower edge of clavicle.

*7.1.9.2.2 For phase 2- Planned dose 20 Gy in 10 Fr photons for anterior neck and 20 Gy in 10 Fr electrons (variable energy) for posterior neck*

In all head and neck cancer cases spine is shielded and the posterior neck is treated with electrons. The electron energy depends on depth of area to be treated.

*7.1.9.2.3 Phase 3*

All gross nodes and gross primary disease are treated in phase 3 up to 70 Gy. Here if the gross disease lies in the territory of or overlapping spinal cord, beam arrangements are made or electrons are used to prescribe the required dose.
Residual nodes and primary can be boosted beyond 70 Gy in selected cases depending on response up to 76 Gy.

#### *7.1.9.3 Palliative Radiotherapy*

Either single fraction 6Gy or 8Gy or 20Gy in 5 fractions or 30 Gy in 10 fractions according to each case and site of metastasis.

### 7.1.10 Dose limitation to OAR:

QUANTEC recommendations are followed (Table C.1.d)

| Organ | Endpoint | Rate (%) | Dose-volume parameter | $D_{max}$ (Gy) | $D_{mean}$ (Gy) |
|---|---|---|---|---|---|
| Brain | Symptomatic necrosis | <3<br><5 | | <60<br><65 | |
| Brainstem | Necrosis or cranial neuropathy | <5<br><5 | D100 <54 Gy<br>D1–10 cc ≤59 Gy | <64 Point | |
| Spinal cord | Grade ≥2 myelopathy | <1 | | 50 | |
| Optic nerve & chiasm | Optic neuropathy | <3<br>3–7 | | <55<br>55–60 | <50 |
| Retina | Blindness | <1 | | <50 | |
| Cochlea | Hearing loss | <15 | | | ≤45 |
| Parotid 1 | Grade 4 xerostomia | <20 | | | <20 |
| Parotid 2 | | <20 | | | <25 |
| Mandible | ORN | <5 | | <70 Point | |
| Pharyngeal constrictors | PEG tube dependent<br>Aspiration | <5<br><5 | | | <50<br><60 |
| Larynx | Grade ≥2 edema | <20 | V50 <27% | | <44 |
| Brachial plexus | Clinically apparent nerve damage | <5 | | <60 | |
| Lung | Symptomatic pneumonitis | 5 | V5 <42%,<br>V20 <22% | | 7 |

### 7.1.11 Verification

Weekly review for all patients in the OPD throughout treatment course.used protocol is for the treatment isocentre on lateral and anterior DRRs from the CT simulation to be compared with porta; images from the treatment machine taken on days 1–3 and weekly thereafter. An off-line correction is made relative to the isocentre position if the mean error in any one plane is 3 mm.

## 7.2 Brachytherapy: when applicable

**7.2.1 Introduction:** Brachytherapy is a promising alternative to surgery for some hypopharyngeal cancer patients. Because there is no incision and no surgical wound to heal, recovery from the procedure is generally rapid.

**7.2.2 Methods**:

#### *7.2.2.1 High-dose rate (HDR)*

Brachytherapy offers a fast, precise way to give radiation treatment for some cancer patients. The radiation is deposited inside a tumor, delivering a maximum dose while minimizing exposure to the

surrounding healthy tissue. Each HDR brachytherapy treatment takes about 15-20 minutes.

*7.2.2.2 Low-dose rate (LDR)*

Brachytherapy involves placing radioactive seeds directly into the oral cancer tumor. Also sometimes called permanent seed implants, LDR brachytherapy uses radioactive seeds bound together in short rows and permanently implants them into the organ. These pellets emit low levels of radiation for several weeks. When this radiation treatment ends, the harmless seeds are left in place permanently

**Brachytherapy of oral cavity tumours is not practiced in referral center.**

## 7.3 Sequleae of Treatment:

### 7.3.1 Acute: (Table C.1.e)

| Likely (more than 10%) | Less Likely (3- 9%) | Rare but serious(less than 2 %) |
|---|---|---|
| Redness and skin pigmentation in radiated area. Loss of hairs in treated zones. | Confluent to grade III mucositis. Secondary infection on top of mucositis | Grade IV mucositis, Skin Necrosis |
| Genralised fatigue, nausea. | Cataract if lens receive more than tolerance dose | Prolong dryness and persistent xerostomia |
| Dry Skin peeling, mucositis patchy to grade II, dysphagia with pain.Change of taste and loss of taste. | | |
| Xerostomia | | |

### 7.3.2 Late:

*7.3.2.1* Some skin pigmentation which is more evident in fair skin individuals.

*7.3.2.2* Dryness of mouth and chronic xerostomia this depends on the dose received by parotids. In cases where both parotids receive a good amount of dose the possibility of xerostomia in long run is emphasized to patients.

*7.3.2.3* Apical lung fibrosis evident on chest x ray can cause some symptoms this is due to the area of lung in lower neck portals.

All side effects during the course of EBRT are expected to resolve gradually by 6 weeks post radiation.

# 8 Principles of Hormonal Treatment:

Not Applicable

# 9 Principles of Chemotherapy:

**9.1 Concurrent chemotherapy** as mentioned in radiotherapy treatment.

9.2 **Induction or adjuvant chemotherapy** is decided in MDT meeting and is applied by medical oncology department, TPF or PF is practiced in referral center.

TPF chemotherapy (docetaxel 75 mg/m(2), followed by intravenous cisplatin 100 mg/m(2) and fluorouracil 1000 mg/m(2) per day, administered as a continuous 24-h infusion for 4 days) or PF (intravenous cisplatin 100 mg/m(2), followed by fluorouracil 1000 mg/m(2) per day as a continuous 24-h infusion for 5 days).

## 10 Management of Recurrence/Relapse

Is decided in MDT meeting according to initial treatment, symptoms and patient performance status.

## 11 Follow Up

### 11.1 Follow Up Investigations:

11.1.1 DLs copy and endoscopy once every 3 to 6 months in first 2 years.

11.1.2 CT scan or MRI at least once and twice in a year with residual.

11.1.3 Routine labs and assessment of Thyroid function in post RT cases.

11.1.4 Nutritional and swallowing assessment and also recovery from RT side effects.

### 11.2 Follow Up Visits Schedule

11.2.1 1 YEAR-Every month

11.2.2 2 YEAR-Every 2 months

11.2.3 3 to 5 YEARS- Every 4 to 6 months

## 12 Ongoing Randomized Studies:

Phase II-III randomized controlled study of concomitant cetuximab plus hyperfractination radiation therapy versus chemotherapy plus hyperfractination radiation therapy in advanced non metastatic head and neck cancer.

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## CANCER LARYNX:

### 1. Epidemiology:

According to the data available from Kuwait cancer registry 2012, the incidence rate in Kuwait (ASR) was 2 per 100000 population in comparison to the worldwide incidence of 3.9 per 100000 population. The ASR for Gulf region according to GCC registry 2011 was 1.6.

Sub-sites include:

**1.1 Supraglottis:** epiglottis, aryepiglottic folds, arytenoids and false cords.
**1.2 Glottis:** vocal cords and anterior and posterior commissures.
**1.3 Sub glottis:** lower border of the glottis to lower border of cricoid cartilage

### 2. Clinical Presentation:

2.1 Dysphonia/aphonia
2.2 Dysphagia
2.3 Dyspnea
2.4 Aspiration
2.5 Blood-tinged sputum
2.6 Fatigue and weakness
2.7 Cachexia
2.8 Pain
2.9 Halitosis
2.10 Neck mass

### 3. Diagnosis Work up

3.1 Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.
3.2 Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.
3.3 Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.
3.4 Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.
3.5 Radiologic investigation CT scan of whole body and MRI face neck as per discretion of clinician.
3.6 PET scan for staging and RT planning.
3.7 Biopsy of primary and FNAC of neck nodes. Immuno histochemistry for better pathological assessment.

3.8 Excision biopsy of node if the primary is not assesible.

3.9 Nutritional assessment and swallowing status prior to radical radiotherapy.

3.10 Review of pathology at referral center.

#### 3.10.1 Assessment of cytology

**3.10.1.1** Histological type

**3.10.1.2** Grading

#### 3.10.2 Histopathological examination for post-operative cases

**3.10.2.1** Histological type

**3.10.2.2** Grading

**3.10.2.3** Size of primary and gross nodes.

**3.10.2.4** Status and measurement of margins with proper orientation of directions.

**3.10.2.5** Regional lymph nodes numbers removed and from which stations.

**3.10.2.6** Evidence of any ECE.

**3.10.2.7** Vascular and nerve invasion should be evaluated.

## 4. Staging

As per the TNM/AJCC staging 7th edition, 2010.

## 5. Prognostic Factors

**5.1 Tumour-related prognostic factors:** The primary tumour (T) site (early glottis carcinoma is better prognosis) and size and its depth of invasion, the Grade of tumor, and the presence or absence of vascular invasion.

**5.2** The presence of lymph node metastasis (N), and their size, number, and position (level), as well as signs of extracapsular tumour spread (ECS)

**5.3** The incidence of distant metastatic disease increases with rising tumour stage and nodal metastasis.

## 6. Treatment:

Primary treatment modalities are surgery, radiotherapy and chemotherapy, Often a multimodality approach is needed in cases with advanced stage, early stage can be managed with combination of one or two modalities.

### 6.1 Supraglotic Cancers:

#### 6.1.1 T1/T2N0M0- Stage I & II

Radiotherapy By 3DCRT to dose of 70 Gy in 35 Fr in seven weeks with/out concurrent cisplatin chemotherapy:

Or Surgery alone or followed by local radiotherapy according to pathology and risk of relapse.

Or Surgery: Supra-glottic laryngectomy OR Hemilaryngectomy.

Bilateral or Ipsilateral neck dissection with primary surgery as per primary location and imaging.

### 6.1.2 T3N0M0, T1,2 N1M0-Stage III

EBRT is preferable (Organ preservation)
Or Partial laryngectomy or endoscopic resection or laryngectomy with neck dissection
Post operatively any nodal positivity mandates need for EBRT with CCT.

### 6.1.3 T4N0 or AnyT, N2 –Stage IV

Laryngectomy with ipsilateral thyroidectomy and bilateral neck dissection adjuvant EBRT indicated if pathology reveal positive nodes and adverse pathological features.
Post surgery EBRT as per pathology.
EBRT with concomitant CT in cases who wish for preservation of organ function, residual recurrent disease salvaged by surgery.
Induction chemotherapy followed by EBRT/CCT is an option in stage IV bulky neck nodes with or without organ metastasis.

## 6.2 Glottic Carcinoma:

### 6.2.1 STAGE (I) AND (II)

Radical radiotherapy is given to the larynx only.

OR

Conservation surgery (preserving more than half of the free margin of contralateral cord) give equivalent results but needs expert surgeon. If there is extensive superficial T2 disease, there will be a better functional outcome with radiotherapy.

### 6.2.2 STAGE (III & IV)

Stage T3 is a heterogeneous group. Treatment options include:

- Primary radiotherapy and salvage surgery.
- Total laryngectomy and postoperative RT.
- Concurrent chemoradiotherapy.

If the tumour is bulky and causing respiratory compromise or stridor, surgical debulking or elective tracheostomy before starting radical RT maybe considered in order maintaining an adequate airway throughout treatment.

Stage T4 requires total laryngectomy and neck dissection and postoperative RT. If the patient is medically, unfit for surgery or declines surgery then radiotherapy with or without chemotherapy is offered.

## 6.3 Subglottis Carcinoma:

Patients often present with late-stage disease. A total laryngectomy and postoperative radiotherapy are usually required.

OR

Laryngeal preservation by EBRT/CCRT is an option though mostly ends in total laryngectomy in event of residual or recurrence.
At K.C.C.C Hyperfractionation with chemotherapy with dose, protocol as above in Stage III and IV laryngeal cancer is advised if KPS permits.

# 7. Radiotherapy Treatment

## 7.1 External Beam: Planning Technique

### 7.1.1 Patient preparation:

Patients can have light breakfast or drinks this will not hamper the process of simulation; any history of allergy should be noted. Contrast should be used with caution in such cases. History of asthma, allergic disorders, angioedema & individuals with food allergy are addressed with caution.

### 7.1.2 Immobilization:

Patient is immobilized in supine position by use of head rest, base plate and or fit cast. The spine should be straight. The shoulders are immobilised in the shell as inferiorly as possible so that the shoulder tips are inferior to the lower border of the cricoid cartilage thus permitting lateral radiation beams to treat the larynx without the need to angle them inferiorly. Grip bars on the side of the couch may help to achieve this.

7.1.3 **Orientation, set-up, marking and reference points:** Patient lie in supine position, the customized or fit is fixed with base plate and head rest. Use of traction is optional depending on patient comfort and clinical situation.Three reference radiopaque markers are placed over the orfit in same plane orthogonally with help of lasers. This may or may not be over the centre of tumor. At least one of the axial cut should have two of the reference markers. This is not only for patient set up but also for the planning purpose and execution of plan.

**7.1.4 Image acquisition:** CT simulation is performed on spiral CT scanner with slice thickness of 2 millimeters are obtained from the base of skull to the top of the aortic arch with the patient immobilised in the treatment position..As treatment of locally advanced glottic cancer or adjuvant radiation after a laryngectomy may require lateral beams angled inferiorly, the CT scan in these patients should be extended inferiorly to the carina

7.1.5 **Target definition:**

**7.1.5.1 GTV-** Is defined as the gross tumor as evident by initial examination, imaging studies and endoscopy examinations. This will include gross tumors and nodes.PET is valuable in precise delineation of gross tumors. All cases treated by radical radiation as primary treatment modality will have GTV p for the primary tumor and GTV n for nodal component depending on its presence or absence.

7.1.4.2 T1 N0 glottic larynx **CTV-** is including the whole laryngeal mucosal surface.

7.1.4.3 **PTV :** CTV is expanded isotropically 5 mm to get the PTV , the superior should be at the mid-body of hyoid and inferior should be at the inferior margin of cricoid)

7.1.4.4 Other curative radiotherapy, GTV is grown isotropically by 10 mm and then edited to take into account likely patterns of spread and barriers to tumour growth. The high dose CTV70 also includes lymph nodes of normal size that are at high risk of having microscopic tumor involvement. This includes the level II & III nodes immediately adjacent to the primary tumor. PTV is drown by isotopically expanding the CTV by 5 mm.

7.1.4.5 Adjuvant radiotherapy The CTV after a laryngectomy is determined by the initial site of the tumor and which local structures were invaded, and by the pattern of lymph node spread found on initial imaging and at neck dissection. A CTV66 can be defined as sites where surgical margins were involved or where there was extracapsular nodal spread. other volumes are included in CTV60.

**7.1.5** **The technique:** Three –D conformal treatment is practised for laryngeal cancer.

**7.1.6** **Beam arrangement:**

Is individualized according to subsite for example: early glottic carcinoma is treated by two lateral Opposing lateral beams of approximately 5 x 5 cm require 15–45° wedges to compensate for missing tissue anteriorly. A 1 cm tissue equivalent bolusis needed over the apex of the larynx if the anterior commissure is involved.

**7.1.7** **Beam Energy:**

It is adjusted individually according to plan of each case.

**7.1.8** **Dose prescription and fractionation:**

***7.1.9.1 Adjuvant Radiotherapy:*** Concomitant 60 Gy of normal fractionation with weekly chemotherapy with cisplatinum is used in almost all cases. Cisplatinum in dose of 40 mg/m2 or carboplatin in AUC of 2 are used. Concomitant weekly targeted therapy with cetuximab is used in selected cases. A loading dose of 450 mg/m2 is administered week before planned date of RT later this is followed with weekly dose of 250 mg/m2 till the duration of radiotherapy. Particular care of the tracheostomy site is needed if the stoma is included in the treated volume.

***7.1.9.2 Radical Radiotherapy:*** as mentioned in treatment per each site.

***7.1.9.3 Palliative Radiotherapy:*** Palliative radiotherapy to the primary site can also be useful when metastases are present at diagnosis, or in locally recurrent disease to ameliorate fungating tumour or reduce bleeding GTV, CTV and PTV are defined as for curative treatment either on a planning CT scan or lateral simulator radiograph. To minimise normal tissue toxicity (particularly mucositis), smaller margins can be used than for curative treatment – e.g. 5 mm from GTV to CTV20Gy in 5 fractions or 30 Gy in 10 fractions.

7.1.10 **Dose limitation to OAR:** the spinal cord is the main organ at risk for laryngeal cancer and the risk of permanent neurological damage is very low, Provided the total dose is less than 45-50 Gray.

7.1.11 **Verification:** Portal images are taken twice per week, compared to DRR and is reviewed by treating radiation oncologist for shift assessment. Weekly review for all patients in the opd through out treatment course.

## 7.2 Brachytherapy:

Not Applicable

## 7.3 Sequleae of treatment

### 7.3.1 Acute:

More with advanced cases and large radiation fields. (Table C.1.f)

| Likely (more than 10%) | Less Likely (3- 9%) | Rare but serious(less than 2 %) |
|---|---|---|
| Redness and skin pigmentation in radiated area. Loss of hairs in treated zones. | Confluent to grade III mucositis. Secondary infection on top of mucositis | Grade IV mucositis, Skin Necrosis |
| Genralised fatigue, nausea. | Cataract if lens receive more than tolerance dose | Prolong dryness and persistent xerostomia |
| Dry Skin peeling, dysphagia with pain. | | |

### 7.3.3 Late:

**7.3.2. 1** Some skin pigmentation which is more evident in fair skin individuals.

**7.3.2.2** Dryness of mouth and chronic xerostomia this depends on the dose received by parotids. In cases where both parotids receive a good amount of dose the possibility of xerostomia in long run is emphasized to patients.

**7.3.2.3** Apical lung fibrosis evident on chest x ray can cause some symptoms this is due to the area of lung in lower neck portals.

All side effects during the course of EBRT are expected to resolve gradually by 6 weeks post radiation.

# 8 Principles of Hormonal Treatment:

**Not Applicable**

# 9 Principles of Chemotherapy:

**9.1** Concurrent chemotherapy as mentioned in radiotherapy treatment.

**9.2** Induction or adjuvant chemotherapy is decided in MDT meeting and is applied by medical oncology department. TPF or PF is practiced in referral center.

- TPF chemotherapy (docetaxel 75 mg/m(2), followed by intravenous cisplatin 100 mg/m(2) and fluorouracil 1000 mg/m(2) per day, administered as a continuous 24-h infusion for 4 days) or PF (intravenous cisplatin 100 mg/m(2), followed by fluorouracil 1000 mg/m(2) per day as a continuous 24-h infusion for 5 days)

# 10 Management of Recurrence/Relapse:

It is decided in MDT meeting according to initial treatment, symptoms and patient performance status.

# 11 Follow Up:

## 11.1 Follow Up Investigations:

11.1.1 DL scopy and endoscopy once every 3 to 6 months in first 2 years.
11.1.2 CT scan or MRI at least once and twice in a year with residual.
11.1.3 Routine labs and assessment of Thyroid function in post RT cases.
11.1.4 Nutritional and swallowing assessment and also recovery from RT side effects.

## 11.2 Follow Up Visits Schedule

11.2.1 1 YEAR-Every month
11.2.2 2 YEAR-Every 2 months
11.2.3 3 to 5 YEARS- Every 4 to 6 months

# 12 Ongoing Randomized studies

Phase II-III randomized controlled study of concomitant cetuximab plus hyperfractination radiation therapy versus chemotherapy plus hyperfractination radiation therapy in advanced non metastatic head and neck cancer

# 13. References:


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## CARCINOMA NASOPHARYNX:

### 1. Epidemiology:

According to the data available from Kuwait cancer registry 2012, the incidence rate in Kuwait was 1.9 per 100000 population in comparison to the annual incidence of 3.1 per 100000 population worldwide.. According to the data available from cancer registry in Kuwait, it represents the second most common head and neck cancer after laryngeal cancers. The ASR for GCC according to Gulf region registry 2011 was 2.6.

### 2. Clinical Presentation

**2.1** Nasal symptoms: including bleeding, obstruction, and discharge (78%)
**2.2** Ear symptoms: including infection, deafness, and tinnitus (73%)
**2.3** Neck swelling (63%)

### 3. Diagnosis Work up

**3.1** Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.
**3.2** Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.
**3.3** Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.
**3.4** Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.
**3.5** Radiologic investigation CT scan of whole body and MRI face neck for cancer nasopharynx and as per discretion of clinician.
**3.6** PET scan for staging and RT planning.
**3.7** Biopsy of primary and FNAC of neck nodes. Immuno histochemistry for better pathological assessment.
**3.8** Excision biopsy of node with tumor markers if the primary is not assesible.
**3.9** Ebstein barr virus quantitative assessment for nasopharyngeal cancers.
**3.10** Nutritional assessment and swallowing status prior to radical radiotherapy.
**3.11** Review of pathology at referral center.

**3.11. 1 Assessment of Pathology** (biopsy of the primary lesion or neck node )

3.11.1.1 Histological type

3.11.1.2 Grading

### 4. Staging

As per the TNM/AJCC staging 7th edition, 2010.

### 5. Prognostic Factors

5.1 WHO type III has better prognosis.
5.2 Cases, which express EBV antigen on tumor biopsy, have good response to treatment.

## 6. Treatment

**6.1** Non-metastatic disease

Non-metastatic disease is managed by locoregional radiotherapy with concomitant chemotherapy. Radical EBRT (3DCRT) with concomitant chemotherapy. Prescribed RT dose is 70 Gy/35 Fr@2Gy/Fr.

Chemotherapy, usually Cisplatin, is given weekly ( 40mg/m2) or weekly carboplatinum (AUC 2)

**6.2**

Induction chemotherapy (combination of Cisplatin, fluorouracil with/out docetaxel), bulky nodal disease. (2 to 3cycles). EBRT and CCT follows this.

**6.3**

Residual bulky nodes after 70 Gy can be boosted by EBRT up to cumulative dose of 76Gy. Or

Neck node dissection for residual nodal disease is another treatment option.

**6.4**

Metastatic disease is treated primarily with palliative chemotherapy. EBRT and CCT later as per response and KPS.

## 7. Radiotherapy Treatment

**7.1 External Beam: Planning Technique**

### 7.1.1 Patient preparation

Patients can have light breakfast or drinks this will not hamper the process of simulation; any history of allergy should be noted. Contrast should be used with caution in such cases. History of asthma, allergic disorders, angioedema & individuals with food allergy are addressed with caution.

### 7.1.2 Immobilization

Patient is immobilized in supine position by use of head rest, base plate and orfit cast. The entire head neck and shoulders are immobilized by 5 point fixation areas. The aim of positioning is to elevate chin, depress shoulder to desirable position as per patient comfort. Aim here is to have spine as straight as possible.

### 7.1.3 Orientation, set-up, marking and reference points:

Patient lie in supine position, the customized or fit is fixed with base plate and head rest. Use of traction is optional depending on patient comfort and clinical situation. Three reference radiopaque markers are placed over the or fit in same plane orthogonally with help of lasers. This may or may not be over the centre of tumor. At least one of the axial cut should have two of the reference

markers. This is not only for patient set up but also for the planning purpose and execution of plan.

### 7.1.4 Image acquisition

CT simulation- This is performed on spiral CT scanner with slice thickness of 2 millimetres cuts from vertex to carina. Contrast will help in better delineation of the vessels this in turn will help for contouring nodal stations.

### 7.1.5 Target definition:

*7.1.5.1* ***GTV-*** All the gross disease as seen on the radiological studies and endoscopic and clinical findings is GTV. Any retropharyngeal node more than 5 mm and any cervical node more than 10 mm are contoured as GTV.

#### *7.1.5.2 C T V for Nasopharynx cancers-*

- Proximally CTV delineation starts at sphenoid sinus and all T3 and T4 tumors entire sinus is delineated, posterior nasal space, posterior third of maxillary sinus are included in CTV. Pterygoid CTV for nasopharynx comprises of 1 centimeter margin around the gross tumor in early T1 lesion, the delineation of adjacent structure and skull base region depends on T stage.
- plates, pharyngeal spaces, ptregomaxillary fissure are contoured in CTV. Clivus is contoured depending on involvement but good volume of bone is delineated in involved tumors. Entire gross tumor should have a margin of 1 centimeter and contouring should not extend beyond the bony landmarks however in case of bony involvements bones should be included with fair margin.
- Nodal CTV- All Nasopharyngeal cancers retropharyngeal, level I b, level II, level III, level IV and level V are included as nodal CTV.Bilateral supraclavicular fossa is essentially part of CTV in all nasopharyngeal cancers this is treated by a low anterior neck field.
- Involved Nodal stations in our practice are treated to dose of 70 Gy and residual nodes are further boosted to cumulative dose of 76 Gy. Non-involved nodal stations are treated up to dose of 60 Gy.

***7.1.5.3 PTV*** Entire CTV is added with margin of 0.5 centimeter to get the PTV

#### *7.1.5.4 ORGANS AT RISK-*

Bilateral parotids, bilateral eyes and optic nerves, optic chiasma, brain stem & temporallobes, Spinal cord, TM joints, mandible, bilateral cochlea and internalear

### 7.1.6 Technique: Three –D or IMRT both are practised

### 7.1.7 Beam arrangement:

For conformal radiotherapy combination of 7 and more beams are used. Upper border usually supra orbital region.MLC are used to block eyes. Gross nodes at junction of 2 fields are avoided and at least 1 centimeter margin is desired beyond the palpable node. Lower border is placed lower neck below the cricoids cartilage. Preferably it should not about the gross nodes and should be away from shoulder. A gap of 5 mm is maintained between the lower border of conformal fields and the low anterior neck field.

**7.1.8 Beam Energy:** is adjusted by physicist according to plan of each case.

**7.1.9 Dose prescription and fractionation:**

***7.1.9.1* Conformal CCRT**

*7.1.9.1.1 PTV for phase 1*

This includes Gross tumor, microscopic disease sites and above mentioned nodal regions these areas are irradiated to dose of 40 Gy in 20 Fr @ 2 Gy /Fr 5 days a week.

*7.1.9.1.2 PTV for phase 2*

20 Gy in 10 Fr @ 2 Gy /Fr 5 days a week.Spinal cord is shielded and the posterior neck is treated by electrons with same dose as for photons. Energy of electrons is selected as per nodal disease and usually prescribed at 90 %.

*7.1.9.1.3 PTV for phase 3*

10 Gy/5Fr@ 2 Gy /Fr 5 days a week .The volume is gross tumor of primary and nodal stations as seen clinically or imaging studies. Usually we consider atleast 1 centmeter margin around gross disease in phase 3.

*7.1.9.1.4*

Lower neck and bilateral supraclavicular fossa are irradiated to dose of 50 Gy in 25 Fractions with separate field.

Concomitant chemotherapy with cisplatin or carboplatin is given with RT. The dose of cisplatin is 40 mg/m2 in weekly schedule and 100 mg/m2 in 3 week schedule.

***7.1.9.2 Hyperfractionated radiotherapy for locally advanced cases of head and neck cancers with***

The planning techniques and target delineation remains the same however the dose for various phases is different

*7.1.9.2.1* Phase 1 for hyperfractionated radiotherapy- 39.6 Gy/33 Fr @ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week.

*7.1.9.2.2* Phase 2 for hyperfractionated radiotherapy-20.40 Gy/17 Fr@ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week.

*7.1.9.2.3* Phase 3 for hyperfractionated radiotherapy- 9.6 Gy/ 8Fr @ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week.

*7.1.9.2.4* Lower neck field and supraclavicular region is treated to dose of 50.4 Gy/42 Fr@ 1.2 Gy/Fr x 2 Fr/day 6 hour apart /5 days a week. Usually prescribed at Dmax.

*7.1.9.2.5* Posterior neck electrons for phase 2 and other boost techniques for phase 3 remains same as above.

***7.1.9.3 IMRT:*** Kindly refer to IMRT protocol.

***7.1.9.4 Palliative Radiotherapy:*** either single fraction 6Gy or 8Gy or 20Gy in 5 fractions or 30 Gy in 10 fractions according to each case and site of metastasis.

7.1.10 **Dose limitation to OAR:** QUANTEC recommendations are followed. (Table C.1.g)

| Organ | Endpoint | Rate (%) | Dose-volume parameter | $D_{max}$ (Gy) | $D_{mean}$ (Gy) |
|---|---|---|---|---|---|
| Brain | Symptomatic necrosis | <3<br><5 | | <60<br><65 | |
| Brainstem | Necrosis or cranial neuropathy | <5<br><5 | D100 <54 Gy<br>D1–10 cc ≤59 Gy | <64 Point | |
| Spinal cord | Grade ≥2 myelopathy | <1 | | 50 | |
| Optic nerve & chiasm | Optic neuropathy | <3<br>3–7 | | <55<br>55–60 | <50 |
| Retina | Blindness | <1 | | <50 | |
| Cochlea | Hearing loss | <15 | | | ≤45 |
| Parotid 1 | Grade 4 xerostomia | <20 | | | <20 |
| Parotid 2 | | <20 | | | <25 |
| Mandible | ORN | <5 | | <70 Point | |
| Pharyngeal constrictors | PEG tube dependent<br>Aspiration | <5<br><5 | | | <50<br><60 |
| Larynx | Grade ≥2 edema | <20 | V50 <27% | | <44 |
| Brachial plexus | Clinically apparent nerve damage | <5 | | <60 | |
| Lung | Symptomatic pneumonitis | 5 | V5 <42%,<br>V20 <22% | | 7 |

7.1.11 **Verification:** portal images are taken twice per week, compared to DRR and is reviewed by treating radiation oncologist for any shift.

## 7.2 Brachytherapy:

7.2.1 **Introduction:** The primary indication for a brachytherapy implant is in the management of residual disease after standard treatment or for management of recurrent disease, most experience has been with low-dose-rate implant as with iodine-125 or gold-198 seeds can be used.

7.2.2 **Methods:** not practiced in referral center.

## 7.3 Sequleae of treatment

### 7.4.1 Acute: (Table C.1.h)

| Likely (more than 10%) | Less Likely (3- 9%) | Rare but serious(less than 2 %) |
|---|---|---|
| Redness and skin pigmentation in radiated area. Loss of hairs in treated zones. | Confluent to grade III mucositis. Secondary infection on top of mucositis | Grade IV mucositis, Skin Necrosis |
| Genralised fatigue, nausea. | Cataract if lens receive more than tolerance dose | Prolong dryness and persistent xerostomia |
| Dry Skin peeling, mucositis patchy to grade II, dysphagia with pain. Change of taste and loss of taste. | | |
| Xerostomia | | |

### 7.4.2 Late:

**7.4.2.1** Some skin pigmentation which is more evident in fair skin individuals.

**7.4.2.2** Dryness of mouth and chronic xerostomia this depends on the dose received by parotids. In cases where both parotids receive a good amount of dose the possibility of xerostomia in long run is emphasized to patients.

**7.4.2.3** Apical lung fibrosis evident on chest x ray can cause some symptoms this is due to the area of lung in lower neck portals.

All side effects during the course of EBRT are expected to resolve gradually by 6 weeks post radiation.

## 8. Principles of Hormonal Treatment:

Not Applicable.

## 9. Principles of Chemotherapy:

**9.1** Concurrent chemotherapy as mentioned in radiotherapy treatment.

**9.2** Induction or adjuvant chemotherapy is decided in MDT meeting and is applied by medical oncology department. TPF or PF is practiced in referral center.

- TPF chemotherapy (docetaxel 75 mg/m(2), followed by intravenous cisplatin 100 mg/m(2) and fluorouracil 1000 mg/m(2) per day, administered as a continuous 24-h infusion for 4 days) or PF (intravenous cisplatin 100 mg/m(2), followed by fluorouracil 1000 mg/m(2) per day as a continuous 24-h infusion for 5 days)

## 10. Management of Recurrence/Relapse

Is decided in MDT meeting according to initial treatment, symptoms and patient performance status.

## 11. Follow Up

### 11.1 Follow Up Investigations:

11.1.1 DL scopy and endoscopy once every 3 to 6 months in first 2 years.
11.1.2 CT scan or MRI at least once and twice in a year with residual.
11.1.3 Routine labs and assessment of Thyroid function in post RT cases.
11.1.4 Nutritional and swallowing assessment and also recovery from RT side effects.

### 11.2 Follow Up Visits Schedule

11.2.1 1 YEAR-Every month
11.2.2 2 YEAR-Every 2 months
11.2.3 3 to 5YEARS- Every 4 to 6 months

## 12. Ongoing Randomized studies

Adjuvant Chemotherapy Following CCRT In Locally Advanced Nasopharyngeal carcinoma.

## 13. References:


1. Gregoire, Levandang et al CT based delineation of nodal levels and related CTV volumes in node negative neck DAHANCA, RTOG, GORTEC, NCIC consensus guidelines (Radiotherapy Oncology 69)
2. Practical radiotherapy planning (Ann barrett, Dobbs) IV edition.
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4. Pathmanathan R, Prasad U, Sadler R, Flynn K, Raab-Traub N. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. *N Engl J Med*. 1995 Sep 14. 333(11):693-8
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## SINO NASAL CANCERS:

## 1. Epidemiology:

Sino nasal malignancies are less common cancers in head and neck region, According to the data available from Kuwait cancer registry 2012 , the incidence rate in Kuwait ( ASR ) was 0.6 per 100000 population in comparison to the worldwide incidence of 1.2 per 100000 population. The ASR for Gulf region according to GCC registry 2011 was 0.4.

### 1.1 Sub-sites include

**1.1.1** tumors that arise from nasal cavity,
**1.1.2** nasal vestibule,
**1.1.3** maxillary sinus,
**1.1.4** ethmoid sinus,
**1.1.5** sphenoid sinus and frontal sinus.

It is commonly seen are nasal cavity and maxillary sinus cancers. Unlike head and neck cancers these site in nearly 50 % cases non-squamous pathological types are seen.

### 1.2 Histopathologic Subtypes

**1.2.1** Squamous cell carcinoma is uncommon pathology in sinuses except maxillary but common for nasal vestibule cancer.

**1.2.2** Esthesioneuroblastoma- These tumors originate from the olfactory epithelium of nasal cavity.

**1.2.3** Sinonasal undifferentiated carcinoma- Is an aggressive cancer affecting Men more and is often refractory to treatment.

**1.2.4** Lethal mid line granuloma- These cancers are aggressive lesions associated with destruction of facial soft tissue and progressive disseminated fatal course. They are T cell lymphoma, which are CD 56 positive, and component of EBV is associated with these.

**1.2.5** Inverting papilloma- These are benign lesions seen in sinonasal region with potential for recurrence. Some 10 % transform to squamous cell carcinoma. Proliferating epithelial growth inverting into underlying stroma rather a surface growth that gives the name.

## 2. Clinical Presentation

**2.1** epistaxis,
**2.2** nasal obstruction,
**2.3** recurrent sinusitis,
**2.4** cranial neuropathy,
**2.5** sinus pain,
**2.6** facial paresthesia,
**2.7** proptosis,
**2.8** diplopia,
**2.9** painess neck mass.

## 3. Diagnostic Work up

3.1 Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.
3.2 Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.
3.3 Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.
3.4 Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.
3.5 Radiologic investigation CT scan of whole body and MRI face neck as per discretion of clinician.
3.6 PET scan for staging and RT planning.
3.7 Biopsy of primary and FNAC of neck nodes. Immuno histochemistry for better pathological assessment.
3.8 Excision biopsy of node with tumor markers if the primary is not assesible.
3.9 Nutritional assement and swallowing status prior to radical radiotherapy.
3.10 Review of pathology at referral center.

### *3.10.1 Assessment of cytology*

*3.10.1.1* Histological type
*3.10.1.2* Grading

### 3.10.2 *Histopathological examination for post-operative cases*

*3.10.2.1* Histological type
*3.10.2.2* Grading
*3.10.2.3* Size of primary and gross nodes.
*3.10.2.4* Status and measurement of margins with proper orientation of directions.
*3.10.2.5* Regional lymph nodes numbers removed and from which stations.
*3.10.2.6* Evidence of any ECE.
*3.10.2.7* Vascular and nerve invasion should be evaluated.

## 4. Staging

As per the TNM/AJCC staging 7$^{th}$ edition, 2010.

## 5. Prognostic Factors

5.1 Lymph node involvement in these cancers is uncommon and when present at diagnosis the outcome of treatment is poor.
5.2 Sinonasal undifferentiated carcinoma is of poor prognosis.

## 6. Treatment:

Surgery by wide local excision and reconstruction is the main treatment.
In advanced stage surgery becomes difficult so, radiotherapy with chemotherapy is indicated in such cases.

### 6.1 T1-T2 N0 Tumors

T1, T2 N0 tumors with complete surgery require regular close follow up, adenoid cystic pathology requires adjuvant EBRT.

Adjuvant EBRT is needed if other adverse features exist like LVI, positive margins or perineural invasion is seen. The dose of radiotherapy in such cases is 60 Gy in 30 Fractions over 6 weeks.

Radical RT to 70 Gy in cases where surgery is ruled out.

### 6.2 T3-T4 tumors & locally advanced cases

It is often managed by multimodality treatment approach: Primary treatment modality for T3-T4 is surgery if respectable OR EBRT /CCRT followed by feasible surgery.

If surgery is not feasible, radical radiotherapy until 70 Gy over 35 fractions is indicated with concomitant chemotherapy.

There is role for down staging by combination chemotherapy with TPF in bulky tumors followed by possible surgical intervention in non-metastatic cases.

## 7. Radiotherapy Protocol:

### 7.1 External Beam: Planning Technique

**7.1.1 Patient preparation:** Patients can have light breakfast or drinks this will not hamper the process of simulation; any history of allergy should be noted. Contrast should be used with caution in such cases. History of asthma, allergic disorders, angioedema & individuals with food allergy are addressed with caution.

**7.1.2 Immobilization:** Patient is immobilized in supine position by use of head rest, base plate and orfit cast. The entire head neck and shoulders are immobilized by 5-point fixation areas. The aim of positioning is to elevate chin, depress shoulder to desirable position as per patient comfort. Aim here is to have spine as straight as possible. A mouth bite is used to depress the tongue and oral cavity away from the treated volume and reduce acute morbidity.

**7.1.3 Orientation, set-up, marking and reference points:** Patient lie in supine position, the customized orfit is fixed with base plate and head rest. Use of traction is optional depending on patient comfort and clinical situation. Three reference radiopaque markers are placed over the orfit in same plane orthogonally with help of lasers. This may or may not be over the centre of tumor. At least one of the axial cut should have two of the reference markers. This is not only for patient set up but also for the planning purpose and execution of plan.

**7.1.4 Image acquisition:** CT simulation is performed on spiral CT scanner with slice thickness of 2 millimetres from vertex to carina. Contrast will help in better delineation of the vessels this in turn will help for contouring nodal stations.

**7.1.5 Target definition:**

*7.1.5.1* GTV- Is defined as the gross tumor as evident by initial examination, imaging studies and endoscopy examinations. Preoperative imaging should be viewed beside the CT planning dataset to ensure that initial sites of disease are covered.

*7.1.5.2* CTV should encompass all initial sites of disease (presurgery GTV), themucosa of adjacent compartments of the sinonasal complex and a 10 mm marginat least from initial sites of GTV where no good bony barrier to

invasion exists.CTV for tumours involving the ethmoid sinuses should include the sphenoid sinus. Where initial disease came close to the orbit or invaded the lamina papyracea, the CTV should include that portion of the medial and inferior orbital wall.

*7.1.5.3* PTV: The CTV is expanded isotropically by 5 mm to form the PTV.Organs at risk to be outlined include the lenses, lacrimal glands (in the superolateral orbit and upper eyelid), optic nerves and chiasm, spinal cord, brainstem and pituitary gland.

**7.1.6** **Specify the technique:** Three –D or IMRT both are practised in referral center.

**7.1.7** **Beam Arrangement:** For sinonasal tumours uses an anterior beam to provide most of the dose with an ipsilateral or bilateral wedged lateral beams added to provide extra dose to the posterior part of the PTV. The lateral fields have their anterior border behind the lens and can be angled 5° posteriorly to avoid exiting through the contralateral lens. As a result, not all the PTV will be within the lateral beams.

**7.1.8** **Beam Energy:** is adjusted individually according to plan of each case.

**7.1.9** **Dose prescription and fractionation**

*7.1.9.1* ***Adjuvant radiotherapy:*** For larger T2 (3 cm), T3 and T4 tumours, local control is best achieved by surgery and adjuvant radiotherapy. Adjuvant local radiotherapy is also indicated where a smaller primary tumour is excised with positive margins and the preferred option of further excision is not possible. Where a small primary tumour has been excised with close (5 mm) margins, Concomitant 60 Gy of normal fractionation with weekly chemotherapy with cisplatinum is used in almost all cases. Cisplatinum in dose of 40 mg/m2 or carboplatin in AUC of 2 are used.

*7.1.9.2* ***Radical Radiotherapy:*** If the primary was close to or invading the nasopharynx, the adjacent ipsilateralretropharyngeal nodes should be included in the CTV. When cervical noderadiotherapy is indicated, the intraparotid nodes, level Ib and superior level II nodes can be included in the CTV but including these nodes will make a complex volume harder to treat adequately. As local relapse in the primary site is usually the greatest risk, the nodes are often not treated in sinonasal tumours. PTV is treated by conventional fractionation 70y\35fr. IMRT is practised and dose escalation is feasible. Kindly refer to IMRT protocol.

*7.1.9.3* ***Palliative Radiotherapy:*** Palliative radiotherapy to the primary site can also be useful when metastases are present at diagnosis, or in locally recurrent disease to ameliorate fungating tumour or reduce bleeding GTV, CTV and PTV are defined as for curative treatment either on a planning CT scan or lateral simulator radiograph. To minimise normal tissue toxicity (particularly mucositis), smaller margins can be used than for curative treatment – e.g. 5 mm from GTV to CTV 20Gy in 5 fractions or 30 Gy in 10 fractions

**7.1.10** **Dose limitation to OAR:**

QUANTEC recommendations are followed. Hotspots in the mandible of 107 per cent should be avoided to reduce the risk of osteoradionecrosis. Excessive dose in the temporomandibular joint (TMJ) should also be avoided to reduce the risk of long-term TMJ dysfunction and trismus. The cochlear dose should be kept below 50 Gy if possible to reduce the risk of long-term sensorineural hearing damage. dose limit of 50 Gy for the optic nerve and chiasm,

(Table C.1.i)

| Organ | Endpoint | Rate (%) | Dose-volume parameter | $D_{max}$ (Gy) | $D_{mean}$ (Gy) |
|---|---|---|---|---|---|
| Brain | Symptomatic necrosis | <3<br><5 | | <60<br><65 | |
| Brainstem | Necrosis or cranial neuropathy | <5<br><5 | D100 <54 Gy<br>D1–10 cc ≤59 Gy | <64 Point | |
| Spinal cord | Grade ≥2 myelopathy | <1 | | 50 | |
| Optic nerve & chiasm | Optic neuropathy | <3<br>3–7 | | <55<br>55–60 | <50 |
| Retina | Blindness | <1 | | <50 | |
| Cochlea | Hearing loss | <15 | | | ≤45 |
| Parotid 1 | Grade 4 xerostomia | <20 | | | <20 |
| Parotid 2 | | <20 | | | <25 |
| Mandible | ORN | <5 | | <70 Point | |
| Pharyngeal constrictors | PEG tube dependent<br>Aspiration | <5<br><5 | | | <50<br><60 |
| Larynx | Grade ≥2 edema | <20 | V50 <27% | | <44 |
| Brachial plexus | Clinically apparent nerve damage | <5 | | <60 | |
| Lung | Symptomatic pneumonitis | 5 | V5 <42%,<br>V20 <22% | | 7 |

**7.1.11** **Verification:** Weekly review for all patients in the OPD throughout treatment course used protocol is for the treatment isocentre on lateral and anterior DRRs from the CT simulation to be compared with porta; images from the treatment machine taken on days 1–3 and weekly thereafter. An off-line correction is made relative to the isocentre position if the mean error in any one plane is 3 mm.

## 7.2 Brachytherapy:

Not Applicable

## 7.3 Sequleae of treatment

### 7.3.1 Acute: (Table C.1.j)

| Likely (more than 10%) | Less Likely (3- 9%) | Rare but serious(less than 2 %) |
|---|---|---|
| Redness and skin pigmentation in radiated area. Loss of hairs in treated zones. | Confluent to grade III mucositis. Secondary infection on top of mucositis | Grade IV mucositis, Skin Necrosis |
| Genralised fatigue, nausea. | Cataract if lens receive more than tolerance dose | Prolong dryness and persistent xerostomia |
| Dry Skin peeling, mucositis patchy to grade II, dysphagia with pain.Change of taste and loss of taste. | | |
| Xerostomia | | |

### 7.3.2 Late:

**7.4.2.1** Some skin pigmentation which is more evident in fair skin individuals.

**7.4.2.2** Dryness of mouth and chronic xerostomia this depends on the dose received by parotids. In cases where both parotids receive a good amount of dose the possibility of xerostomia in long run is emphasized to patients.

**7.4.2.3** Chronic dry eye or even loss of vision in ipsilateral eye if dose limitations can't be followed in advanced cases with orbital invasion.

## 8. Hormonal Treatment:

Not Applicable

## 9. Chemotherapy:

**9.1** Concurrent chemotherapy as mentioned in radiotherapy treatment.

**9.2** Induction or adjuvant chemotherapy is decided in MDT meeting and is applied by medical oncology department. TPF or PF is practiced in referral center.

- TPF chemotherapy (docetaxel 75 mg/m(2), followed by intravenous cisplatin 100 mg/m(2) and fluorouracil 1000 mg/m(2) per day, administered as a continuous 24-h infusion for 4 days) or PF (intravenous cisplatin 100 mg/m(2), followed by fluorouracil 1000 mg/m(2) per day as a continuous 24-h infusion for 5 days)

## 10. Management of Recurrence/Relapse:

Is decided in MDT meeting according to initial treatment, symptoms and patient performance status.

## 11. Follow Up

### 11.1 Follow Up Investigations:

**11.1.1** DL scopy and endoscopy once every 3 to 6 months in first 2 years.

**11.1.2** CT scan or MRI at least once and twice in a year with residual.

**11.1.3** Routine labs and assessment of Thyroid function in post RT cases.

**11.1.4** Nutritional and swallowing assessment and also recovery from RT side effects.

### 11.2 Follow Up Visits Schedule

**11.1.1** 1 YEAR-Every month

**11.1.2** 2 YEAR-Every 2 months

**11.1.3** 3 to 5 YEARS- Every 4 to 6 months

## 12. Ongoing Randomized studies:

Phase II-III randomized controlled study of concomitant cetuximab plus hyperfractination radiation therapy versus chemotherapy plus hyperfractination radiation therapy in advanced non metastatic head and neck cancer.

## 13. References:


1) Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. *Clin Otolaryngol Allied Sci*. 1979 Dec. 4(6):431-56
2) Golabek W, Drop A, Golabek E, Morshed K. Site of origin of paranasal sinus malignancies [in Polish]. *Pol Merkuriusz Lek*. 2005 Sep. 19(111):413-4
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9) Practical radiotherapy planning (Ann barrett, Dobbs) IV edition.
10) NCCN guidelines 2016.


## SALIVARY GLAND TUMOR:

### 1. Epidemiology:

According to the data available from Kuwait cancer registry 2012, the incidence rate in Kuwait (ASR) was 0.4 per 100000 population in comparison to the worldwide incidence of 0.6 per 100000 population. The ASR for Gulf region according to GCC registry 2011 was 0.6.

Tumors in this sub site include tumors of major and minor salivary gland.

### 2. Clinical Presentation

2.1 Slowly enlarging painless mass

2.2 Cheek fullness if parotid neoplasm, Submandibular neoplasms often appear with diffuse enlargement of the gland, whereas sublingual tumors produce a palpable fullness in the floor of the mouth.

2.3 Minor salivary gland tumors have a varied presentation, depending on the site of origin. Most common is Painless masses on the palate or floor of mouth

2.4 Facial paralysis or other neurologic deficit

### 3. Diagnosis Work up

**3.1** Complete physical and local examination, sketches to demarcate the extent of primary and nodal involvement.

**3.2** Blood counts, serum biochemistry, Thyroid function test, 24-hour urine for creatinine clearance.

**3.3** Dental Evaluation and extraction if needed for caries tooth. Audiogram for assessment of auditory function in nasopharyngeal cancers.

**3.4** Fiberoptic endoscopy, Laryngoscopy or Examination under anesthesia for primary assessment.

**3.5** Radiologic investigation CT scan of whole body and MRI face neck as per discretion of clinician.

**3.6** PET scan for staging and RT planning.

**3.7.** Biopsy of primary and FNAC of neck nodes. Immunohistochemistry for better pathological assessment.

**3.8** Excision biopsy of node with tumor markers if the primary is not assessable.

**3.9** Nutritional assessment and swallowing status prior to radical radiotherapy.

**3.10** Review of pathology at referral center.

### 3.10.1 Assessment of cytology

3.10.1.1 Histological type

3.10.1.2 Grading

### 3.10.2 Histopathological examination for post-operative cases

3.10.2.1 Histological type

3.10.2.2 Grading

3.10.2.3 Size of primary and gross nodes.

3.10.2.4 Status and measurement of margins with proper orientation of directions.

3.10.2.5 Regional lymph nodes numbers removed and from which stations.

3.10.2.6 Evidence of any ECE.

3.10.2.7 Vascular and nerve invasion should be evaluated.

## 4. Staging

As per the TNM/AJCC staging 7$^{th}$ edition, 2010.

## 5. Prognostic Factors

**5.1** **Site:** major alivary gland tumours carry better prognosis than minor salivary tumours.

**5.2** **Histopathologic type:** Acinic cell type has better prognosis than mucoepedermoid and adenoid cystic type.

**5.3** **Tumour Grade:** The biologic behavior of mucoepidermoid carcinoma is dependent on the grade of tumor. Low-grade lesions are fairly nonaggressive, and appropriate treatment imparts a good prognosis. High-grade neoplasms are much more aggressive, with high rates of regional lymph node metastases.

**5.4** Presence of capsular invasion and perineural infiltration carry unfavorable prognosis.

## 6. Treatment

**6.1** Surgery- Radical surgery for involved salivary gland and nodal dissection

**6.2** Adjuvant RT in cases with positive margins, incomplete removal, high grade or perineural invasion. (60Gy/30 Fr)

**6.3** EBRT to Radical dose up to 70 Gy if surgery is not feasible or locally advanced disease.

## 7. Radiotherapy Treatment

### 7.1 External Beam: Planning Technique

**7.1.1 Patient Preparation:** Patients can have light breakfast or drinks this will not hamper the process of simulation, any history of allergy should be noted. Contrast should be used with caution in such cases. History of asthma, allergic disorders, angioedema & individuals with food allergy are addressed with caution.

**7.1.2 Immobilization:** Patient is immobilized in supine position by use of head rest, base plate and orfit cast. The entire head neck and shoulders are immobilized by 5 point fixation areas. The aim of positioning is to elevate chin, depress shoulder to desirable position as per patient comfort. Aim here is to have spine as straight as possible. A custom-made mouth bite may help to push the tongue inferiorly when irradiating the hard palate or upper alveolus or to separate the roof of the mouth from the inferior oral cavity when irradiating the tongue.

**7.1.3 Orientation, set-up, marking and reference points:**
Patient lie in supine position, the customized orfit is fixed with base plate and head rest. Use of traction is optional depending on patient comfort and clinical situation. Three reference radiopaque markers are placed over the orfit in same plane orthogonally with help of lasers. This may or may not be over the centre of tumor. At least one of the axial cut should have two of the reference markers. This is not only for patient set up but also for the planning purpose and execution of plan.

**7.1.4 Image Acquisition:** CT simulation is performed on spiral CT scanner with slice thickness of 2 millimetres from vertex to carina. Contrast will help in better delineation of the vessels this in turn will help for contouring nodal stations.

**7.1.5 Target definition:**

*7.1.5.1* **GTV-** Is defined as the gross tumor as evident by initial examination, imaging studies and endoscopy examinations. This will include gross tumours and nodes.PET is valuable in precise delineation of gross tumors. All cases treated by radical radiation as primary treatment modality will have GTV p for the primary tumor and GTV n for nodal component depending on its presence or absence.

*7.1.5.2* The **CTV** is a hetrogenous entity and not fixed rather it depends on the pathology of the tumor. Usually in all cases where deep margin of parotid tumor or positive margins are documented entire jugular vein on involved site is contoured laterally CTV extends close to skin. In adenoid cystic carcinomas of parotid entire facial nerve up to skull base is treated. Usually neck is treated in involved nodes and ipsilateral level Ib, level II and III are treated.

*7.1.5.3* **PTV:** CTV is expanded isotropically 5 mm to get the PTV however the skin interface with PTV is to be avoided and PTV at such places is tailored.

**7.1.6 Technique:**
Three –D or IMRT are both practised in referral center.

**7.1.7 Beam arrangement:**
Two or three ipsilateral photon beams will usually provide homogeneous dose distribution to the CTV without exceeding the tolerance of adjacent critical structures. The anterior oblique beam angle is chosen according to the shape of the anteromedial

edge of the PTV while trying to minimise dose to the mucosa of the oral cavity and oropharynx. The posterior oblique angle is chosen according to the contour of the posterolateral edge of the PTV and should be lateral to the spinal cord and brainstem. The exit dose from this beam should be inferior to the contralateral eye. An additional lateral photon beam may provide a more homogeneous distribution but will increase dose to the contralateral parotid gland and possibly to the spinal cord. The PTV may come close to the skin surface, in which case it can be difficult to cover the lateral surface of the PTV unless tissue equivalent bolus is used. However, bolus is only recommended if there is a risk of microscopic residual disease in the skin. If level III and IV nodes are to be treated as an adjuvant to neck dissection, a matched anterior neck beam can be used. The match plane should be inferior to any preoperative lymphadenopathy to avoid a junction through microscopic residual disease.

**7.1.8 Beam Energy:**
It is adjusted individually according to plan of each case.

**7.1.9 Dose prescription and fractionation:**

*7.1.9.1* ***Adjuvant Radiotherapy:*** Adjuvant RT in cases with positive margins, incomplete removal, high grade or perineural invasion. (60Gy/30 Fr)

*7.1.9.2* ***Radical Radiotherapy:*** EBRT to Radical dose up to 70 Gy if surgery is not feasible or locally advanced disease.

*7.1.9.3* ***Palliative Radiotherapy:*** Palliative radiotherapy to the primary site can also be useful when metastases are present at diagnosis, or in locally recurrent disease to ameliorate fungating tumour or reduce bleeding GTV, CTV and PTV are defined as for curative treatment either on a planning CT scan or lateral simulator radiograph. To minimise normal tissue toxicity (particularly mucositis), smaller margins can be used than for curative treatment e.g. 5 mm from GTV to CTV 20Gy in 5 fractions or 30 Gy in 10 fractions.

**7.1.10** ***Dose limitation to OAR:*** Hotspots in the mandible of 107 % should be avoided to reduce the risk of osteoradionecrosis. Excessive dose in the temporomandibular joint (TMJ) should also be avoided to reduce the risk of long-term TMJ dysfunction and trismus. The cochlear dose should be kept below 50 Gy if possible to reduce the risk of long-term sensorineural hearing damage.

**7.1.11** ***Verification:*** Weekly review for all patients in the OPD throughout treatment course used protocol is for the treatment isocentre on lateral and anterior DRRs from the CT simulation to be compared with porta; images from the treatment machine taken on days 1–3 and weekly thereafter. An off-line correction is made relative to the isocentre position if the mean error in any one plane is 3 mm.

## 7.2 Brachytherapy:

**7.2.1 Introduction:** brachytherapyis considered good alternative to postoperative radiation in salivary gland malignancies have been proven effective.

**7.2.2 Methods:** Brachytherapy (radioactive seeds or sources are placed in or near the tumor itself, giving a high radiation dose to the tumor while reducing the radiation exposure in the surrounding healthy tissues). Iodine-125 seeds have been found to be an

effective treatment for incompletely resected or unfavorable histological salivary gland malignancies of the hard and soft palate.

Not practised in referral center

## 7.3 Sequleae of treatment

### 7.3.1 Acute: (Table C.1.k)

| Likely (more than 10%) | Less Likely (3- 9%) | Rare but serious(less than 2 %) |
|---|---|---|
| Redness and skin pigmentation in radiated area. Loss of hairs in treated zones. | Confluent to grade III mucositis. Secondary infection on top of mucositis | Grade IV mucositis, Skin Necrosis |
| Genralised fatigue, nausea. | Cataract if lens receive more than tolerance dose | Prolong dryness and persistent xerostomia |
| Dry Skin peeling, mucositis patchy to grade II, dysphagia with pain. Change of taste and loss of taste. | | |
| Xerostomia | | |

### 7.3.2 Late:

**7.4.2.1** Some skin pigmentation which is more evident in fair skin individuals.

**7.4.2.2** Dryness of mouth and chronic xerostomia this depends on the dose received by parotids. In cases where both parotids receive a good amount of dose the possibility of xerostomia in long run is emphasized to patients.

**7.4.2.3** Apical lung fibrosis evident on chest x ray can cause some symptoms this is due to the area of lung in lower neck portals.

All side effects during the course of EBRT are expected to resolve gradually by 6 weeks post radiation.

# 8 Principles of Hormonal Treatment:

Not Applicable

# 9 Principles of Chemotherapy:

**9.1 Concurrent chemotherapy as mentioned in radiotherapy treatment.**

**9.2 Adjuvant Chemotherapy:**

Salivary gland neoplasms respond poorly to chemotherapy, and adjuvant chemotherapy is currently indicated only for palliation if the patient is symptomatic. Doxorubicin- and platinum-based agents are most commonly used with the platinum-based agents that induce apoptosis versus the doxorubicin-based drugs that promote cell arrest. Platinum-based agents, in combination with mitoxantrone or vinorelbine, are also effective in controlling recurrent salivary gland malignancy.

## 10 Management of Recurrence/Relapse

It is decided in MDT meeting according to initial treatment, symptoms and patient performance status.

## 11 Follow Up:

### 11.1 Follow Up Investigations:

*11.1.1* DL scopy and endoscopy once every 3 to 6 months in first 2 years.
*11.1.2* CT scan or MRI at least once and twice in a year with residual.
*11.1.3* Routine labs and assessment of Thyroid function in post RT cases.
*11.1.4* Nutritional and swallowing assessment and also recovery from RT side effects.

### 11.2 Follow Up Visits Schedule

*11.2.1* 1 YEAR-Every month
*11.2.2* 2 YEAR-Every 2 months
*11.2.3* 3 to 5 YEARS- Every 4 to 6 months

## 12 Ongoing Randomized Studies:

No studies about salivary gland tumours at current time.

## 13 References:


1. Practical radiotherapy planning (Ann barrett, Dobbs) IV edition.
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3. Yuan WH, Hsu HC, Chou YH, Hsueh HC, Tseng TK, Tiu CM. Gray-scale and color Doppler ultrasonographic features of pleomorphic adenoma and Warthin's tumor in major salivary glands. *Clin Imaging*. 2009 Sep-Oct. 33(5):348-53
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# C.2- THYROID CANCER: CLINICAL MANAGEMENT GUIDELINES

## 1. Epidemiology:

Thyroid cancer is one of the common endocrine malignancies. The annual incidence of thyroid cancer varies considerably by geographic area, age and sex. As per figures from Globocan 2012 data base worldwide age standardized incidence rate (ASIR) was 1.9 for thyroid cancers.

Among the GCC nations highest ASIR was seen in Saudi Arabia (ASIR 1.7 for males & ASIR 7.5 for females. The lowest ASIR was seen in UAE males (0.9) and Yemeni females (3.1) respectively.

According to the data from Kuwait Cancer registry (2012) it is the third most common malignancy in Kuwaiti females. Age standardised incidence rate for Kuwaiti patients was 6.3/100000 population while that for Non Kuwaiti was 3.9/100000 population.

The current thyroid cancer guidelines were prepared by a dedicated multidisciplinary task force committee. A review of the literature was done through a Medline, PubMed searches as well as review of the standard guidelines developed by NCCN, ATA, and ETA & ESMO.

## 2. Clinical Presentation:

Presentation is variable either:

2.1 Low anterior neck swelling without any symptoms or pressure symptoms due to enlarged thyroid or neck nodes.

2.2 Dysphagia, breathing difficulty, hoarseness whenever present signify advanced local disease.

2.3 Pathology like anaplastic type can have rapid course and aggressive local or distant behaviour while an indolent course can be a feature with other pathologies.

2.4 Rarely presentation can be in form of bone pain or sudden fracture.

## 3. Diagnosis & Work up:

3.1 History & Physical examination

3.2 CBC, Biochemistry profile

3.3 Review of pre & post-op imaging studies

3.4 Review of histopathology at referral center

## 4. Staging:

As per the 7$^{th}$ edition TNM (tumor, node, and metastasis) staging, proposed by The American Joint Committee on Cancer (AJCC), 2010 and the International Union against Cancer Committee (UICC).

## 5. Prognostic Factors:

Cancer staging is an essential prognostic and integral part of cancer management. 17 different staging systems were described for patients with thyroid carcinoma. The most current standard is the 7th edition TNM (tumor, node, and metastasis) staging, proposed by The American Joint Committee on Cancer (AJCC) and the International Union against Cancer Committee (UICC). Other important staging systems include the AGES (Age, Grade, Extent, Size), and the MACIS (Metastasis, Age, Completeness of resection, Invasion, Size), both proposed by the Mayo Clinic, and both stratify patients into four risk groups, and the AMES (Age, Metastasis, Extension, Size) proposed by the Lahey clinic.

**5.1.1** Age of patient
**5.1.2** Grade of tumor
**5.1.3** Size of tumor and extent
**5.1.4** Presence of metastasis
**5.1.5** Completeness of resection

## 6. Treatment:

➢ **DIFFERENTIATED THYROID CANCER:**

Initial management of differentiated thyroid cancer consists of thyroidectomy and often radioactive iodine therapy to ablate remnant remaining tissue and perhaps metastatic cancer. These are generally followed by long term therapy with thyroxine with the aim of reducing circulating levels of thyrotropin (thyroid stimulating hormone, TSH) below normal. We categorise our patients according to risk of recurrence to 2 risk groups

**Low risk**

- No local or distant metastasis.
- All local macroscopic tumors is resected.
- No gross regional nodal involvement by tumor (note: microscopic nodal involvement at level VI is still considered low risk).
- Absence of pathology like tall cell, insular, angio-invasive types, columnar and absence of vascular invasion.
- No evidence of any radioactive iodine activity outside thyroid bed on post treatment ablation whole body iodine scan.

**High risk**

- Microscopic invasion of tumor into perithyroidal soft tissue. (pT3, pT4a & pT4b).
- Tumor with aggressive histology or vascular invasion.
- Presence of peri nodal metastasis.
- Evidence of radioactive iodine activity outside thyroid bed on post treatment ablation WBS.
- Incomplete tumor resection ie, gross residual disease post thyroidectomy.
- Distant metastasis.

- Thyroglobulin levels which are high and not correlated with the post treatment scan.

➢ **MEDULLARY THYROID CANCER (MTC):**

This type accounts for 5 -10% of thyroid malignancies. The cells of origin are Para follicular C cells. They are ectodermal in origin. Calcitonin is actively secreted by these neoplasms .They are non-iodine avid, Few of cases they are part of MEN IIA & MEN IIB syndromes. These syndromes in such cases are associated with a mutation of RET proto oncogene.

➢ **ANAPLASTIC THYROID CANCER (ATC):**

These tumours are less frequent and are lethal in spite of aggressive treatment. Local disease progression cause distressing symptoms. In spite of combined modalities of treatment, the 5 year survival rate is 5 to 10 % as per various datas. All anaplastic carcinomas are Stage IV.

## 6.1 SURGERY:

**6.1.1** Total thyroidectomy with central neck dissection or sampling is indicated in tumors of more than 1 cm, multicentric disease, gross nodes, extra thyroidal spread, history of neck irradiation, family history or radiation exposure. Lateral neck dissection is indicated if there's evidence of lateral nodal involvement.

**6.1.2** Lobectomy or less than thyroidectomy is treatment option for favorable T1 & small T2 diffrentiated tumors in patients younger than 45 years old.

**6.1.3** Completion thyroidectomy is justified after lobectomy in patients with tumor more than 4 cm in size, extra capsular, extra thyroidal spread & detection of aggressive pathology in post surgery pathology.

**6.1.4** Medullary thyroid cancers are managed by total thyroidectomy and neck dissection. High nodal positivity and perinodal spread is common so entire ipsilateral or contralateral neck should be addressed in event of gross nodes. The decision rest as per individual case and clinical presentation.

**6.1.5** Total thyroidectomy and or maximal surgical debulking is indicated for anaplastic thyroid tumors. Often the surgery is difficult in big tumors .

## 6.2 Post operative Radioactive iodine whole body scan:

Since most of the thyroidectomies in Kuwait are done in peripheral hospitals with no central review or auditing from referral center, pre-therapy scans &/or measurement of thyroid bed uptake is useful when the extent of the thyroid remnant cannot be accurately ascertained from the surgical report or neck ultrasonography, or when the results would alter either the decision to treat or the activity of RAI that is administered.

**6.2.1** Patients are to be referred to us 2 weeks after surgery or as early as clinical recovery for further treatment

**6.2.2** Patients usually are not on Levothyroxin and they need 4-6 weeks post surgery for TSH to rise enough for scan.

**6.2.3** Patients who cannot tolerate prolonged hypothyroidism, could be priscribed short acting thyroid hormone preparation Liothyronine (Tetroxin) which should be stopped 2 weeks before I131 scan or ablation.

**6.2.4** Patients who can not sustain hypothyroid stste are started with eltroxine hormone alternative for such patients is use of recombinant TSH (Thyrogen). This is administerd via IM injections 0.9 mg in the previous 2 days before I131 scan or ablation. This will elevate serumTSH levels which in turn will help in achieving desired therapeutic or diagnostic goal.

## 6.3 RADIOACTIVE IODINE TREATMENT

### 6.3.1 GROUP 1: No Ablation Indicated

**6.3.1.1** All patients younger than 45 years, with unifocal or multifocal cancers less than 1 cm without other high risk features.

### 6.3.2 GROUP 2: Ablation with 30 mci RAI.

**6.3.2.1** All patients older than 45 years with uptake in neck in post-operative iodine scan.

**6.3.2.2** Patients with tumor size from 1-4 cm with disease confined to thyroid (T1-2) and absence of aggressive pathology or vascular invasion.

**6.3.2.3** Nodal metastasis may be present but with no perinodal spread.

### 6.3.3 GROUP 3: Ablation with 100 mci RAI

**6.3.3.1** Tumor size more than 4 cm, extra thyroidal invasion or skeletal muscle invasion (T3-4)

**6.3.3.2** Adverse pathologies and vascular invasion.

**6.3.3.3** Macroscopic unresectable residual.

**6.3.3.4** Peri nodal spread.

### 6.3.4 GROUP 4 – Therapeutic dose or doses in range of 150-200 mci.

**6.3.4.1** All patients with metastatic disease.

**6.3.4.2** Gross cervical nodal involvement requiring neck dissection of lateral compartment.

**6.3.4.3** The suggested dose for pulmonary metastasis is 150 mci and for skeletal osseous metastasis the dose up to 200 mci.

# 7. Radiotherapy Protocol:

***External Beam Radiotherapy:***

External beam radiotherapy is not used in most of differentiated thyroid cancer patients. The indications for this modality are:

- Recurrent disease in neck.

- Residual tumor in post-operative setting which cannot be operated. (R2 resection).
- Iodine Non avid differentiated tumors, where there is a gross residual disease.
- Evidence of muscle or nearby structures invasion.
- Poorly differentiated, tall cell, insular variant.
- EBRT is highly individual case selective for pathologies like medullary and anaplastic thyroid cancers. Often anaplastic thyroid cancers are treated by palliative EBRT.

## 7.1 External Beam: Planning Technique

### 7.1.1 Patient preparation:

None

### 7.1.2 Immobilisation:

Patient is treated in supine position and base plate and proper head rest is used to keep neck in slight extended position .Orfit cast is made with 5 fixation points. Hands are tucked to side of trunk with or without traction.

### 7.1.3 Set up marking and reference point:

Fidutial markers are placed on the orfit cast and placed orthogonally. They are matched with aligned lasers so that all lie in one plane.

### 7.1.4 Image acquisition:

CT scan is done on a four-detector spiral CT scanner using a slice thickness of 3 mm. to aid volume definition and to create high quality DRRs to aid verification.Slices are acquired from the vertex of skull to the inferior aspect of D10 vertebra.The aim is to cover the lungs completely as RT fields extends to mediastinum. IV contrast may be given upon request of the referring radiation oncologist to help define extent of disease but is not essential if a contrast-enhanced diagnostic CT scan is available.

### 7.1.5 Target definition

#### *7.1.5.1 GTV:*

To define the GTV accurately it is important to have all diagnostic imaging available including clinical information and post operative reports. In the case of adjuvant radiotherapy, a discussion with the surgeon and pathologist is essential to define sites at highest risk of relapse. Clips placed at surgery at sites of incomplete excision are valuable, but must not be confused with clips used to ligate vessels. The residual tumor in vicinity of trachea or recurrent laryngeal nerve needs to be contoured as these are potential areas for dose

escalation. Similarly this is applicable for heavy nodal disease with perinodal extensionand positive margins.
In palliative cases for anaplastic variant of thyroid carcinoma the entire disease volume is marked as GTV.

Anatomical knowledge, contrast CT scans and radiologist input can help differentiate tumour from normal structures.

#### *7.1.5.2 CTV:*

GTV is isotropic ally expanded by one centimetre to get CTV and than CTV is edited for normal barriers like bone air spaces, organs.
Nodal CTV comprises of level VI, II, III, IV, V & VII, volume of nodal radiation varies from case to case.
Extension of the CTV margins in superior neck region depends on the extent of surgery, nodal positivity.

#### *7.1.5.3 PTV:*

CTV to PTV margins of 5 mm all around are added to account for tumour motion and setup errors. Overlapping areas beyond skin are cropped.

#### *7.1.5.4 OAR:*

- The spinal cord is contoured on axial slices throughout the PTV and an isotropic 5 mm margin applied to produce a PRV.
- The parotids are contoured in representative axial cuts.
- Automatic contouring tools can be used to contour the lungs.

### 7.1.6 Technique: 3 DCRT:

Modern conformal radiotherapy aims for placement of 5 or 7 beams at different angles to cover the PTV. The dose to parotids and spinal cord can be minimised with this approach. There are no fixed parameters for beam direction and angles in conformal RT. Segmental field, field in field and beam modifying devices all can be used depending on individual case.
Overall aim is to cover PTV adequately respecting the tolerance of OAR.

### 7.1.7 Beam Arrangement:

As per the individual case, patient's anatomy and planning physicist.

### 7.1.8 Beam Energies

As per the individual case, patient anatomy and planning physicst.

### 7.1.9 Dose Prescription -

#### *7.1.9.1 Radical adjuvant ( post op)*

50 Gy in 25daily fractions given in 5 weeks.

#### *7.1.9.2 High risk, recurrent positive margins*

60 Gy in 30 daily fractions given in 6 weeks & boost of 6 Gy in 3 Fr in selective high risk cases.

**7.1.9.3 Palliative Radiotherapy –**

Various fractionation protocol as per clinical scenario.

### 7.2 Brachytherapy:

Not Applicable

### 7.3 Sequlae of treatment:

- A mild speech discomfort, dysphagia or cough is common but rarely needs treatment.
- Advice on skin care is given.
- When the oesophagus is within the treated volume, pain on swallowing and dysphagia usually begin in the third week of treatment. Systemic analgesia, topical local anaesthetic agents and advice on soft and high calorie diets from a dietician should be available.

## 8. Principle of Hormonal treatment:

**Levothyroxine Treatment:**

**8.1 Low Risk**

Maintenance of the TSH at or slightly below the lower limit of normal (0.1–0.5mU/L) is appropriate. Similar recommendations apply to low-risk patients who have not undergone remnant ablation, i.e., serum TSH 0.1–0.5mU/L.

**8.2 High-risk and intermediate-risk thyroid cancer**

*TSH suppression* to below 0.1mU/L is recommended.

8.3 **Eltroxine replacement therapy** and not TSH suppression is justified in medullary and anaplastic thyroid carcinomas.

## 9. Principle of Chemotherapy:

Not applicable

## 10. Management of Recurence:

Treatment of recurrent disease is based on the combination of surgery, rechallenge with radioiodine therapy in differentiated thyroid cancers, EBRT or TKI inhibitors. Each case is an individual case and decision of single modality or combination is decided after concensus of multidisciplinary team.

**10.2** External beam radiotherapy is indicated when complete surgical excision is not possible or when there is no significant radioiodine uptake in the tumor.

**10.3** Radioiodine-avid metastases should be treated with RAI and treatment should be repeated when objective benefit is demonstrated (decrease in the size of the lesions, decreasing Tg), reponse in metastatic disease is variable.

**10.4** Chemotherapy is seldom indicated because of poor response rates.

**10.5** Tyrosine Kinase Inhibitors (TKI), such as Sorafinib, are considered an option therapy for those patient with metastatic non iodine responsive disease.

**10.6** Tyrosine kinase inhibitors like Vandatinib and Cabozatinib are indicated in metastatic medullary thyroid or recurrent medullary thyroid cancers.

## 11. Follow up

11.1 The follow up is usually every 3 months for first 2 years.

11.2 Clinical examination, thyroid hormones assays (TFT) as well as other laboratory parameters including serum calcium and renal functions are done each visit.

11.3 Serum thyroglobulin (TG) and antibodies, as well as vitamin D levels are evaluated every 6-12 months for differentiated types.

11.4 Serum calcitonin levels and CEA levels are assessed in medullary thyroid cancers.

11.5 Neck US is done periodically for high risk cases or for other patients when clinically warranted.

11.6 Whole body iodine scan with recombinant TSH is advised in cases with rising thyroglobulin or other clinical evidence of recurrence/metastatic disease.

11.7 $FDG^{18}$ PET/CT is indicated in case of rising thyroglobulin levels in absence of avid uptake in $I^{131}$ scan.

## 12. Ongoing departmental studies:

None

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# C.3- LUNG CANCER CLINICAL MANAGEMENT GUIDELINES

## 1. EPIDEMIOLOGY:

Lung cancer has been the most common in the world for several decades. There is marked geographic variation with the highest ASR in Eastern and Central Europe (53.5 in men and 33.8 for women per 100,000). It is the most common cause of death in cancer worldwide contributing for nearly 1/5 of them.

In GCC states, lung cancer is the seventh most common cancer. 4,588 lung cancer cases (4.8% from all cancers) were reported from 1998 to 2007. The overall ASR was 7.0 and 2.1 per 100,000 population for males and females respectively.

In Kuwait, it is the sixth most common cancer. In 2012, (the overall ASR was 6.4 cases /100,000 and 6.3 cases /100,000 populations for Kuwaiti and non-Kuwaiti respectively. More than 70% of cases were males.

## 2. CLINICAL PRESENTATION:

**2.1.** Asymptomatic lung cancer patients: Diagnosed with modern imaging techniques performed due to other indications.

**2.2.** Typical symptoms from centrally located lung cancer:

- **2.2.1.** Haemoptysis
- **2.2.2.** Cough
- **2.2.3.** Wheezing
- **2.2.4.** Dyspnoea
- **2.2.5.** Chest pain
- **2.2.6.** Frequent infections due to atelectasis.

**2.3.** Peripheral lesion may be manifested by:

- **2.3.1.** Cough
- **2.3.2.** Pain due to invasion of chest wall
- **2.3.3.** Dyspnoea

**2.4.** Tumours located in the superior sulcus are frequently associated with:

- **2.4.1.** Shoulder pain irradiating to forearm, $4^{th}$, and $5^{th}$ fingers
- **2.4.2.** Involvement of the lower brachial plexus is sometimes present with various degrees of neurological deficit
- **2.4.3.** Horner's syndrome (myosis, ptosis, enophthalmos, and anhydrosis) is due to direct involvement of sympathetic chain.

**2.5.** Mediastinal invasion may cause:

- **2.5.1.** Superior vena cava syndrome
- **2.5.2.** Dysphagia due to oesophageal compression or phrenic nerve palsy.

**2.6.** Tumours or lymph nodes located at the aorto-pulmonary window typically result in hoarseness of voice due to recurrent laryngeal nerve palsy

**2.7.** Pleural involvement frequently results in accumulation of pleural fluid and dyspnoea (more frequent in ALK +)

**2.8.** Pericardial involvement is a relatively infrequent: causing dyspnoea and other symptoms of cardiac tamponade (more frequent in ALK +)

**2.9.** Symptoms from metastatic spread

**2.9.1.** Brain metastases may lead to symptoms of increased intracranial pressure, seizures, or focal neurologic deficits

**2.9.2.** Bone metastases may cause pain and pathological fractures

**2.9.3.** An adrenal mass may occasionally be misdiagnosed as primary adrenal gland malignancy

**2.10.** Paraneoplastic syndromes (frequent)

**2.10.1.** Syndrome of inappropriate antidiuretic hormone (ADH) excretion (SIADH)

**2.10.2.** Cushing syndrome

**2.10.3.** Hypercalcaemia due to production of parathyroid hormone-related protein (PTH-rp),

**2.10.4.** Carcinoid syndrome

**2.10.5.** Neurological syndromes

**2.10.6.** Hypertrophic pulmonary osteoarthropathy

**2.10.7.** Venous thromboembolism

## 3. DIAGNOSTIC WORK UP:

**3.1** Complete history, chief complaints, addiction and other aspects related with cause for disease are noted.

**3.2** Complete general and clinical examination.

**3.3** Complete blood counts and serum biochemistry.

**3.4** Pulmonary function test before considering surgery or radical radiation is a must

**3.5** Sputum cytology in undiagnosed or early cases.

**3.6** CEA and CYFRA-21 as tumor markers

**3.7** Imaging studies c x-ray, CT scan of neck chest and abdomen.

**3.8** CT or MRI brain

**3.9** PET CT Scan

**3.10** Pathological Assessment:

**3.10.1.** Bronchoscopy and biopsy

**3.10.2.** Endo bronchial ultrasound (EBUS) & biopsy as per case

**3.10.3.** Guided core biopsy is preferred in peripheral lesions.

**3.10.4.** Immunohistochemistry to define histological type of lung cancer: SCC, adenocarcinoma, SCLC. etc.

**3.10.5.** Assessment of genetic mutation studies:

**3.10.5.1.** EGFR mutation status (exon 19 deletions, mutations 21 and exon 18)

**3.10.5.2.** KRAS mutation

**3.11** CT guided FNAC indicated where core biopsy is technically difficult or risky.

**3.12** Mediastinoscopy is indicated for operable cases and assessment of contralateral hilar region.

**3.13** Thoracocentesis, pleural & pericardial fluid cytology needs to be addressed in all cases where indicated.

## 4. STAGING:

The American Joint Commission on Cancer (AJCC) 7$^{th}$ edition 2010 is used.

## 5. PROGNOSTIC FACTORS:

**5.1** Stage: most important
**5.2** Adjuvant chemotherapy: improves overall survival in surgical patients by about 5%. Overall 5-year survival increased from 40 to 45% and treatment is likely to be of more benefit in patients with stage II and III disease.
**5.3** Performance status.
**5.4** Weight Loss: Greater than 10%
**5.5** Severe symptoms.
**5.6** Large-cell histology
**5.7** Bone, liver or subcutaneous metastases.
**5.8** Male gender.

## 6. Treatment modality according to stage and resectability of disease, and operability of patient:

### 6.1 NSCLC: Medically fit patients with resectable, non metastatic disease:

6.1.1 **T1, T2 tumours:** Surgery in form of lobectomy or pneumonectomy are the primary treatment options, mediastinal sampling and dissections +/- Adjuvant Chemotherapy
6.1.2 **Adjuvant chemotherapy** in T3-4 and/or N+ and selected T2 lesions (more than 4 cm)
6.1.3 **Radiation:** in R1 resection (for stumb and tumor bed) or N+ cases (inadequately dissected or N2-3)

### 6.2 NSCLC: Medically fit patients with potentially resectable, non metastatic disease

6.2.1 **Neo adjuvant chemotherapy**: 2 - 4 cycles if achieving R0 resection is doubtful or limited N2. Followed by assessment for surgery
6.2.2 **Surgery** (see 6.1.1) if possible.
6.2.3 **Adjuvant chemotherapy** may be considered according to response and tolerance to neoadjuvant chemotherapy and pathological stage.
6.2.4 **Radiotherapy** see section 3.1.3.

### 6.3 NSCLC: Medically fit patients with non resectable, non metastatic disease

6.3.1. **Concurrent chemoradiotherapy**
6.3.2. **Neoadjuvant chemotherapy** 2 to 3 cycles if tumor is large and anticipated radiation toxicity is hight. This should be followed assessment for **surgery**. If not possible for radiation alone or chemoradiation

### 6.4 NSCLC: Medically unfit patients with resectable, non metastatic disease

6.4.1. **Concurrent chemoradiotherapy** if patient can tolerate
6.4.2. **Radiation** alone on palliative basis
6.4.3. **Best supportive care** if patient condition and PS is poor

### 6.5 NSCLC: Medically unfit patients with metastatic disease

**3.5.1** **Palliative radiotherapy** to metastatic sites or primary
**3.5.2** **Palliative chemotherapy**

**3.5.3 Targeted therapy**
**3.5.4 Best Supportive Care.**

### 6.6 SCLC: limited disease

6.6.1 **Concomittent Chemoradiation:** To start as soon as possible with RTH starting with 1st or 2nd cycle of chemotherapy

6.6.2 **Sequential chemotherapy then radiation:** if patient cannot tolerate combined treatment of teqnically radiation expected toxicity is high

6.6.3 **Palliative radiotherapy alone** if patient with poor performance status

6.6.4 **Prophylactic Cranial Irradiation**: if patient achieved at least stable disease in primary site

### 6.7 SCLC: Extensive Disease

6.7.1 **Palliative Chemotheapy**

6.7.2 **Consolidation radiation therapy:** if patient achieved marked regression in extrathoracic disease sites can be considered

6.7.3 **Palliative radiotherapy alone** if patient with poor performance status with localized symptoms related to primary or metastatic disease

## 7. RADIOTHERAPY PROTOCOL:

### 7.1. External Beam Planning technique

#### 7.1.1 Patient preparation

- **The day before simulation**

  No special preparation is required.

- **The day of simulation**

  Patient should eat light meals before simulation.

#### 7.1.2 Immobilization

- Thoracic board
- Supine position - Arms elevation - Hands grasping the (T) handle - Elbows supported laterally
- A knee support provides a more comfortable and therefore reproducible set-up.

#### 7.1.3 Orientation, set-up, marking and reference points

- Patient aligned with 3 laser beams. Set 3 marks on the patient skin.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points
- In case of PET/CT planning, the radiographer is responsible to ensure patient positioning in the same imaging position with the thoracic board in the simulator &PET machine

### 7.1.4 Image acquisition

**CT simulation**

- CT examination is performed on a spiral CT scanner using a slice thickness of 3 mm.
- Slices are acquired from the cricoid cartilage to the superior aspect of the L2 vertebra.
- IV contrast may be given upon request of the referring radiation oncologist
- An isocentre is tattooed in the CT scanner, as are lateral reference points.
- Free-breathing technique is used during simulation

**PET/CT simulation:**

- A co-registered PET scan can be used to aid volume definition.

**X-ray Simulator**

- If AP beams are to be used for palliation, the borders can be defined in the x-ray simulator.
- The beam centre is marked with a reference tattoo and the borders are drawn on the skin.
- Fluoroscopy can be used to view tumour movement if IGRT implemented later on.

### 7.1.5 Target Definition:

#### *7.1.5.1 GTV:*

- Have all diagnostic imaging available including clinical information and bronchoscopy or mediastinoscopy reports.
- In the case of *adjuvant radiotherapy*, discuss with the surgeon and pathologist sites at highest risk of relapse
- Clips placed at surgery at sites of incomplete excision are valuable
- Radiologist and oncologist collaborating when needed
- The parenchymal extent of the GTV is defined with CT images viewed on a standardised lung window
- The spiculated edge of the tumour is included within the GTV
- Tumour can be very difficult to differentiate from adjacent lung collapse or atelectasis and PET/Ct can help
- CT images should be viewed on a mediastinal window setting to define mediastinal extent of disease and any involved lymph nodes
- If chemotherapy is used before radiation, the GTV should include all sites of disease at presentation, e.g. any enlarged nodes that have shrunk to less than 10 mm with treatment.

#### *7.1.5.2 CTV:*

- 8 mm margin from GTV to CTV
- The CTV is edited to take account of natural barriers to tumour spread (e.g. uninvolved bone or great vessels)
- Elective nodal irradiation is not recommended
- If neoadjuvant (induction) chemotherapy received, the pretreatment involved nodal station (not the volume) is included

#### *7.1.5.3 PTV:*

- CTV to PTV margins of 7mm axially and 12 mm longitudinally
- **In Palliative setting:**
  - If CT planning is used, the GTV + 10 mm margin applied to produce a PTV
  - If X-ray simulator is used, 15 mm margin from this virtual GTV to the beam edge will give the same effect.

### 7.1.6 The Radiotherapy Technique:

The above protocol applies only to 3D CRT. If patient to be treated by IMRT, the dedicated IMRT protocol should be applied (outside the context of this Guidleines)

### 7.1.7 Beam Arrangement:

#### *7.1.7.1. Conventional*

- Palliative therapy given by anterior and posterior photon beams with dose prescribed to the midplane.
- MLC shielding may reduce the dose to normal lung tissue.

#### *7.1.7.2. 3D Conformal*

- When curative radiotherapy is used for stage I or II disease a three-field conformal plan is commonly used.
- Many tumours are closer to the chest wall than to the mediastinum and ipsilateral beams will minimise the dose to contralateral normal lung tissue and normally provide a homogeneous dose distribution.
- Beam angles are chosen to reduce lung dose with anterior oblique, posterior oblique and lateral beams often used.
- Wedges compensate for the obliquity of the beams in relation to the chest wall, and MLC shielding is used to conform each beam shape to the PTV.
- In stage IIIA disease a similar three-field conformal plan is often used.
- The beam angles are chosen using the BEV tool while viewing the PTV, spinal cord PRV and oesophagus contour so as to reduce dose to the spinal cord and oesophagus as much as possible and with the aim of minimising lung dose.
- For larger tumours, in particular those crossing the midline in the mediastinum, it is more difficult to cover the medial extent of the tumour with ipsilateral beams.
- Adding a contralateral beam will significantly increase the dose to normal lung.
- Such tumours can be treated in two phases.
  - In phase 1, an arrangement of opposing MLC-shaped photon beams ensures all the mediastinal extent is treated and also reduces lung dose, at the expense of a poorly conformal plan with oesophagus and cord within the treated volume.
  - Phase 2 uses a conformal three or four-beam plan which will give a higher lung dose.

- By varying the number of fractions in each phase it can be possible to deliver adequate dose to the PTV and remain within cord tolerance, lung and oesophageal tolerance.

➢ Primary tumours close to the spinal cord may have a PTV that is very close to, or even overlaps the spinal cord PRV.
➢ Rather than miss some of the PTV throughout a course, it is preferable to use two phases for treatment accepting full dose to the cord for phase 1 with the addition of MLCs to shield the cord from at least two beams in phase 2.
➢ Again, the number of fractions in each phase is varied until the sum of the two plans is within to cord tolerance.

### 7.1.8 Beam energies:

6MV photons are adequate unless the separation at the centre is more than 28 cm, in which case a higher energy (e.g. 10-12 MV) is needed.

### 7.1.9 Dose prescription and fractionation:

#### *7.1.9.1 Adjuvant NSCLC*

➢ 60 Gy in 30 daily fractions given in 6 weeks.

#### *7.1.9.2 Radical NSCLC*

➢ 66 Gy in 33 daily fractions given in 6.5 weeks.

#### *7.1.9.3 Radical SCLC*

➢ 45 Gy in 30 fractions given in 3 weeks (2 fractions per day – 5 days per week) if given concomittent
➢ 66 Gy in 33 daily fractions given in 6.5 weeks if given sequential

#### *7.1.9.4 Palliative*

➢ 20 Gy in 5 fractions given in one week.
➢ 30 Gy in 10 fractions 2 weeks.
➢ 4-6 Gy hemostatic dose for bleeding
➢ 8 Gy single fraction for bone metastasis

#### *7.1.9.5 Prophylactic cranial irradiation*

➢ 24 Gy in 10 daily fractions of 2.4 Gy given in 2 weeks.

### 7.1.10 Dose Limitations to OAR

➢ The spinal cord is contored on axial slices throughout the PTV and an isotropic 5 mm margin applied to produce a PRV to keep max. point dose bellow 45 Gy for spinal cord and bellow 48 Gy for spinal PRV
➢ Heart & brachial plexus are contoured
➢ Automatic contouring tools can be used to contour the lungs
➢ A lung minus PTV structure is constructed by subtraction
➢ Keep the V20 (volume of lung -GTV receiving >20Gy) below 32%
➢ The risk of radiation pneumonitis depends not only on the dose absorbed but also on the use of concomitant chemotherapy, pre-existing lung disease, the lobe being treated and vascular perfusion.
➢ Other targets such as minimising V5 and having a mean lung dose lower than 20 Gy have also been shown to correlate with pneumonitis.

- A V20 of 32 per cent is a useful target but for patients with poor lung function, a lower target may be needed, whereas for those with good lung function a value closer to 40 per cent may be acceptable.
- Beam energies above 10 MV should be avoided because secondary electrons have a greater range in lung tissue so higher energy photon beams have a wider penumbra.
- The oesophagus is contoured throughout the PTV if the tumour is close to or involves the mediastinum
- Concomitant chemotherapy increases the risk of oesophagitis
- There are several parameters of the oesophageal DVH identified that correlate with the risk of grade 3 or 4 acute oesophagitis or the risk of strictures
- Recommended to keep the length of oesophagus within the treated volume to less than 8 cm where possible and certainly to less than 12 cm.
- For some patients it may be appropriate to accept some underdosing of the PTV to achieve this.

### 7.1.11 Plan Verification and Execution/FU

- Plan approval should be done by a senior oncologist in presence of the concerned physicist and a radiotherapist (the unit coordinator)
- Ideally the treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging
- KV/MV portal images are taken for the first 3 days of treatment then weekly at least
- These images to be approved by the treating oncologist before attempting subsequent treatment sessions
- In Case of suspecioun of a major shift, a CBCT or resimulation CT may be done.
- The therapist should pay attention on matching of portal images to both the bony landmarks (to confirm same positioning) and to the soft tisse including the airway and the mass if visible (to detect soft tissue variation early especially in case of postoperative radiation where the pneomenectomy side may change and medistinal shift can be marked)
- Weekly review in OPD for treatment toxicity:
- Patients should be reviewed weekly so that acute side effects are treated proactively.
- For patients receiving chemotherapy CBC weekly with RFT and LFT are indicated.
- Dietary supplements are useful to maintain adequate nutritional needs.
- Patients should be weighed and assessed weekly throughout treatment and should be given prophylactic antiemetic's (5-HT antagonist) if required.
- Many patients experience grade 3 or 4 toxicity and nausea, lethargy and haematological side effects are common.
- A mild increase in dyspnoea or cough is common but rarely needs treatment though intercurrent infections should be excluded.
- Advice on skin care is given.

- When the oesophagus is within the treated volume, pain on swallowing and dysphagia usually begin in the third week of treatment. Systemic analgesia, topical local anaesthetic agents and advice on soft and high calorie diets from a dietician should be available.

### 7.2. Brachytherapy:

***Not Available in current referral center setting***

### 7.3. Sequalae of treatment:

- 7.3.1 **Acute:** esophagitis, skin irritation, fatigue, and nausea/vomiting.
- 7.3.2 **Subacute and late toxicities:** radiation pneumonitis, pericarditis, pericardial effusion, esophageal stricture/fistula, myelitis and second cancers

## 8. Principles of hormonal treatment:

Not Applicable

## 9. Principles of chemotherapy regimens:

### 9.1. Chemotherapy for neoadjuvant and adjuvant NSCLC: most commonly used

- 9.1.1 **Cisplatin** 100 mg/m$^2$ D1; **etopside** 100 mg/m$^2$ D1-3 every 28 days for 4 cycles
- 9.1.2 **Cisplatin** 75 mg/m$^2$ D1; **gemcitabine** 1250 mg/m$^2$ D1, 8 every 21 days for 4 cycles
- 9.1.3 **Cisplatin** 75 mg/m$^2$ D1; **docetaxel** 75 mg/m$^2$ D1 every 21 days for 4 cycles
- 9.1.4 **Cisplatin** 75 mg/m$^2$ D1; **pemetrexed** 500 mg/m$^2$ D1 every 21 days for 4 cycles **for nonsquamous histology**
- 9.1.5 **Carboplatin** AUC 6 D1; **Paclitaxel** 200 mg/m$^2$ D1 every 21 days for 4 cycles in patients **cannot tolerate cisplatin**
- 9.1.6 **Cisplatin/vinorelbine** different dosages

### 9.2. Chemotherapy regimen with concomittent radiation NSCLC:

- 9.2.1. **Paclitaxel** 45 mg/m$^2$ , **Carboplatin** AUC 2 weekly
- 9.2.2. **Cisplatin** 50 mg/m$^2$ D1, 8, 29, 36; **etopside** 50 mg/m$^2$ D1-5, D29-33

### 9.3. Systemic therapy for advanced or metastatic disease NSCLC:

- 9.3.1. Many different **chemotherapy** combinations and single agents regimens exist (e.g. cisplatin, carboplatin, pemetrexed, pacliteaxel, etopside, docetaxel, bevacizumab, gemcitabine, vinorelbine, nap-paclitaxel)
- 9.3.2. **Targeted** therapy regimens e.g. erlotinib, gefitinib, afatinib, bevacizumab, ramucirumab, crizitonib
- 9.3.3. **Maintainance** therapy (continuation or switching)
- 9.3.4. **Immunotherapy** e.g. nivolumab, pembrolizumab

### 9.4. Systemic therapy for Limited Disease SCLC:

- 9.4.1. **Cisplatin** 80 mg/m$^2$ D1**;** **etopside** 100 mg/m$^2$ D1-3 every 21 days for 4-6 cycles

**9.4.2.** **Carboplatin** AUC 5 D1; etopside 100mg/$^{m2}$ D1-3 every 21 days for 4-6 cycles

### 9.5. Systemic therapy for Extensive Disease SCLC:

Different **chemotherapy** combinations and subsequent single agents regimens exist (e.g. cisplatin, etopside, carboplatin, irinotecan, pacliteaxel, docetaxel, gemcitabine, topotecan)

## 10. MANAGEMENT OF RECURRENCE/RELAPSE:

### 10.1 Localized chest recurrence

10.1.1 Surgery if possible
10.1.2 Radioptherapy with radical dose if not received before
10.1.3 Palliative chemotherapy if surgery nor possible and irradiated before
10.1.4 Palliative radiotherapy for bleeding, pain, or compression symptoms (consider previous irradiation dose)
10.1.5 Best Supportive Care

### 10.2 Localized extrathoracic relapse

10.2.1 Surgery i.e. metastatectomy: if good PS and expected good survival
10.2.2 Radiotherapy if surgery not possible
10.2.3 Palliative chemotherapy
10.2.4 Best Supportive Care if poor PS

### 10.3 Wide spread metastasis

10.3.1 Palliative chemotherapy
10.3.2 Palliatve radiotherapy to control pain, bleeding, compression symptoms, bone lesions, brain lesions etc.
10.3.3 Best supportive care if poor PS

## 11. Follow Up:

11.1 **History and physical examination** every 2 months in 1$^{st}$ year, every 3 months 2$^{nd}$ & 3$^{rd}$ years and every 6 months afterwards.
11.2 **CT chest & abdomen** every 6 month in 1$^{st}$ 3 years then annually CT scan abdomen till 5$^{th}$ year.
11.3 **PET scan** for follow up is indicated after 3 months of completion treatment, repeated annually. PET scan for response assessment during the course of chemotherapy in locally advanced cases can be done
11.4 Monitor side effects of chemotherapy & radiotherapy, patients needs dietary supplements, physiotherapy and adequate counseling as per stage of disease

## 12. Ongoing Department Studies:

Not Applicale

## 13. References:


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# C.4- CARCINOMA ESOPHAGEOUS CLINICAL MANAGEMENT GUIDELINES

## 1. EPIDEMIOLOGY:

Oesophageal cancer is the 8th most common cancer in the world, with 456,000 new cases diagnosed in 2012. It is the 6th most common cause of death in cancer worldwide contributing for nearly 1/5 of them.

In GCC states, oesophageal cancer is ranked 20th among the most common cancer. The overall ASR was 1.4 per 100,000 population.

In Kuwait, it is ranked 22nd among most common cancers. In 2012, the overall ASR was 0.8 cases /100,000.

## 2. CLINICAL PRESENTATION:

**2.1** Dysphagia.
**2.2** Chest pain.
**2.3** Vomitting.
**2.4** Haematemesis.
**2.5** Symptoms of invading the nearby structures:
- **2.5.1 F**ood aspiration.
- **2.5.2 I**nvasion to main vessels cause haemoptesis.
- **2.5.3 C**ardiac involvement causing dyspnea and cardiac temponade.

**2.6** Symptoms of metastaic disease:
- **2.6.1** Brain metastasis causing symtoms of increase intracranial pressure as headache, vomiting or neurologic dificits.
- **2.6.2** Bone meatstasis causing bony ache and /or pathological fractures.
- **2.6.3** Liver meatstasis can be asymptomatic or cause jaundice, right hypochondrial pain.

## 3. DIAGNOSTIC WORK UP:

**3.1** Complete history, chief complaints and other aspects related to the cause of the disease.
**3.2** Complete general and Clinical examination.
**3.3** Complete blood counts and serum biochemistry.
**3.4** Endoscopic ultrasound.
**3.1** CT scan of chest neck and abdomen
**3.2** PET scan.
**3.3** Bronchoscopy if indicated as per case
**3.4** Assessment of swallowing status and need for stenting or other modalities are to be explored at first presentation.

**3.5 Pathological assessment**:
- **3.5.1** Endoscopy and biopsy.
- **3.5.2** Immunohistochemistry to define histopathological subtype.
- **3.5.3** HER2 neu expression for adenocarcinomas.

## 4. STAGING:

American joint commission on cancer (AJCC) staging system and TNM staging system, 7th edition 2010 is used.

## 5. PROGNOSTIC FACTORS:

Patients with earlier stage disease have better prognosis than high T and nodal positive disease. Most of patients die within 10 months of diagnosis. The 5 year survival rate ranges from 35% in localized disease to 10% or less in metastatic disease despite all treatment efforts.

## 6. Treatment modality according to stage and resectability of disease, and operability of patient:

### *6.1* Good performance status and resectable disease

***6.1.1*** Stage Tis (in situ) N0 M0-Endoscopic mucosal resection.

***6.1.2*** Stage T1a, N0- Endoscopic mucosal resection or Esophagectomy.Stage T1bNo-Esophagectomy for non-cervical primary while RT for cervical esophagus.

***6.1.3*** For stage T2 or higher (except T4b)&any N (T1 -4(a) N+) options are:

***6.1.4*** Preoperative chemo radiotherapy with dose of 41.4 Gy – 50.4 Gy (EBRT) with concurrent chemotherapy. Two cycles of platinum / 5FU or paclitaxel/carboplatin (low dose weekly) are chemotherapy options.

***6.1.5*** Preoperative chemotherapy for adenocarcinoma of lower esophagus and GE junction –The chemotherapy options are- ECF or cisplatin /5FU.

***6.1.6*** Esophagectomy with postoperative adjuvant chemo radiotherapy for adenocarcinoma with node positive disease.Also included are T2 and higher stage.

***6.1.7*** Definitive chemo radiation for cervical esophagus any tumor within 5 centimeters of Cricopharngeus muscle are managed by EBRT as surgery will be extremely radical. EBRT dose of 60 Gy with cisplatinum and 5fU as concurrent chemotherapy. Further boost is feasible as per need. Persisting local disease salvaged by surgery.

### *6.2* Medically unfit for surgery or unresectable (T4b) disease the treatment options are

***6.2.1*** Definitive concurrent chemo-radiotherapy dose 45 to 50 Gy as per the tolerance.

***6.2.2*** Palliative chemotherapy

***6.2.3*** Palliative radiotherapy or ILRT (if feasible).

***6.2.4*** No treatment or Best Supportive measures for nutrition, surgical bypass for obstruction, stenting.

# 7. RADIOTHERAPY PROTOCOL:

## 7.1. External Beam Planning Technique

### 7.1.1 Patient Preparation:

- The day before simulation
  No special preparation is required.
- The day of simulation
  Patient should be fasting before simulation.
  Oral contrast given just befor simulation.

### 7.1.2 Immobilization:

- Thoracic board.
- Supine position - Arms elevation - Hands grasping the (T) handle - Elbowssupported laterally
- A knee support provides a more comfortable and therefore reproducible set-up.

### 7.1.3 Orientation, set-up, marking and reference points:

- Patient aligned with 3 laser beams. Set 3 marks on the patient skin.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points
- In case of PET/CT planning, the radiographer is responsible to ensure patient positioning in the same imaging position with the thoracic board in the simulator & PET machine

### 7.1.4 Image acquisition

- CT simulation
  - CT examination is performed on a spiral CT scanner using a slice thickness of 3 mm.
  - Slices are acquired from the cricoid cartilage to the superior aspect of the L2 vertebra.
  - IV contrast may be given upon request of the referring radiation oncologist.
  - An isocentre is tattooed in the CT scanner, as are lateral reference points.

- PET/CT simulation:
  - A co-registered PET scan can be used to aid volume definition

- X-ray Simulator
  - If AP beams are to be used for palliation, the borders can be defined in the x-ray simulator.
  - The beam centre is marked with a reference tattoo and the borders are drawn on the skin.

### 7.1.5 Target definition:

#### *7.1.5.1 GTV:*

To define the GTV accurately it is important to have all diagnostic imaging available including clinical information, PET scan, upper GI endoscopy and endoscopic ultrasound reports.

Clips placed at surgery at sites of incomplete excision are valuable, but must not be confused with clips used to ligate vessels. Uncertainty in GTV definition can be reduced by a radiologist and oncologist collaborating to define the GTV.

#### *7.1.5.2 CTV:*

The GTV is grown craniocaudal 1.5 cm and laterally 0.5 cm to produce a CTV. The CTV is edited to take account of natural barriers to tumour spread (e.g. uninvolved bone or great vessels). Elective nodal irradiation is not recommended as most recurrences after radiotherapy are within the primary tumour or as distant metastases rather than as isolated nodal recurrences.

#### *7.1.5.3 PTV:*

CTV to PTV margins of 0.5 cm axially and 2 cm longitudinally are added to account for tumour motion and setup errors. Larger margins may make it difficult to keep within dose constraints for critical normal structures

#### *7.1.5.4 OAR:*

The spinal cord is contoured on axial slices throughout the PTV and an isotropic 5 mm margin applied to produce a PRV.

Heart & brachial plexus are contoured

Automatic contouring tools can be used to contour the lungs.

#### *7.1.5.5 Palliative:*

If CT planning is used, the GTV is defined as above and a 1cm margin applied axial and 2 cm longitudinal to produce a PTV. If beams are defined on the simulator, the diagnostic CT images can still be used to define a virtual GTV which can be superimposed onto the simulator radiograph.

### 7.1.6 The Radiotherapy Technique:

The above protocoal applied only to 3D conformal radiotherapy, if patient to be treated with IMRT, the dedicated IMRT protocoal should be applied.

### 7.1.7 Beam arrangement

#### *7.1.7.1 Conventional*

Palliative therapy given in 5 or 10 fractions can be defined in the simulator as above. Anterior and posterior photon beams are used with dose prescribed to the midplane. MLC shielding may reduce the dose to organs at risk; 6MV photons are adequate unless the separation at the centre is more than 28 cm, in which case a higher energy (e.g. 10 MV) is needed.

#### *7.1.7.2 Conformal*

Beam angles are chosen to reduce lung, heart and cardiac dose with anterior oblique, posterior oblique and lateral beams often used. Wedges compensate for the obliquity of the beams in relation to the chest wall, and MLC shielding is used to conform each beam shape to the PTV.

**7.1.8** Beam energies above 10 MV should be avoided because secondary electrons have a greater range in lung tissue so higher energy photon beams have a wider penumbra.

7.1.9 **Dose prescription and fractionation**

***7.1.9.1 Definitive Radiochemotherapy***

50.4 Gy in 28 daily fractions given in 6 weeks.

***7.1.9.2 Adjuvant Radiotherapy Dose***

50.4 Gy in 28 daily fractions given in 6 weeks.

***7.1.9.3 Preoperative Chemoradiotherapy***

41.4 Gy in 23 daily fractions given in 5 weeks

***7.1.9.4 Palliative***

20 Gy in 5 fractions given in one week.

30 Gy in 10 fractions of 3 Gy given in 2 weeks.

**7.1.10 Dose limitations to OAR**

- For Spinal cord keep max. point dose 45 Gy to spinal cord and 48 Gy to spinal PRV
- Keep V20 for lung below 30%, minimizing V5 and keep mean lung dose below 20 Gy.
- For heart keep mean dose below 25 Gy and V30 not to exceed 46%.

7.1.11 **Verification and on treatment investigations**:

***7.1.11.1 Verification***

Ideally the treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging. Images are taken on days 1–3 and weekly thereafter with a correction made if the mean error in any one plane is >5 mm.

***7.1.11.2 On treatment Investigations***

Weekly review in OPD for treatment toxicity: Patients should be reviewed weekly so that acute side effects are treated proactively.

- For patients receiving chemotherapy CBC weekly with RFT and LFT are indicated.
- Dietary supplements are useful to maintain adequate nutritional needs.
- Patients should be weighed and assessed weekly throughout treatment and should be given prophylactic antiemetic's (5-HT antagonist) if required.
- Many patients experience grade 3 or 4 toxicity and nausea, lethargy and haematological side effects are common.
- Advice on skin care is given.
- Systemic analgesia, topical local anaesthetic agents and advice on soft and high calorie diets from a dietician should be available.

## 7.2 Brachytherapy

Currently not applicable in referral center for oesophageal cancer.

## 7.3 Sequelae of Treatment

7.3.1 Acute toxicity skin irritation ,nausea ,vomitting

7.3.2 Late toxicity radiation pneumonitis, pericarditis, pericardial effusion, myelitis.

## 8. PRINCIPLES OF HORMONAL TREATMENT:

**NOT APPLICABLE**

## 9. PRINCIPLES OF CHEMOTHERAPY REGIMENS

9.1 Chemotherapy preoperative in adenocarcinoma GEJ tumours (ECF)
9.2 Chemothrepy concurrently with radiotherapy preoperatively in resectable cases (taxol, carboplatin).
9.3 Chemotherapy concurrent with radiotherapy as definitive treatment(taxol, carboplatin)
9.4 Chemotherapy concurrent with radiotherapy in post operative cases (cisplatin and FU)
9.5 Palliative chemotherapy.

## 10. MANAGEMENT OF RECURRENT OR RELAPSE

### 10.1 Localized recurrence resectable

10.1.1 Surgery if possible.
10.1.2 Radiotherapy (palliative or radical )if radical dose not received befor.
10.1.3 Palliative chemotherapy.
10.1.4 Best Supportive Care if poor performance status.

### 10.2 Localized unresectable.

10.2.1 palliative Radiotherapy.
10.2.2 palliative chemotherapy.
10.2.3 Best Supportive Care if poor performance status.

### 10.3. Metastatic disease

10.3.1 Palliative Radiotherapy to control pain ,bleeding,compression symptoms, bony lesions or brain metastasis.
10.3.2 Palliative chemotherapy.
10.3.3 Best Supportive Care if poor performance status.

## 11. FOLLOW UP

11.1 For post esophagectomy and post radical RT/CT cases- Patient are seen every 3 months for first 2 years.Complete physical examination, necessary labs, nutritional and swallowing status is assessed. Imaging twice in first 2 years and endoscopy at least once or twice in first 2 years. Later years the examination is every 4 months to 6 months until completion of 5 years.

11.2 Patients who have EMR for T1 tumor are subjected to at least 3 endoscopies for first 2 years. However, such patients are rarely seen.

## 12. ONGOING DEPARTMENTAL STUDIES:

12.1 Retrospective study for the pattern of failure in cancer esophagus and GEJ after chemoradiation.

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# C.5- GASTRIC CANCER CLINICAL MANAGEMENT GUIDELINES

## 1. EPIDEMIOLOGY:

Gastric cancer is the fifth most commonly diagnosed malignancy and the second most common cause of cancer deaths worldwide. 952,000 new cases diagnosed in 2012

GCC Countries it is ranked the 13th among the most common cancers with an estimated ASR in 2012 to be 3.4 per 100,000 population.

According to the data available from Kuwait cancer registry, 40 cases were newly diagnosed in 2012, giving an ASR of 2.6 per 100,000 populations.

## 2. CLINICAL PRESENTATION:

**2.1** Abdominal pain
**2.2** Nausea and vomiting
**2.3** Haematemesis and Melena.
**2.4** Weight loss.
**2.5** Anaemia.
**2.6** If metastatic can complaint of body ache or jaundice according to site of metastasis.

## 3. DIAGNOSTIC WORK-UP:

3.1 History & Physical examination.
3.2 CBC, Biochemistry profile.
3.3 Upper GI endoscopy and biopsy.
3.4 Endoscopic US on individualized basis.
3.5 CT scan Chest, Abdomen & Pelvis.
3.6 PET scan is considered on individualized basis.
3.7 Histopathological review
- 3.7.1 Invasion if present
- 3.7.2 Histological type and grade
- 3.7.3 Depth of tumor invasion
- 3.7.4 Vascular invasion
- 3.7.5 Status of margins
- 3.7.6 Tumor location
- 3.7.7 Lymph nodes number and status
- 3.7.8 HER2 status for metastatic cases

## 4. STAGING:

American joint commission on cancer and TNM staging system7th ed 2010.

## 5. PROGNOSTIC FACTORS:

5.1T stage and nodal involvement.

5.2 weight loss >10% in last 3 months, and general condition of the patient.
5.3 Performance status.
5.4 Poor histology as signt ring poorly differentiated.

## 6. Treatment modality according to stage and resectability of disease, and operability of patient:

### 6.1 Good performance status and resectable disease

6.1.1 EMR or surgery are the primary treatment options for patients with Tis or T1a tumours while surgery is the primary treatment option for T1b, T2 or higher, any N).

6.1.2 Preoperative chemotherapy with ECF or its modifications could be offered as a part of perioperative chemotherapy (MAGIC TRIAL), for locally advanced resectable disease.

### 6.2 Medically fit patients with potentially resectable, but metastatic disease

6.2.1 Palliative therapy.

### 6.3 Medically fit patients with non resectable, non metastatic disease

6.3.1 Concurrent chemoradiotherapy.
6.3.2 If the expected morbidity is high, palliative chemotherapy is offered.

### 6.4 Medically unfit patients with potentially resectable, non metastatic disease

6.4.1 Concurrent chemoradiotherapy.
6.4.2 If the expected morbidity is high, palliative chemotherapy or best supportive care are offered.

### 6.5 Medically unfit patients with metastatic disease

6.5.1 Palliative chemotherapy. If the expected morbidity is high, best supportive care is offered.

### 6.6 SURGERY

Adequate surgical resection to achieve negative resection margin, usually >/= 4cm, and including regional lymphatics; perigastric lymphatics (D1), and those along named vessels of the celiac axis (D2), with a goal of examining at least 15 LNs.

### 6.7 Postoperative management according to surgical outcome:

#### 6.7.1 R0 resection:

**Tis-T1 N0** : observation & follow up.

**T2 N0**: observation & follow up, or chemoradiotherapy for selected high risk patients ( poorly differentiated or high grade tumors, lympho-vascular or peri-neural invasion and patients younger than 50 year old)

**T3-4 or any T N+**: Chemoradiotherapy.

#### 6.7.2 R1 resection:

Chemoradiotherapy.

#### 6.7.3 R2 resection:

Chemoradiotherapy, or palliative chemotherapy.

#### 6.7.4 Locoregional RT:

- Starts 3 weeks after 1st cycle of CT.
- A planned dose of 45 Gy/25Fr/5Ws is delivered using 3D-CRT or IMRT technique.
- A localized dose escalation upto 50.4 Gy is considered for patients with residual disease.

## 7. Radiotherapy Protocol

### 7.1. External Beam Planning technique

#### 7.1.1 Patient preparation

The day before simulation: No special preparation is required.
The day of simulation: Patient should eat light meals before simulation.

#### 7.1.2 Immobilization

Patients undergoing conformal radiotherapy are planned and treated lying supine with arms above the head

#### 7.1.3 Orientation, set-up, marking and reference points

- Patient aligned with 3 laser beams. Set 3 marks on the patient skin.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points
- A barium swallow is given to the patient immediately before image acquisition.

#### 7.1.4 Image acquisition

- CT simulation
  - For adjuvant stomach radiation the volume scanned should extend from the carina to the iliac crests.
  - CT examination will be performed on a four-detector spiral CT scanner using a slice thickness of 3-5 mm.
  - IV contrast may be given upon request of the referring radiation oncologist.
- Simulator
  - For palliation, treatment volumes can be defined in the simulator.
  - The patient lies supine with arms by their sides as lateral or oblique beams are not used.
  - The GTV is defined from endoscopic and CT information.

- Barium can be used to determine the superior extent of the tumour on fluoroscopy.
- No CTV is defined. The PTV is the GTV with a 2 cm supero-inferior margin and a 1 cm axial margin.
- In effect, the beam edges are defined as 2–3 cm proximal and distal to the GTV with a 2 cm lateral margin.

### 7.1.5 Target definition:

7.1.5.1 GTV: Definitions of gross target volume (GTV) in definitive radiation therapy or palliation for local symptoms for gastric cancer is suggested as the tumor as per preoperative imaging and endoscopy data.

7.1.5.1 CTV: tumor or tumor bed, residual stomach, anastomosis and regional lymph nodes.

- The surgeon, oncologist and pathologist should meet to discuss the most likely sites of recurrence if adjuvant radiotherapy is to be considered, in view of its complexity.
- Major nodal chains at risk include the lesser and greater curvature; celiac axis; pancreaticoduodenal, splenic, suprapancreatic, and porta hepatis groups; and, in some, para-aortics to the level of mid-L3.
- The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall.
- Recently, guidelines for defining the clinical target volume for postoperative irradiation fields have been developed based on location and extent of the primary tumor (T stage) and location and extent of known nodal involvement (N stage).
- In general, for patients with node-positive disease, there should be wide coverage of tumor bed, remaining stomach, resection margins, and nodal drainage regions.
- For node-negative disease, if there is a good surgical resection with pathologic evaluation of at least 10 to 15 nodes, and there are wide surgical margins on the primary tumor (at least 5 cm), treatment of the nodal beds is optional.
- Treatment of the remaining stomach should depend on a balance of the likely normal tissue morbidity and the perceived risk of local relapse in the residual stomach.
- However, accurate identification of regional gastric LN stations may be difficult, particularly because postoperative gastric anatomy can vary substantially based on the type of surgical resection performed. Recently Jennifer et al published a report serves as a template for the identification of the gastric LN stations to aid in definition of the elective clinical target volumes (CTV) for 3D-CRT and IMRT planning for gastric cancer.

7.1.5.2 PTV: A 10 mm margin is added isotropically considering organ motion and setup Uncertainties.

7.1.5.3 OAR contouring: The liver, kidneys and heart are contoured as OAR on all slices.

### 7.1.6 Technique

7.1.6.1 The above protocoal applied only to 3D conformal radiotherapy.

7.1.6.2 Complex: IMRT has been used in both oesophageal and adjuvant stomach cancer. IMRT with seven coplanar beams has significant theoretical advantages in sparing normal tissues in stomach cancer but there is little published clinical data to support its use compared with conformal radiotherapy for either tumour type. Not practiced currently at referral center.

### 7.1.7 Beam arrangement:

- Anterior and posterior opposing beams were used to cover the target volume in the Macdonald trial.
- In referral center, we are using more conformal volume-based techniques using five coplanar or four non-coplanar beams.

### 7.1.8 Beam Energeis:

- Using 6–10MV photons, or more as per plan.

### 7.1.9 Dose prescription and fractionation:

#### *7.1.9.1 Adjuvant radiotherapy*

- 45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks with concomitant 5FU and leucovorin.

#### *7.1.9.2 Radical Radiotherapy*

- A dose of 45 Gy in 25 daily fractions is administered for treatment of inoperable disease, followed by a 5.4- to 9-Gy cone-down boost to GTV plus 1.5 cm to a total dose of 50.4–54 Gy with concurrent chemotherapy.

#### *7.1.9.3 Palliative radiotherapy*

- 30 Gy in 10 fractions of 3 Gy given in 2 weeks.
- 20 Gy in 5 fractions of 4 Gy given in 1 week.

### 7.1.10 Dose Limitation to OAR:

- The spinal cord PRV dose should be kept below 40Gy in view of the likely length of cord adjacent to the PTV and the use of concomitant chemotherapy.
- The heart V40 should be less than 30 per cent and the lung V20 less than 25 per cent.
- Pericardium: V30 < 46%, V25 < 10 %.
- The liver V30 should be below 60 per cent and two thirds of one kidney (and ideally both) should be below 20 Gy.
- Small bowel: No more than 250 cc should receive 45 Gy
- Bilateral entire kidney: Mean dose <15-18 Gy.

**As per QUANTEC recommendation:**

***Both kidneys***

- For Bilateral kidneys irradiation:
  Mean dose to one kidneys < 18 Gy, V 28 < 20 %, V23 < 30%,
  V 20< 32%, V 12< 55 %.
- If mean dos to one kidney >18 Gy, V6 to remaining kidney < 30%.

#### 7.1.11 Verification and plan execution:

- The treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.
- Off-line correction protocols are used for standard conformal treatment.
- Images are taken on days 1–3 and weekly thereafter with a correction made if the mean error in any one plane is _5 mm.

## 8. PRINCIPLES OF HORMONAL TREATMENT;

Not Applicable

## 9. Principles of Chemotherapy regimens:

Chemotherapy starts withen 4 weeks of surgery after complete healing.

$1^{st}$, $4^{th}$ & $5^{th}$ cycles: 5FU 425 mg/m² D1-5 Q28 days.

Leucovorin 20 mg/m² D1-5 Q28 days.

$2^{nd}$ cycle: 5FU 400 mg/m² D1-4 of RT

Leucovorin 20 mg/m² D1-4 of RT

$3^{rd}$ cycle: 5FU 400 mg/m² D 31-33 of RT

Lecuovorin 20 mg/m² D 31-33 of RT

## 10. Management Of recurrent or relapse

### 10.1 Localized recurrence resectable

10.1.1 Surger if possible.

10.1.2 Radiotherapy (palliative or radical )if radical dose not received befor.

10.1.3 palliative chemotherapy.

10.1.4 Best Supportive Care if poor performance status.

### 10.2 Localized unresectable.

10.2.1 Palliative Radiotherapy.

10.2.2 Palliative chemotherapy.

10.2.3 Best Supportive Care if poor performance status.

### 10.3. Metastatic disease

10.3.1 Palliative Radiotherapy to control pain ,bleeding, compression symptoms, bony lesions or brain metastasis.

10.3.2 Palliative chemotherapy.

10.3.3 Best Supportive Care if poor performance status.

## 11. Follow up

### 11.1 Weekly review in OPD for treatment toxicity:

- For patients receiving chemotherapy arrange for CBC weekly, RFT and LFT every other week.
- High calorie supplement drinks are useful to maintain adequate oral intake.

- Patients should be weighed and assessed weekly throughout treatment and should be given prophylactic antiemetics (5-HT antagonist) if required.
- Many patients experience grade 3 or 4 toxicity and nausea, lethargy and haematological effects are common.

**8.1** History and physical examination every 2 months 1st year, every 3 months 2nd & 3rd years and every 6 months afterwards.

**8.2** Upper GI endoscopy and CT abdomen every 6 month in 1st 3 years then annually CT scan abdomen till 5th year.

**8.3** CBC and blood chemistry as needed.

8.4 Monitor vitamin B deficiency and provide supplementation for surgically resected Patients.

## 12. Ongoing trials

Retrospective study for pattern of failure after adjuvant chemoradiation in resectable gastric carcinoma.

## 13. References:


1. GLOBOCAN 2012: Estimated cancer incidence, mortality & prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
2. Kuwait Cancer Registry Annual Report 2012.
3. Gunderson, L. L. and Sosin, H. (1982). Adenocarcinoma of the stomach: areas of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int. J. Rad. Oncol. Biol.Phys., 8, 1–11.
4. Cunningham D et.al.. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11-20
5. Macdonald JS, Smalley SR, Benedetti J *et al.* (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 345: 725–30.
6. American joint commission on cancer 7th ed 2010.

# C.6- Pancreatic Carcinoma
# CLINICAL MANAGEMENT GUIDELINES

## 1. EPIDEMIOLOGY:

Pancreatic cancer barely is the twelfth most common cancers worldwide. However, pancreatic cancer tendency to spread silently before diagnosis makes it the fourth deadliest cancer diagnosis, with more than 40,000 people expected to die from the disease in 2015 in USA.

In GCC states, it represents 14th most common cancer with ASr 2.4 per 100,000 population.

According to the data available from Kuwait cancer registry, it represents roughly 3.1% ASR of all new cancer cases annually ranking as 13th most common. However, it is the 7th most common cause of cancer deaths in Kuwait (3.4%).

## 2. CLINICAL PRESENTATION:

2.1 Abdominal pain
2.2 Jaundice.
2.3 Loss of weight.
2.4 Nausea and vomitting

## 3. PRE-TREATMENT EVALUATION:

On suspecting of a pancreatic cancer clinically (eg. characteristic pain, high CA 19.9) or evidence of dilated pancreatic or biliary duct, initial work-up to reach diagnosis should include:

**3.1** Metastatic work up including chest and whole abdomen imaging (CT scan) and, if suspected, bone scan.

**3.2** If a pancreatic mass detected and *no* evidence of distant metastasis, consider surgery directly.

**3.3** If a pancreatic mass detected *with* evidence of distant metastasis, biopsy from the metastatic site (mostly liver FNA).

3.3.1 If *no* pancreatic mass detected and *no* evidence of distant metastasis, EUS (preferred) or ERCP for biopsy and better visualization.

3.3.2 If *no* pancreatic mass detected *with* evidence of distant metastasis, biopsy from the metastatic site (mostly liver FNA).

**3.4** Review of pathology in referral center if the biopsy performed in other hospital.

**3.5** Pre-operative (initial) CA 19.9 is mandatory.

**3.6** Complete history and physical examination to assess performance status.

**3.7** Complete blood count, liver and renal function tests.

**3.8** CEA and CA 19.9 (should be done after stenting if patient has jaundice).

**3.9** If not performed before, Chest CT and CT of liver and abdomen.

**3.10** If not performed before, MRI/MRCP is recommended in order to select patients for preoperative treatment and extent of surgery.

**3.11** Histopathological examination should include :

- Size and grade.
- Status and measurement of margins with proper orientation of directions.

- regional lymph nodes (at least 12 nodes are recommended to be examined).
- Vascular and nerve invasion should be evaluated.
- Wash and cytology of peritoneal fluid during laparotomy or laparoscopy.

**3.12** PET-CT scan is not required for initial staging but can guide radiotherapy if going to be the initial treatment modality (considering the false positivity in pancreatitis)

## 4. Staging

The TNM staging system should be used version 7th (2010).

## 5. Prognostic Factors:

**5.1** T stage and being resectable disease.
**5.2** Performance stage.
**5.3** Non metastatic disease has better survival than metastatic ones.

## 6. Treatment:

Modality according to stage and resectability of disease, and operability of patient.

### 6.1 RESECTABLE DISEASE:

Consider laparoscopic staging and evaluation if the respectability is doubtful.

#### 6.1.1 Surgery:

The standard surgery for head cancers is pancreaticoduodenectomy with lymph nodes dissection (Whipple's procedure) while distal pancreatectomy may be sufficient in distal tumors.
If exploration done and disease found to be unresectable, biopsy should be performed (if nor done before).

#### 6.1.2 ADJUVANT TREATMENT:

Baseline CEA and CA 19.9 is performed after surgery. Should start 12 weeks.
***Adjuvant chemotherapy*** (Gemcitabine alone, Gem/5FU, 5FU/LV, Capecitabine) can be given before or after chemoradiation.
***Chemoradiation*** in T3 or close (or positive) resection margin.

### 6.2 Borderline Resectable

**6.2.1.** Biopsy before treatment is strongly advisable.
**6.2.2.** Treatment on clinical picture, imaging suspicious and high CA 19.9 should not be attempted except in very rare cases and after through workup and multidisciplinary discussion with the patient.
**6.2.3.** Exploration and biopsy may be the only option for equivocal pancreatic masses.
**6.2.4.** Staging laparoscopy may be considered to confirm the term "borderline"
**6.2.5.** Stentning should be done before starting treatment if presented with jaundice.

**6.2.6.** Neoadjuvant therapy can be chemotherapy alone, concomitant chemoradiation or (in selected patients) radiation alone.

**6.2.7.** Starting with chemotherapy then incorporating radiotherapy after 1-2 cycles is documented in some clinical trials.

**6.2.8.** There is no consensus about both the benefit and the modality of neoadjuvant treatment.

**6.2.9** Assessment of Response to Neoadjuvant Treatment:
Repeat the imaging studies performed before treatment e.g. CT or MRI abdomen (MRCP if initially done). Laparoscopic reassessmet also can be performed before taking the final decision of surgical exploration.
Accordingly, either the patient will go to surgical excision or labeled unresectable (see next section for management)

**6.2.10** Adjuvant treatment should be given to those patients received neoadjuvant therapy. Modality depends on what received before.

## 6.3 Locally advanced unresectable (not metastatic)

**6.2.1** Biopsy before treatment is strongly advisable.

**6.2.2** Treatment on clinical picture, imaging suspicious and high CA 19.9 should not be attempted except in very rare cases and after through workup and multidisciplinary discussion with the patient. Exploration and biopsy may be the only option for equivocal pancreatic masses.

**6.2.3** Performance status of 0-1 ECOG is important to consider further management.

**6.2.4** Patients with good performance status are candidates for palliative chemotherapy.

**6.2.5** If maintained good response and no metastasis for a reasonable time, consolidation chemoradiation may be considered. If disease progressed, 2nd line chemotherapy or chemoradiation if still localized.

**6.2.6** Patients with poor performance status, single agent chemotherapy or best supportive care may be considered.

# 7. Radiotherapy Protocol:

## 7.1. External Beam Planning technique

### 7.1.1 Patient Preparation:

**The day before simulation**

- Patient should avoid eating large amount of fruits and vegetables, beans and dairy products

**The day of simulation**

- Patient should eat light meals before simulation. Avoid large amount of fresh fruits and vegetables, beans and dairy products.

### 7.1.2 Immobilization

The patient lies supine with arms above the head in arm rests and with knee and ankle support.

### 7.1.3 Orientation, set-up, marking and reference points

- Patient aligned with 3-plans laser beams.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points
- In case of PET/CT planning, the radiographer is responsible to ensure patient positioning in the same imaging position in the Gama camera

### 7.1.4 Image Acquisition:

#### CT simulation

- CT examination will be performed on a four-detector spiral CT scanner (120 kV, 300 mAs) using a slice thickness of 3 mm. Scan done from the top of the of T11 to cover lymph nodes, to the lower border of L3 and/or kidneys.
- No IV or oral contrasts are used.

#### PET/CT simulation

- Images acquisition is done as per PET/CT department protocol.
- Images are printed and transferred to viewing station on CD if Digital Imaging and Communication in Medicine (DICOM) is not active.

### 7.1.5 Target Definition:

Because of the difficulty in determining tumour margins, radiologist and radiation oncologist should consult closely to delineate from scans the GTV.

***7.1.5.1 GTV should include:*** the primary disease (GTV-P) and any enlarged regional lymph nodes of >1.5 cm (GTV-N)

***7.1.5.2 CTV*** should include visible tumour and surrounding oedema. Margins must be individually designed.

***7.1.5.3 PTV*** margins are anisotropic to take account of organ movement with respiration or gut motion, as well as set-up variations with:

- 5–10 mm in the AP direction
- 2–4 mm in the transverse plane
- 15–30 mm cranio-caudally

LN stations and margins is adopted from the RTOG guidelines that summarized in Appendix.

7.1.5.4 OAR: refer to gastric cancer.

### *7.1.6* The Technique:

The above protocoal applied only to 3D conformal radiotherapy, if patient to be treated with IMRT, the dedicated IMRT protocoal should be applied.

### 7.1.7 Beam Arrangement

#### *7.1.7.1 Conventional*

Palliative therapy given in 5 or 10 fractions can be defined in the simulator as above. Anterior and posterior photon beams are used with dose prescribed to the midplane. MLC shielding may reduce the dose to organs at risk; 6MV photons are adequate unless the separation at the centre is more than 28 cm, in which case a higher energy (e.g. 10 MV) is needed.

#### 7.1.7.2 *Conformal*

Beam angles are chosen to reduce lung, heart and cardiac dose with anterior oblique, posterior oblique and lateral beams often used. Wedges compensate for the obliquity of the beams in relation to the chest wall, and MLC shielding is used to conform each beam shape to the PTV.

**7.1.8 Beam energies:** Using 6–10MV photons, CT forward planning with volumes shaped with MLC may be used to minimise dose to kidneys, liver, spinal cord and small bowel. Energies **above 10 MV should be avoided because secondary electrons have a** greater range in lung tissue so higher energy photon beams have a wider penumbra.

7.1.9 Dose prescription and fractionation

7.1.9.1 Adjuvant: 45-50.4 Gy in 25-28 fractions of 1.8 Gy in 5–5½ weeks.

7.1.9.2 Radical (in combination with chemotherapy with gemcitabine or 5FU)

45–50.4 Gy in 25–28 fractions of 1.8 Gy given in 5–5½ weeks.

Boost can b eused for residual or unresectable disease.

***Treatment Schedule*:**

Treatment will be delivered once daily, 5 fractions per week. All targets will be treated simultaneously. Breaks in treatment should be minimized.

#### 7.1.9.3 For palliation

30 Gy in 10 daily fractions of 3 Gy given in 2 weeks.

This dose may be used to palliate pain or in association with more intensive chemotherapy.

#### 7.1.10 Organs at risk (OAR)

OAR include the spinal cord, kidneys, liver and small bowel. Dose-limiting small bowel tolerance is reflected in the recommended dose-fractionation. These OAR should be outlined on all slices for DVH assessment. A PRV may be added, but in the transverse plane compromise may be needed to maintain these dose limits to OAR.

*Small bowel:*

- No more than 250 cc should receive 45 Gy

*Both kidneys:*

- TD5/5 for the whole kidney is 23 Gy.
- Dose to two-thirds of one kidney (and ideally both) should be below 20 Gy.

*Liver:*

- If the whole liver is irradiated, dose should be < 30 Gy to avoid radiation hepatitis.
- V30 should be below 60%

*Spinal cord:*

- Dose to any part of the cord should be less than 46 Gy.

- If more than 15 cm length of cord is treated, the dose to any part of the cord should be less than 44 Gy.
- A small part (< 1 cm3) may receive up to 50 Gy
- For palliative or simple low dose treatments, AP/PA beams may give a satisfactory dose distribution, or a plan with an anterior and two lateral wedged beams may be used.

### *7.1.11 Verification and weekly review in OPD for treatment toxicity*

- The treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.
- Off-line correction protocols are used for standard conformal treatment.
- Images are taken on days 1–3 and weekly thereafter with a correction made if the mean error in any one plane is _5 mm.
- For patients receiving chemotherapy arrange for CBC weekly, RFT and LFT every other week.
- High calorie supplement drinks are useful to maintain adequate oral intake.
- Patients should be weighed and assessed weekly throughout treatment and should be given prophylactic antiemetics (5-HT antagonist) if required.
- Many patients experience grade 3 or 4 toxicity and nausea, lethargy and haematological effects are common
- On treatment investigations Weekly review in OPD for treatment toxicity: Patients should be reviewed weekly so that acute side effects are treated proactively.

## 7.2 Brachytherapy:

**Not Applicable**

## 7.3 Sequelae of Treatment

To be included in pre-treatment discussion with patient and consent form.

**7.3.1** Acute toxicity skin irritation ,nausea ,vomiting

**7.3.2** Late toxicity radiation myelitis, radiation nephritis, intestinal structure.

***Radiation Therapy Expected Toxicity: (Table C.6.a)***

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Redness and skin irritation in the treatment area<br>- Tiredness<br>- Nausea and/or vomiting<br>- Gastritis<br>- Diarrhea and abdominal colic | - Sores and bleeding from the bowel (these side effects may occur well after treatment and be serious enough to require surgery)<br>- Long-term dryness of the skin<br>- Radiation hepatitis<br>- Nephropathy | - Narrowing or blockage of the bowel (these side effects may occur well after treatment and be serious enough to require surgery)<br>- Development of an abnormal path or connection between organs (fistulae)<br>- Spinal cord injury and myelopathy |

***Gemcitabine/5FU Chemotherapy Expected Toxicity: (Table C.6.b)***

| *Likely (more than 10%)* | *Less Likely (3-9%)* | *Rare, but serious (less than 2%)* |
|---|---|---|
| - Diarrhea with cramping<br>- Nausea and vomiting<br>- Loss of appetite<br>- Mouth sores and sore throat<br>- Low white blood cell count, which may increase the risk of infection<br>- Low red blood cell count, which may result in anemia, tiredness, and/or shortness of breath<br>- Low platelet count, which may result in increased bruising and bleeding | - Darkening and thinning of the skin<br>- Darkening, dryness, and marking of the nails<br>- Fever<br>- Puffiness of the hands and feet<br>- Redness, tenderness, peeling, and/or tingling of the palms and soles of the feet | - Confusion<br>- Dry cough and shortness of breath<br>- Vomiting blood from the digestive tract<br>- Serious infection, which may be life threatening<br>- Allergic reactions, which can involve flushing, difficulty breathing, and low blood pressure and which can be life threatening<br>- Change in heart rhythm<br>- Damage to the heart or spasm of the heart's blood vessels that can cause chest pain<br>- Heart attack<br>- Inflammation of the liver, which may result in yellowing of the skin and eyes, tiredness, and/or pain on the upper right of the stomach area |

## 8. HORMONAL TREATMENT

Not Applicable

## 9. Principles Of chemotherapy regimens

9.1 Definitive treatment with radiotherapy
9.2 Preoperative treatment
9.3 Adjvunt therapy.

## 10. Management Of recurrent or relapse

10.1 Palliative **chemoradiation** if no radiotherapy given before and pain or bleeding are intractable.
10.2 Palliative **chemotherapy** in cases of distant metastasis or local recurrence previously received radiation.
10.3 Stenting if jaundice developed.
10.4 Best supportive care is an option in patients with poor performance status

## 11. FOLLOW UP

11.1 History and clinical examination every 3 months for the first 2 years then 6 monthly for next 3 years, then annually.
11.2 Tumor markers every visit CEA and CA 19.9
11.3 Abdomenal CT annually
11.4 Bone scan, PET/CT, CT chest requested only if needed on clinical suspicion.

## 12. ONGOING DEPARTMENTAL STUDIES:

Not Applicable

## 13. References:


1. GLOBOCAN 2012: Estimated cancer incidence, mortality & prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
2. Kuwait Cancer Registry Annual Report 2012.
3. NCCN guidelines ver 2.2015
4. American joint commission on cancer 7th ed 2010.

# C.7- GALL BLADDER AND BILIARY TREE CANCER CLINICAL MANAGEMENT GUIDELINES

## 1. EPIDEMIOLOGY:

The peak age for cholangiocarcinoma is the seventh decade, with a slightly higher incidence in men. Given the poor prognosis of cholangiocarcinoma, mortality and incidence rates are similar. Cholangiocarcinoma incidence rates vary markedly worldwide, presumably reflecting differences in local risk factors and genetics. The highest rates are in northeast Thailand (96 per 100,000 men) and are about 100 times greater than in the West. In UK from 1968 to 2001, age-standardized mortality rates (ASMR per 100,000 population) for IHBT increased from 0.10 to 1.49 in males (M) and from 0.05 to 1.24 in females (F).
In GCC states, it ranks as 18$^{th}$ most common cancer with ASR 1.7 per 100,000 population.
In Kuwait, according to 2012 registry, there was 17 cases diagnosed. The ASR is 1.1 per 100,000 populations (ranked 21$^{st}$ most common cancer).

## 2. CLINICAL PRESENTATON

**2.1** Localised disease often only produce non-specific symptoms (e.g.: jaundice, anorexia, weight loss, abdominal pain, nausea, emesis).
**2.2** May be presented with manifestations of metastasis to liver, bone, lung or brain.

## 3. DIAGNOSIS WORKUP:

**3.1.** History, clinical examination.
**3.2.** Imaging studies: Endoechosonography, abdominal ultrasound, three-phase CT scan, MRCP.
**3.3.** Invasive procedures (PTC or ERCP).

## 4. STAGING:

The 7$^{th}$ edition, 2010 of the American Joint Committee on Cancer's (AJCC) *AJCC Cancer Staging Manual* will be used.

## 5. PROGNOSTIC FACTORS:

**5.1** Stage of disease
**5.2** Initial bilirubin level
**5.3** Operability and surgical intervention

## 6. Treatment:

Treatment modality according to stage and resectability of disease, and operability of patient.

### 6.1. Adenocarcinoma of gallbladder:

#### 6.1.1 Localized and Potentially Resectable Disease

- T1 a/b with R0 resection is for Observation and follow up
- >T1 and /or N+ve (resectable) with R0 resection: Adjuvant therapy (chemoradiotherapy / chemotherapy).

6.1.2. **Unresectable or Metastatic Disease:**

- In patients with adequate biliary drainage, acceptable liver and kidney function, and a reasonable performance status (ECOG ≤ 2), the administration of eight twenty-one day cycles of cisplatin 25 mg/m2 IV and gemcitabine 1,000 mg/m2 IV on days 1 and 8 may prolong progression-free survival from 6.5 months to 8.4 months (HR 0.72, CI95% 0.57-0.90; p=0.003) and overall survival from 8.3 months to 11.7 months (HR 0.70, CI95% 0.54-0.89; p=0.002) when compared to gemcitabine alone.
- Offer palliative maneuvers to maintain and/or improve quality of life. Once resection has been deemed impossible, relieve biliary obstruction (if possible) by stent placement via either ERCP or PTC. In certain circumstances, radiotherapy or palliative surgery may be considered.

### 6.2. Intrahepatic, extrahepatic cholangiocarcinoma:

#### 6.2.1: Resectable:

- **R0:** observation, chemoradiotherapy, chemotherapy or clinical trial.
- **R1,2:** reresection, ablation, chemoradiotherapy, chemotherapy.

#### 6.2.2 Unresectable:

- Billiary drainage if indicated, chemotherapy, chemoradiotherapy, supportive care, clinical trial.

#### 6.2.3 Metastatic:

- Billiary drainage if indicated, chemotherapy, supportive care, clinical trial.

## 7. RADIOTHERAPY PROTOCOL:

### 7.1. *External Beam Planning technique*

#### 7.1.1 Patient Preparation:

**The day before simulation**

- Patient should avoid eating large amount of fruits and vegetables, beans and dairy products

**The day of simulation**

- Patient should eat light meals before simulation. Avoid large amount of fresh fruits and vegetables, beans and dairy products.

#### 7.1.2 Immobilization

The patient lies supine with arms above the head in arm rests and with knee and ankle support.

#### 7.1.3 Orientation, set-up, marking and reference points

- Patient aligned with 3-plans laser beams.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points
- In case of PET/CT planning, the radiographer is responsible to ensure patient positioning in the same imaging position in the Gama camera

### 7.1.4 Image Acquisition:

**CT simulation**

- CT examination will be performed on a four-detector spiral CT scanner (120 kV, 300 mAs) using a slice thickness of 3 mm. Scan done from the top of the of T11 to cover lymph nodes, to the lower border of L3 and/or kidneys.
- No IV or oral contrasts are used.

**PET/CT simulation**

- Images acquisition is done as per PET/CT department protocol.
- Images are printed and transferred to viewing station on CD if Digital Imaging and Communication in Medicine (DICOM) is not active.

### 7.1.5 Target Definition:

Because of the difficulty in determining tumour margins, radiologist and radiation oncologist should consult closely to delineate from scans the GTV.

***7.1.5.1 GTV should include:*** the primary disease (GTV-P) and any enlarged regional lymph nodes of >1.5 cm (GTV-N).

For post operative cases it is determined by the preoperative CT/MRI and determine the initial extent of disease and compare the preoperative films with the postoperative location of clips. Delineate the preoperative gross tumor volume.

***7.1.5.2 CTV*** should include GTV, gall bladder fossa, adjacent liver and regional nodal areas. Delineate the nodes which have traditionally been included in adjuvant field design: porta hepatis, periocholedochal, celiac, and pancreaticoduodenal.

***7.1.5.3 PTV:*** Ideally it should be determined by determining the amount of respiratory movement with 4D CT if available. If not, take patient to fluoroscopy and determine the image motion of clips. The usaual practice is CTV margins are expanded isotropicaly to take account of organ movement with respiration or gut motion, as well as set-up variations with:

- 8 mm in the AP direction
- 9 mm in the transverse plane
- 20 mm cranio-caudally

LN stations and margins is adopted from the RTOG guidelines.

7.1.5.4 Organ at risk OAR:

- OAR include the spinal cord, kidneys, liver and small bowel. Dose-limiting small bowel tolerance is reflected in the recommended dose-fractionation.
- These OAR should be outlined on all slices for DVH assessment.
- A PRV may be added, but in the transverse plane compromise may be needed to maintain these dose limits to OAR.

### *7.1.6* TECHNIQUE:

The above protocoal applied only to 3D conformal radiotherapy, if patient to be treated with IMRT, the dedicated IMRT protocoal should be applied. Currently IMRT is not practiced in referral center for gall baldder cancer.

### 7.1.7 Beam Arrangement

#### *7.1.7.1 Conventional*

Palliative therapy given in 5 or 10 fractions can be defined in the simulator as above. Anterior and posterior photon beams are used with dose prescribed to the midplane. MLC shielding may reduce the dose to organs at risk; 6MV photons are adequate unless the separation at the centre is more than 28 cm, in which case a higher energy (e.g. 10 MV) is needed.

#### 7.1.7.2 *Conformal*

Beam angles are chosen to reduce lung, heart and cardiac dose with anterior oblique, posterior oblique and lateral beams often used. Wedges compensate for the obliquity of the beams in relation to the chest wall, and MLC shielding is used to conform each beam shape to the PTV. CT forward planning with volumes shaped with MLC is be used to minimise dose to kidneys, liver, spinal cord and small bowel.

7.1.7.3 IMRT and IORT:

Are not used in referral center currently.

**7.1.8 Beam energies:** Using 6–10MV photons, **above 10 MV should be avoided because secondary electrons have a** greater range in lung tissue so higher energy photon beams have a wider penumbra.

### 7.1.4 Dose prescription and fractionation

#### *7.1.4.1* Adjuvant radiotherapy:

50.4 Gy/ 28 Fr in 5 ½ week concurrent with 5 FU.

#### *7.1.4.2* Radical (in combination with chemotherapy with gemcitabine or 5FU)

45–50.4 Gy in 25–28 fractions of 1.8 Gy given in 5–5½ weeks.
A boost to a reduced field of 5.4–9.0 Gy ca be used.

7.1.9.3 Palliative radiotherapy:

30 Gy in 10 daily fractions of 3 Gy given in 2 weeks.
OR 20 Gy in 5 daily fractions of 4 Gy given in 1 week

### 7.1.10 Organs at risk (OAR)

*Small bowel:*

- No more than 250 cc should receive 45 Gy

*Both kidneys:*

- TD5/5 for the whole kidney is 23 Gy.
- Dose to two-thirds of one kidney (and ideally both) should be below 20 Gy.

- As per QUANTEC recommendation, kidly refer to gastric protocol.

*Liver:*

- If the whole liver is irradiated, dose should be < 30 Gy to avoid radiation hepatitis.
- V30 should be below 60%

*Spinal cord:*

- Dose to any part of the cord should be less than 46 Gy.
- If more than 15 cm length of cord is treated, the dose to any part of the cord should be less than 44 Gy.
- A small part (< 1 cm3) may receive up to 50 Gy
- For palliative or simple low dose treatments, AP/PA beams may give a satisfactory dose distribution, or a plan with an anterior and two lateral wedged beams may be used.

#### *7.1.11 Verification and weekly review in OPD for treatment toxicity*

- The treatment isocentre on a DRR from the CT simulation is compared with portal images of the isocentre on the treatment machines using electronic portal imaging.
- Off-line correction protocols are used for standard conformal treatment.
- Images are taken on days 1–3 and weekly thereafter with a correction made if the mean error in any one plane is _5 mm.

### 7.2 BRACHYTHERAPY:

**Not Applicable**

### 7.3 Sequlea of treatment:

**Kindly refer to pancreatic cancer protocol.**

## 8. PRINCIPLES OF HORMONAL TREATMENT:

Not Applicable

## 9. PRINCIPLES OF CHEMOTHERAPY:

9.1 Definitive treatment with radiotherapy
9.2 Preoperative treatment
9.3 Adjvunt therapy.

Gemcitabine or 5-FU can be given according to concomitant chemotherapy protocol. Antiemetics and other supportive medications should be given during radiation.

## 10. MANAGEMENT OF RECURRENT OR RELAPSE:

10.1 Palliative **chemoradiation** if no radiotherapy given before and pain or bleeding are intractable.
10.2 Palliative **chemotherapy** in cases of distant metastasis or local recurrence previously received radiation.
10.3 Stenting if jaundice developed.

10.4 Best supportive care is an option in patients with poor performance status

## 11. FOLLOW UP:

**11.1** During treatment :

- For patients receiving chemotherapy arrange for CBC weekly, RFT and LFT every other week.
- High calorie supplement drinks are useful to maintain adequate oral intake.
- Patients should be weighed and assessed weekly throughout treatment and should be given prophylactic antiemetics (5-HT antagonist) if required.
- Many patients experience grade 3 or 4 toxicity and nausea, lethargy and haematological effects are common
- On treatment investigations Weekly review in OPD for treatment toxicity: Patients should be reviewed weekly so that acute side effects are treated proactively.

11.1 History and clinical examination every 3 months for the first 2 years then 6 monthly for next 3 years, then annually.
11.2 Tumor markers every visit CEA and CA 19.9
11.3 Abdomenal CT every 6 months or annually
11.4 Bone scan, PET/CT, CT chest requested only if needed on clinical suspicion.

## 12. ONGOING DEPARTMENTAL STUDIES:

Not Applicable

## 13. References:

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# C.8- NON MELANOMA SKIN CANCER CLINICAL MANAGEMENT GUIDELINES

## 1. EPIDEMIOLOGY:

Most of the epidemiological studies focused on white populations in Europe, the U.S.A. and Australia; however, limited data were available for other skin types in regions such as Africa. Worldwide the incidence for NMSC varies widely with the highest rates in Australia [>1000/100, 000 person-years for basal cell carcinoma (BCC)] and the lowest rates in parts of Africa (< 1/100, 000 person-years for BCC).
In GCC States, it is very rare disease and so in Kuwait with ASR 0.5 per 100,000 population.

## 2. CLINICAL PRESENTATION

**2.1** Painless skin lesion
**2.2** Ulcerative or bleeding lesion
**2.3** Regional Lymphnode enlargement.

## 3. DIAGNOSIS WORKUP:

**3.1** History, complete skin examination and regional LN examination
**3.2** Biopsy: If more than superficial lesion, inclusion of deep reticular dermis preferred
**3.3** FNAC of clinicaly palpable LN or seen by imaging studies
**3.4** Imaging studies: indicated for suspicion of extensive disease include deep structure involvement such as bone, perineural or LV invasion. If large nerve is suspected, MRI can be considered to evaluate the extent and R/O skull involvement.
**3.5** Palpable regional or abnormal LN identified by imaging studies
**3.6** Basal cell carcinoma (BCC) rarely metastasizes, thus, a metastatic work-up is usually not necessary

## 4. STAGING:

The 7th edition, 2010 of the American Joint Committee on Cancer's (AJCC) *Cancer Staging Manual and TNM staging* is used.

## 5. PROGNOSTIC FACTORS:

5.1 Tumour size and nodal invovment are the most important prognostic factors, excised tumours have survival exceeds 90%.
5.2 For melanoma: Depth of invasion, narrow safe margins less than 2 cm and nodal involvement considered poor prognostic factors.

# 6. TREATMENT:

## 6.1. Treatment for Basal Cell Carcinoma of the Skin

### 6.1.1. Primary treatment of low risk BCC of the skin

- Curettage and electrodesiccation; in non hair bearing area, if fate reached surgical excision should be performed, then follow up
- Excision with post surgical margin assessment (POMA).
- If lesion can be excised with margin 4 mm and secondary intension, side to side repair, or skin graft.
- If positive margin: MOH or resection with CCPDMA, re-excision with POMA for area L region (Trunk and extremities), or RT (reserved for patient over 60 y for long term sequelae)
- If Negative margin: Follow up
- Non surgical candidate: Radiotherapy

### 6.1.2. Primary treatment of high risk BCC of the skin

- Excision with POMA: Lesion > or = 20 mm in area L with no other high risk factors, if can be excised with 10 mm clinical marginsand primary repair.
  - Positive margin →Mohs or resection with CCPDMA or RT
- Or MOHS or resection with CCPDMA
  - Positive margin→RT
  - Negative margin →if extensive perineural or large nerve involvement recommended adjuvant RT
- Or RT for non surgical candidates.
  - In all cases of BSC If residual disease is present and surgery and RT are contraindicated consider MD tumor board's consultation and combination chemotherapy Cisplatin or carboplatin.

### 6.1.3 Radiation therapy

#### 6.1.3.1 Indications

- Radiation therapy is particularly useful in the management of patients with primary lesions that would otherwise require difficult or extensive surgery (e.g., nose or ears).
- Radiation therapy eliminates the need for skin grafting when surgery would result in an extensive defect. Cosmetic results are generally good, with a small amount of hypopigmentation or telangiectasia in the treatment port.

- Radiation therapy can also be used for lesions that recur after a primary surgical approach.

**6.1.3.2 Contra-indications.**

Radiation therapy is avoided in patients with conditions that predispose them to radiation-induced cancers, such as:

- Xeroderma pigmentosum or
- Basal cell nevus syndrome, and
- Scleroderma.

### 6.1.4 Imiquimod topical therapy

Imiquimod is available as a 5% cream and is used in schedules ranging from twice weekly to twice daily over 5 to 15 weeks. Most of the experience is limited to case series of BCCs that are less than 2 $cm^2$ in area and that are not in high-risk locations (i.e., within 1 cm of the hairline, eyes, nose, mouth, ear; or in the anogenital, hand, or foot regions).
Although imiquimod is an FDA-approved treatment for superficial BCCs, it can be given it for patients with small lesions in low-risk sites who cannot undergo treatment with more established therapies.

## 6.2 Treatment of Squamous Cell Carcinoma of the Skin

### 6.2.1. Treatment for localized, low risk Squamous Cell Carcinoma

- **Surgical excision with margin evaluation**
  - Excision is probably the most common therapy for SCC. This traditional surgical treatment usually relies on surgical margins ranging from 4 mm to 10 mm, depending on the diameter of the tumor and degree of differentiation.
  - Wider margins of 6 mm to 10 mm were needed for larger or less-differentiated tumors or tumors in high-risk locations (e.g., scalp, ears, eyelids, nose, and lips).
  - Re-excision may be required if the surgical margin is found to be inadequate on permanent sectioning.

- **Mohs micrographic surgery**
  - Mohs micrographic surgery is a specialized technique used to achieve the narrowest margins necessary to avoid tumor recurrence, while maximally preserving cosmesis. This surgery is best suited to the management of tumors in cosmetically sensitive areas or for tumors that have recurred after initial excision (e.g., eyelid periorbital area, nasolabial fold, nose-cheek angle, posterior cheek sulcus, pinna, ear canal, forehead, scalp, fingers, and genitalia).
  - Mohs micrographic surgery is also often used to treat high-risk tumors with poorly defined clinical borders or with perineural invasion.

- **Radiation therapy**

- Radiation therapy is a logical treatment choice, particularly for patients with primary lesions requiring difficult or extensive surgery (e.g., nose, lip, or ears).
- Radiation therapy eliminates the need for skin grafting when surgery would result in an extensive defect. Radiation therapy can also be used for lesions that recur after a primary surgical approach.
- Radiation therapy is avoided in patients with conditions that predispose them to radiation-induced cancers, such as xeroderma pigmentosum or basal cell nevus syndrome.
- Radiation therapy, is used for histologically proven clinical lymph node metastases with or without excision of the primary tumor.

### 6.2.2 Treatment of local high risk S C C

- Excision with POMA: lesion more than 20 mm in area L with no other high risk factors if can be excised with 10 mm clinical margin+ primary repair.
- If positive margin: MOH or resection with CCPDMA, or RT
- If Negative margin: Follow up
- MOH or resection with CCPDMA

- Positive margin : RT
- Negative margin: RT can be considered if extensive perineural or large nerve involvement.
- Non surgical candidate: Radiotherapy as pt > 60 years

### 6.2.3 Management of positive regional LN:

For patient with positive FNAC or imaging or suspicious LN should be surgically evaluated:

- Operable disease: Regional LN dissection
- Trunk and extremities: Consider RT if multiple involved LN or extensive ECE
- Head and Neck:
- Solitary node < 3cm: excision of the primary and ipsilateral selective neck dissection
- Solitary node > 3 cm or multiple ipsilateral LN: excision of the primary and ipsilateral comprehensive neck dissection
- Bilateral LN : excision of the primary and bilateral comprehensive neck dissection
- Parotid LN: superficial parotidectomy and ipsilateral neck dissection

### 6.2.4 Adjuvant treatment after neck dissection :

- One positive LN < or = 3 cm, no ECE→RT or FU
- More than or 2 LNor one LN > 3 cm, no ECE→RT
- Any LN with ECE, or incompletly excised nodal disease→RT and consider concurrent chemotherapy Cisplatin 100 mg/m2 every 3 weeks or weekly 30 mg/m2.

## 6.3. Treatment of Actinic Keratosis

### 6.3.1 Topical agents:

- Fluorouracil (5-FU).

- Imiquimod cream.
- Diclofenac sodium 3% gel.
- Trichloroacetic acid.

**6.3.2** Cryosurgery.

**6.3.3** Curettage.

**6.3.4** Dermabrasion.

**6.3.5** Shave excision.

**6.3.6** Photodynamic therapy.

**6.3.7** Carbon dioxide laser.

## 6.4 LOCALLY ADVANCED UNRESECTABLE (or metastatic)

### 6.4.1 Treatment for Metastatic Basal Cell Carcinoma (or Advanced Disease Untreatable by Local Modalities)

- Cisplatin, alone or in combination with other drugs, is the most commonly reported systemic therapy and appears to be associated with the best tumor-response rates.Other including cyclophosphamide, vinblastine, 5-FU, methotrexate, and doxorubicin can be used.
- Because BCCs often exhibit constitutive activation of the Hedgehog/PTCH1-signaling pathway, an orally administered Hedgehog pathway inhibitor (GDC-0449) has produced objective responses in patients with advanced or metastatic sporadic BCC.

### 6.4.2 Treatment for Metastatic Squamous Cell Carcinoma (or Advanced Disease Untreatable by Local Modalities)

- As is the case with BCC, metastatic and far-advanced SCC is unusual, and reports of systemic therapy are limited to case reports and very small case series with tumor response as the endpoint
- Cisplatin-based regimens appear to be associated with high initial tumor response rates.
- High response rates have also been reported with the use of 13-cis-retinoic acid plus interferon-alpha-2a.

# 7. RADIOTHERAPY PROTOCOL:

## 7.1. External Beam Planning technique

### 7.1.1 Patient Preparation:

Counseling with the patient and family for technique, benefit and morbidity and consent form to be signed by both doctors and patients/ relatives.

### 7.1.2 Immobilization

- The patient is positioned supine, prone or semi-prone based on the tumor location so that the tumor to be treated can be accessed by the electron applicators.
- Head rests, pillows, sandbags and other supports are used to aid immobilization as necessary.
- If the patient requires a plan to treat an extensive tumour, immobilization will be similar to that for a head and neck cancer using a Perspex shell.

### 7.1.3 Orientation, set-up, marking and reference points

- Patient aligned with 3-plans laser beams.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points
- Marks are applied to the field borders and isocenter.

### 7.1.4 Image acquisition

- The majority of skin radiotherapy is based on clinical definition of the treatment volumes and the use of single electron beams field.
- In very advanced cases with deep infiltration, a CT-planned photon or electron treatment may be needed.
- CT examination will be performed on a four-detector spiral CT scanner (120 kV, 300 mAs) using a slice thickness of 3 mm.
- Scan range done according to tumor location and whether or not lymph nodes are involved

### 7.1.5 Target volume definition

#### *7.1.5.1 GTV*

- The GTV is defined clinically as described above and marked on the skin.

#### *7.1.5.2 CTV*

- The margin added to the GTV to create the CTV depends on the clinicopathological type, the site and size of the lesion being treated, and organs at risk.

#### *7.1.5.3 PTV*

- A further margin for set-up error is added to create the PTV. The field size is chosen to ensure the PTV receives 95 per cent of prescribed dose.
- This margin needs to be increased when electron therapy is used to allow for the shape of the isodoses. This will depend on the size of the lesion and the energy of the electron beam.
- For a 6 MeV electron beam treating a 5 cm circle, an extra 1 cm should be added to the margins above to define the field size with an electron applicator. i.e. Treatment field created by adding 1.5-2.5 cm to the lesion according to size of the lesion and depth of invasion

#### *7.1.5.4 OAR*

- The OAR should be outlined on all slices in cases with deep penetration which needs CT simulation

### 7.1.6 THE TECHNIQUE:

- Many specialized radiation therapy techniques are used to treat skin cancer, depending on the size, depth, and anatomic location of the lesion.
- Quality of radiation is selected based on the best ratio between surface dose and ideal treatment depth.
- Field size is determined by lesion size and histopathology.
- For superficial lesions a direct feield is used and determined clinically.
- Any bolus required is applied and the treatment applicator positioned over the target volume.
- Skin marks, tattoos if appropriate, and photographs of the planned treatment position are used to ensure the correct set-up each day.
- Scabs over lesions may need to be removed before treatment to ensure adequate depth dose.

### 7.1.7 Beam arrangement and Shielding

**Electron beam radiotherapy**

- Electron beams may be defined by an electron endplate cut-out inserted into the electron applicator or by shaped lead placed on the skin.
- 4 mm of lead is adequate for electrons up to 10 MeV.
- The lead shields for electrons need to be lined with wax or plastic on the inner surface to absorb secondary electrons.
- Internal eye contact lenses have been designed for use with electron beam therapy around the eye and are made of 3–4 mm lead with a 2–3 mm silicon lining depending on the electron energy used.
- Dose prescription and fractionation. The energy of the electron beam is chosen so that the deep surface of the target volume is encompassed by the 90 per cent isodose with a sharp fall in dose beyond to spare the underlying tissues.
- The effective treatment depth expressed in centimetres is about one-third of the beam energy in MeV but depends on the beam size and depth dose data for any particular machine.
- Bolus is placed on the skin surface to increase dose to 100 per cent and to compensate for irregular surfaces. This reduces the depth of the 90 per cent isodose which must be taken into account when choosing the electron energy.

### 7.1.8 BEAM ENERGY:

- The energy of the electron beam is chosen so that the deep surface of the target volume is encompassed by the 90 per cent isodose with a sharp fall in dose beyond. This spares the underlying tissues.
- The effective treatment depth expressed in centimetres is about one-third of the beam energy in MeV but depends on the beam size and depth dose data for any particularmachine.
- Bolus is placed on the skin surface to increase dose to 100 per cent and to compensate for irregular surfaces This reduces the depth of the 90 per cent isodose which must be taken into account when choosing the electron energy. A correction for any stand-off between the applicator and skin surface can be made using the inverse square law and effective SSD.

- Varying electron energy are used and vary with applicator size.

### 7.1.9 Dose prescription and fractionation

- **Lesions < 5 cm diameter**

  45 Gy in 9 fractions of 5 Gy given in 21 days treating on alternate week days.
  54 Gy in 20 fractions of 2.7 Gy given in 4 weeks.

- **Lesions > 5 cm diameter**

  54 Gy in 20 daily fractions of 2.7 Gy given in 4 weeks.
  66 Gy in 33 daily fractions given in 6 1⁄2 weeks.

- **Postoperative radiotherapy**

  50 y in 20 daily fractions of 2.5 Gy given in 4 weeks.
  60 Gy in 30 daily fractions given in 6 weeks.

- **Palliative radiotherapy**

  8 Gy in a single fraction.
  20 y in 5 daily fractions of 4 Gy given in 1 week.
  36 Gy in 6 fractions of 6 Gy once weekly given in 6 weeks (Consider increasing dose by 10 per cent to account for the reduced relative biological dose of electrons)

### 7.3.4 Dos limitation to OAR:

As per QUANTEC recommendation, OAR differ according to tumore anatomical site.

### 7.3.5 Verification:

For superficial lesions, plan is excecuted in the presence of assigned doctor to confirm proper tumore coverage and proper protection.

## 7.4 BRACHYTHEARPY

HDR brachytherapy
A typical fractionation is 45 Gy in 10 fractions. A more prolonged fractionation may be advisable in the lower limb. Not used currently in referral center.

7.5 Sequelae of treatment :

**7.3.1** Acute:

- Erythema, dry desquamation, or peeling, occurs at intermediate dose levels.
- Moist desquamation is expected at doses required to control skin cancers.
- The eradication of all basal cells of the epidermis results in exposure of the dermis and serous oozing from the surface. Epidermal regrowth occurs from the field periphery and from more resistant epithelial cells around hair follicles in the field.
- Management of acute radiation reactions includes avoidance of trauma to the skin, such as shaving, scratching, or sun exposure.
- The skin should be cleansed with mild soap and patted dry. Application of creams, cosmetics, or harsh cleansers, especially those containing alcohol, should be avoided.

- A mild steroid cream such as 1% hydrocortisone or 0.025% triamcinolone treats skin erythema and dry desquamation and relieves pruritis.
- Moist reactions may be treated with dilute hydrogen peroxide or 1% aqueous gentian violet to dry the lesion and prevent infection. Silver sulfadiazine 1% cream also is commonly used to treat moist desquamation and promote healing.
- The new skin formed after irradiation is thin and atrophic and easily injured by mechanical trauma, chemical or sun exposure, or reirradiation.

**7.3.2** Late :

- Capillaries are reduced in number and dilated, resulting in telangiectasia formation.
- Whereas irradiation initially may cause hyperpigmentation by melanocyte stimulation, cancerocidal doses result in permanent hypopigmentation from melanocyte destruction. Permanent hair loss is dose-dependent and usually follows radiation therapy for skin cancer.
- Deeper-penetrating, skin-sparing megavoltage irradiation often results in subcutaneous fibrosis.
- Sebaceous and sweat glands show decreased or absent function in the treated area after therapy for skin cancer.

## 8 PRINCIPLES OF HORMONAL TREATMENT :

Not Applicable

## 9 PRINCIPLES OF CHEMOTHERAPY:

Relatively active drugs that mostly used as single agents include:
- Cisplatin - cyclophosphamide - vinblastine - 5-FU - methotrexate - doxorubicin
BCCs: Hedgehog pathway inhibitor (GDC-0449) has produced objective responses in patients with advanced or metastatic sporadic BCC.

## 10 MANAGEMENT OF RECURRENT OR RELAPSE

### 10.1 Treatment for Recurrent Basal Cell Carcinoma of the Skin

Local recurrence: Mohs micrographic surgery is commonly used for local recurrences of BCC Regional or distant mets: MD tumor board consultation and combination chemotherapy with cisplatin or carboplatin.

### 10.2 Treatment for Recurrent Squamous Cell Carcinoma of the Skin

Recurrent nonmetastatic SCCs are considered high risk and are generally treated with excision, often using Mohs micrographic surgery. Radiation therapy is used for lesions that cannot be completely resected.

## 11 FOLLOW UP:

11.1 During treatment weekly assessment of response, and toxicities.

11.2 History and clinical examination including complete skin examination every 3-6 m for 2 years then every 6-12 months for 3 years then annually life for life include for the first 2 years then 6 monthly for next 3 years, then annually.

11.3 For patient with regional disease: History and clinical examination including complete skin examination every 1-3 m for 1 years then every 2-4 months for 1 years then 4-6m for 3 years then annually.

## 12. ONGOING TRIALS

Not Applicable

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# C.9- MALIGNANT MELANOMA OF SKIN CLINICAL MANAGEMENT GUIDELINES

## 1. EPIDEMIOLOGY:

Melanoma is a common cancer in Western countries with ASR of about 3.7 per 100,000 population. There is a marked geographical variation in incidence.
In GCC States, melanoma is a rare disease. ASR is around 0.3 per 100,000 population (ranking 16$^{th}$)
In Kuwait, only one case was diagnosed in 2012.

## 2. CLINICAL PRESENTATION

2.1 Suspisious pigmented skin lesion.
2.2 ulcerative or bleeding lesion
2.3 Regional Lymphnode enlargement.

## 3. DIAGNOSIS WORKUP:

**3.1** Complete history: It is recommended to record the presence or absence of risk factors including family or prior history of melanoma, atypical moles or dysplastic nevi, immunosuppressant, sun and environmental exposure.

**3.2** Complete skin examination and regional LN examination

**3.3** Complete blood count, liver and renal function tests are not recommended in early stages unless indicated symptoms or signs requiring blood tests. LDH is required for stage IV.

**3.4** Imaging studies: for stage I &II disease, CT, MRI, or PET scan CT s are only indicated to evaluate specific signs and symptoms.
For pathological stage III: consider imaging study for staging and to evaluate specific signs and symptoms.
For stage IV Melanoma: MRI Brain and PET/ CT scan are recommended as baseline imaging.

**3.5** Biopsy: preferably by local excision, should be performed for any suspicious lesions, and the specimens should be examined by an experienced dermatopathologist.

3.5.1 Location, Size, and depth of invasion.
3.5.2 Measurement of margin.
3.5.3 Berslow thickness and/or level of invasion of the melanoma.
3.5.5 Histologic subtype, pure dermatoplasia, Mitotic index, presence of tumour infiltrating lymphocytes, LVI, microscopic satellites, and ulceration or bleeding at the primary site.
3.5.4 Number of regional lymph nodes involved.
3.5.6 BRAF (V-raf murine sarcoma viral oncogene homolog B1) gene

## 4. STAGING

The 7th edition, 2010 of the American Joint Committee on Cancer's (AJCC) *AJCC Cancer Staging Manual and TNM staging* will be used

## 5. PROGNOSTIC FACTORS

1.1 Most powerful prognostic factor for recurrence and survival sentinel LN status.
1.2 Other prognostic factors: ulceration, thickness (Breslow = measured depth, Clark = related to histologic level of dermis), anatomic site (trunk worse), gender (male worse), age (young better), number of nodes.
1.3 Patients who are younger, female, and who have melanomas on the extremities generally have a better prognosis.

## 2. TREATMENT

Treatment modality According to stage and resectability of disease.

### 6.1 Treatment for Patients With Resectable Stage I, II Disease

**6.1.1 Surgical excision is the primary treatment:**

SLN biopsy followed by WLE and completion of regional LN dissection if SLN+.Minimum surgical margins:
Tis = 5 mm, T1 = 1 cm, T2–T4 = 2 cm;

6.1.2 **Adjuvant Treatment:**

**High-dose interferon.** High-dose interf eron alpha-2b can be used for the adjuvant treatment of patients with melanoma who have undergone a complete surgical resection but who are considered to be at a high risk of relapse.

**Radiotherapy**: can be given for nodal basin if multiple lymph nodes involved or extra capsular extension. Radiation therapy indication:

***Primary disease:*** Adjuvant treatment for selected patients with desmoplastic melanoma with narrow margins, recurrent disease, or extensive neutropism.

***-Regional disease:***

| | |
|---|---|
| Adjuvant: | Gross nodal ECE, > OR = 4 involved nodes,size of tumour within a node > or = 3 cm. Following resection of recurrent nodal disease |
| Palliative: | Unresectable nodal, satellite, or in-transit disease |

### 6.2 Treatment for Patients With Unresectable Stage III Disease

6.2.1 Ipilimumab.

6.2.2 Vemurafenib for patients who test positive for the *BRAF* V600 mutation.

6.2.3 Local therapy for extremity melanoma. For patients with in-transit and/or satellite lesions (stage IIIC) of the extremities, hyperthermic isolated limb perfusion (ILP) with melphalan (L-PAM) with or without tumor necrosis factor-alpha (TNF-alpha) has resulted in high tumor response rates and palliative benefit.

6.2.4 Intralesional injection: BCG or interferon alpha.
6.2.5 Local ablation therapy.
6.2.6 Topical Imiquimode for dermal lesion.
6.2.7 Consider palliative radiotherapy.

## 6.3 Stage IV and Recurrent Melanoma

### 6.3.1-Checkpoint inhibitors

- **Anti-CTLA-4: Ipilimumab**

**Previously treated patients**: stage IV disease, who were HLA-A*0201-positive patients.
**Previously untreated patients:** for metastatic disease but received adjuvant treatment ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m$^2$) at weeks 1, 4, 7, and 10 followed by dacarbazine alone every 3 weeks through week 22.

- **Anti-PD-1 and PD-L1**

Anti-PD-1 and PD-L1 are immune checkpoint inhibitors; however, they inhibit different targets than ipilimumab. Promising early data have supported testing anti-PD-1 against DTIC in a phase III trial.

### 6.3.2- IL-2

Response to high-dose IL-2 regimens generally ranges from 10% to 20%.
Approximately 4% to 6% of patients may obtain a durable complete remission and be long-term survivors.

### 6.3.3 Signal transduction inhibitors

Studies to date indicate that both BRAF and MEK (mitogen-activated ERK-[extracellular signal-regulated kinase] activating kinase) inhibitors can significantly impact the natural history of melanoma, although as single agents, they do not appear to provide a cure.

### 6.3.4 BRAF inhibitors

- **Vemurafenib** is an orally available, for patients with unresectable or metastatic melanoma that tests positive for the *BRAF* V600E mutation.
- **Vemurafenib** (960 mg orally twice daily) . The most common AEs with vemurafenib are cutaneous events, arthralgia, and fatigue.
- **Dabrafenib**: 150 mg orally twice a day or DTIC 1000 mg/m$^2$ IV every 3 weeks).

**6.3.5 MEK inhibitors:** Trametinib; 2 mg once daily

**6.3.6 Multikinase inhibitors:** Sorafenib

**6.3.7 KIT inhibitors.**

### 6.3.8 Chemotherapy

- The objective response rate to DTIC and the nitrosoureas, carmustine and lomustine, is approximately 10% to 20%.
- Temozolomide (TMZ),
- Other agents with modest, single-agent activity include vinca alkaloids, platinum compounds, and taxanes.

## 6.4 Palliative local therapy

- Melanoma metastatic to distant, lymph node-bearing areas may be palliated by regional lymphadenectomy.
- Isolated metastases to the lung, gastrointestinal tract, bone, or sometimes the brain, may be palliated by resection with occasional long-term survival.
- Although melanoma is a relatively radiation-resistant tumor, palliative radiation therapy may alleviate symptoms. High-dose-per-fraction schedules are sometimes used to overcome tumor resistance.

# 7. RADIOTHERAPY PROTOCOL

## 7.1. *External Beam Planning technique*

7.1.1 **Patient preparation:** counseling with the patient and family for technique, benefit and morbidity and consent form to be signed by both doctors and patients/ relatives.

### 7.1.2 Immobilization

- The patient is positioned supine, prone or semi-prone based on the tumor location so that the tumor to be treated can be accessed by the electron applicators.
- Head rests, pillows, sandbags and other supports are used to aid immobilization as necessary.
- If the patient requires a plan to treat an extensive tumour, immobilization will be similar to that for a head and neck cancer using a Perspex shell.

### 7.1.3 Orientation, set-up, marking and reference points

- Patient aligned with 3-plans laser beams.
- Permanent ink (or tattoo) is applied to the lateral and midline reference points
- Marks is applied to the field borders and isocenter.

### 7.1.4 Image acquisition

The majority of skin radiotherapy is based on clinical definition of the treatment volumes and the use of single electron beams field.

- In very advanced cases with deep infiltration, a CT-planned photon or electron treatment may be needed.

- CT examination will be performed on a four-detector spiral CT scanner (120 kV, 300 mAs) using a slice thickness of 2mm or 3 mm.
- Scan range done according to tumor location and whether or not lymph nodes are involved.

### 7.1.5 Target volume definition

#### *7.1.5.1 GTV*

- The GTV is defined clinically as described above and marked on the skin.

#### *7.1.5.2 CTV*

- The margin added to the GTV to create the CTV depends on the clinicopathological type, the site and size of the lesion being treated, and organs at risk.

#### *7.1.5.3 PTV*

- A further margin for set-up error is added to create the PTV. The field size is chosen to ensure the PTV receives 95 per cent of prescribed dose.
- This margin needs to be increased when electron therapy is used to allow for the shape of the isodoses. This will depend on the size of the lesion and the energy of the electron beam.
- For a 6 MeV electron beam treating a 5 cm circle, an extra 1 cm should be added to the margins above to define the field size with an electron applicator. i.e. Treatment field created by adding 1.5-2.5 cm to the lesion according to size of the lesion and depth of invasion

#### *7.1.5.4 OAR:*

- The OAR should be outlined on all slices in cases .

### 7.1.6 Technique:

Adjuvant treatment of the primary tumor bed employs 2- to 4-cm margins using electron beam with appropriate bolus. Irradiation for a head and neck primary consists of comprehensive electron beam coverage of the primary site and ipsilateral neck, including supraclavicular nodes. Electron energies are determined by CT-guided treatment planning and appropriate bolus employed for prescription to $D_{max}$ with field junctions moved twice during treatment. Axillary nodal irradiation includes ipsilateral low cervical, supraclavicular, and axillary levels I through III with shaped anterior and posterior fields containing wedges or compensating filters. Inguinal lymph node treatment is delivered to involved nodes only, without prophylaxis of external or common iliac nodes, in an attempt to avoid late lymphedema.

### 7.1.7 Beam arrangement and Shielding

**Electron beam radiotherapy**

- Electron beams may be defined by an electron endplate cut-out inserted into the electron applicator or by shaped lead placed on the skin.
- 4 mm of lead is adequate for electrons up to 10 MeV.
- The lead shields for electrons need to be lined with wax or plastic on the inner surface to absorb secondary electrons.
- Internal eye contact lenses have been designed for use with electron beam therapy around the eye and are made of 3–4 mm lead with a 2–3 mm silicon lining depending on the electron energy used.

### 7.1.8 Beam Energies:

- Electron beam with different energies according to the thickness of the lesion.
- Photon beam is used for deep lesion as in palliative cases.

### 7.1.9 Dose prescription and fractionation

- The energy of the electron beam is chosen so that the deep surface of the target volume is encompassed by the 90 per cent isodose with a sharp fall in dose beyond to spare the underlying tissues.
- The effective treatment depth expressed in centimetres is about one-third of the beam energy in MeV but depends on the beam size and depth dose data for any particular machine.
- Bolus is placed on the skin surface to increase dose to 100 per cent and to compensate for irregular surfaces. This reduces the depth of the 90 per cent isodose which must be taken into account when choosing the electron energy.

### 7.1.10 Dose prescription and fractionation

**Elective/adjuvant RT dose**:

50 Gy /25 fraction.

Or 6 Gy/fraction to 30 Gy delivered twice weekly.

**If microscopic residual disease is present**:

an additional boost fraction is given for total dose of 36 Gy.

**Palliative radiotherapy**

**20 Gy in 5 daily fractions.**

**30 Gy in 10 fractions .**

### 7.1.11 Verification and weekly review in OPD

*For response/treatment toxicity scored according to RTOG toxicity scoring.*

## 8. HORMONAL TREATMENT

Not Applicable

## 9. PRINCIPLES OF CHEMOTHERAPY REGIMENS

### 9.1 Stage II as adjuvant –

A high-dose regimen of interferon alpha-2b (20 mU/$m^2$ of body surface per day given intravenously for 5 days a week every week for 4 weeks, then 10 mU/$m^2$ of body surface per day given subcutaneously 3 times a week every week for 48 weeks)

### 9.2 Stage IV

Dacarbazine, Temozolomide. based combination.Paclitaxel. Paclitaxel/ carboplatin.

## 10. MANAGEMENT OF RECURRENT OR RELAPSE

10.1 Local tumor recurrence: re-excision of tumor site with proper margin +/- lymphatic mapping according to the thickness.

10.2 Local, satellite and or in –transite recurrence: local therapy as mentioned above.

10.3 Nodal recurrence

10.3.1 No previous dissection: LN dissection

10.3.2 Previous dissection:

Resectable: excision the recurrence, if no previous complete dissection: complete LND

Unresectable: systemic therapy or best supportive care

10.3.3 Metastatic disease: Brain metastasis

Stereotactic radio surgery and or whole brain radiation therapy either as adjuvant or as primary treatment

## 11. FOLLOW UP:

11.1 For stages IA-IIA every 3-12 m for 5 years then annually as clinically indicated.

11.2 For stages IIB-IV every 3-6 m for 2 years, then every 3-6 months for 3 years, then annually as clinically indicated.

11.3 Consider chest x ray, ct scan or PET scan every 3-12 m to screen for recurrence or metastasis. Consider brain MRI annually.

## 12. ONGOING DEPARTMENTAL STUDIES:

Not Applicable

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