PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

HEAD AND NECK

HYPOPHARYNX

Head & Neck Site Group – Hypopharynx

1. Introduction

- Squamous cell carcinoma (SCC) is the most common type of hypopharyngeal malignancy, and most occur in the 6^{th}-7^{th} decades of life
- Other histologies occur, but are rare; this guideline relates to SCC of the hypopharynx

2. Prevention

- Tobacco and alcohol are the main risk factors for hypopharyngeal SCC
  - Studies from India have shown an association between chewing tobacco and hypopharyngeal SCC
  - Effect of alcohol is stronger, and the effect of smoking is weaker, relative to laryngeal SCC risk factors
- Avoidance of tobacco and reduction in alcohol intake could prevent most hypopharyngeal SCC

3. Screening and Early Detection

- There is at present no proven role for screening / early detection in improving outcomes from hypopharyngeal malignancy

4. Diagnosis / Initial Assessment

All patients should be assessed prior to treatment intervention, by the multidisciplinary Head & Neck Team

History and Physical evaluation:

- Record height, weight and ECOG performance status
- History and Physical examination including mucosal survey for synchronous primaries
  - Direct fibreoptic nasolaryngoscopy
  - Record smoking and alcohol history
    - smoking
      - Non-smoker / Current / ex-smoker
      - pack years
    - alcohol history in standard drinks/week;
- None / Light <10 drink/wk/ Mod 10-20 / Heavy >20Specify location of primary including dimensions and involvement of anatomic subsites:
  - Pyriform
  - Post-cricoid
  - Posterior pharyngeal wall
- Documentation of specific nodal level(s) involved
  - Size and extent of nodal involvement (e.g. fixed/mobile)

Investigations (Baseline):

- Panendoscopy or examination under anaesthesia if deemed necessary

- Biopsy
    - pathology review; molecular diagnostic testing (e.g. HPV status), if indicated
- CT scan Head and Neck
- CT thorax if indicated (e.g. node-positive disease, smoking history), or otherwise CXR
- Bloodwork: CBC, creatinine, electrolytes, liver function, glucose, coagulation studies (APTT, INR)
- Pregnancy test where indicated
- Other staging investigations as clinically indicated (bone scan etc)

5. Pathology

- SCC is the most common histopathology
    - graded as well, moderately or poorly-differentiated
- Pathology reporting (for surgical specimens) should follow a standard format for hypopharynx carcinoma, and include the following SYNOPTIC DATA, as per College of American Pathologists 2011 cancer protocols (see www.cap.org for full detail):
    - Specimen:
    - Procedure:
    - Unopened Specimen Size:
        - Greatest dimension:
        - Additional dimension(s):
    - Tumor Laterality:
    - Site:
        - Additional Sites Involved by Tumor:
        - Tumor Focality:
    - Histologic Type:
        - Histologic Grade:
    - Tumor Size:
        - Additional dimension(s):
    - Margins:
        - Margin status (invasive)
            - Distance of tumor from closest margin:
            - Margin(s):
        - Margin status for carcinoma in situ:
    - Lymph-Vascular Invasion:
    - Perineural Invasion:
    - Lymph Nodes:
        - Number of regional lymph nodes examined:
        - Number of regional lymph nodes involved:
        - Size (greatest dimension) of the largest positive lymph node:
        - Extranodal Extension:
    - TNM Descriptors:
        - Primary Tumor (pT):

- Nodes (pN):
- Distant Metastasis (pM):

6. Management

Overall Management Approach

- These guidelines apply to patients with SCC of the hypopharynx
- Laryngeal/pharyngeal function preservation using a radical radiotherapy approach +/ surgery for the neck as required
- All patients should be assessed for inclusion on available current trial protocols and, if eligible and appropriate, offered inclusion on trial

Clinical TanyNanyM0, if resectable:

<u>TREATMENT: ALL HYPOPHARYNX SITES</u>

<u>T1/2 N0/N1</u>

- **Radical Radiotherapy**
  - 70 Gy in 35 fractions, over 6 weeks DAHANCA schedule (6 fractions/wk)

<u>Any T, N2/3; M0</u>

Treatment Options:
Concurrent chemo-radiotherapy preferred
Altered fractionation radiotherapy for selected cases (e.g. unfit for chemoRx)

- **Standard chemo-radiotherapy**: 70 Gy in 35 fractions, over 7 weeks (5 fractions/wk) + concurrent cisplatin (100mg/m2, wks 1, 4, 7 of radiotherapy)

  OR

- **Standard radiotherapy + molecular-targeted agent:** 70Gy in 35 fractions, DAHANCA schedule over 6 weeks (6 fractions/wk)
  + concurrent cetuximab Rx (loading dose week prior to commencing RT, then weekly during RT)

  OR

- **HARDWINS accelerated radiotherapy alone:** 64Gy in 40 fractions, over 4 weeks (bid, 10 fractions/week)

OR

- **DAHANCA schedule** 70 Gy in 35 fractions, over 6 weeks (6 fractions/wk), for pts not fit for above options

T3/T4, any N0/1, M0

Treatment options:
Altered fractionation radiotherapy preferred
Concurrent chemo-radiotherapy for selected cases

- **HARDWINS accelerated radiotherapy alone:** 64Gy in 40 fractions, over 4 weeks (bid, 10 fractions/week)

  OR

- **Standard chemo-radiotherapy**: 70 Gy in 35 fractions, over 7 weeks (5 fractions/wk) + concurrent cisplatin (100mg/m2, wks 1, 4, 7 of radiotherapy)

  OR

- **Standard radiotherapy + molecular-targeted agent:** 70Gy in 35 fractions, DAHANCA schedule over 6 weeks (6 fractions/wk)
  + concurrent cetuximab (400mg/m^2 loading dose week prior to radiotherapy, then 250mg/m weekly concurrent with radiotherapy)

Standard Post-Operative Radiotherapy - Adjuvant (any hypopharynx site)

- Consider adjuvant radiotherapy for the following:
  - Primary site:
    - T3-T4
    - Microscopic margins <5mm (irrespective of intra-operative revision or additional post-resection sampling of the surgical site)
    - >1 additional features at primary:
      - High-grade disease
      - Peri-neural invasion (PNI)
      - Lymph-vascular invasion (LVSI)
  - Neck
    - Lymph node involvement at pathology:
      - ≥2 lymph nodes
      - Any lymph node >3 cm (N2+)
      - Level IV-V lymph node positive
      - Extracapsular extension (ECE)

        - If number of sampled nodes <10, consider risk of neck involvement based on primary risk features including:
            - Tumor thickness (>5mm)
            - LVSI
            - PNI
            - Tumor size

- Chemo-radiotherapy for
    - Positive margins (inked margin)
    - extracapsular extension (ECE)

Patients not suitable for radical treatment

Refer to separate guideline: Palliative Management of Patients with H&N malignancy (***SECTION 12***)

6.1 Surgery

- Initial treatment (no prior treatment administered)
    - Primary site & neck
        - hypopharynx
            - T1 – T3: organ preservation strategies
                - N0: elective neck treatment
                - N+: definitive neck treatment
            - T4a: total laryngectomy and bilateral neck dissections (levels II – IV, VI)
                - +/- primary tracheoesophageal puncture
                - Fasciocutaneous microvascular free tissue transfer vs pectoralis major myocutaneous flap if insufficient mucosa for closure of neopharynx
                - Adjuvant radiotherapy or chemoradiotherapy where appropriate
                - In selected low volume T4a disease and residual laryngeal function, consideration of laryngeal preservation protocol
            - T4b: tracheostomy for airway control, otherwise inoperable
                - Consider organ preservation strategy in select patients
- Salvage treatment (recurrence or persistence following treatment)
    - Primary site
        - All subsites and stages of recurrence (except T4b)
            - Salvage total laryngectomy and bilateral neck dissections (levels II – IV, VI)

- Fasciocutaneous microvascular free tissue transfer vs pectoralis major myocutaneous flap if insufficient mucosa for closure of neopharynx or poor quality of native tissue
- In *chemo*radiation failure, strongly consider vascularized soft tissue reconstruction for augmentation in the majority of patients

- Neck
  - Following non-surgical treatment of neck:
    - Definition: persistent neck mass 3 months after completion of treatment and size ≥ 1.5 cm on MRI or CT imaging
    - Salvage selective neck dissection based on extent of initial tumor disease and residual tumor volume

6.2 Chemotherapy

- Used in the setting of primary chemo-radiotherapy for the indications listed above (*Overall Management, SECTION 5*)
- For post-operative treatment, for the indications listed above (positive margin, or extracapsular nodal extension)

- CONCURRENT CHEMO-RADIOTHERAPY:
  - DEFINITIVE:
    - Cisplatin 100mg/m^2 , concurrent with weeks 1, 4, 7 of radiotherapy
  - POST-OPERATIVE:
    - Cisplatin 100mg/m^2 , concurrent with weeks 1, 4 of radiotherapy

  - SETTING:
    - Overnight admission in inpatient chemotherapy suite
  - Pre-treatment Assessment:
    - Bloodwork: CBC, lytes, creatinine, liver function
  - Pre-Medication / Hydration
    - Anti-emetics:
      - granisetron 1 mg IV q24hrs day 1,2
      - dexamethasone 10 mg IV day 1, then 2 mg IV day 2 (AM)
      - aprepitant 125 mg PO day 1, 80 mg PO day 2
      - prochlorperazine 10 mg IV/PO q6hrs prn
    - Hydration with
      - 1000 mL Normal Saline (0.9%) + Potassium Chloride 20mEq + magnesium sulfate 2g IV over 2 hr, pre-cisplatin

  - CHEMO: CISPLATIN 100mg/m^2 IV in 1000mL normal saline, with mannitol 20g over 2 hrs
  - Post-chemo supportive care:
    - 1000mL Normal Saline (0.9%) over 4 hours post-cisplatin, then decrease to 30 mL/hr until discharge

        - Anti-emetics on discharge on day 2:
            - ondansetron 24 mg po q24hrs day 3,4
            - dexamethasone 2 mg PO bid starting day 2 (PM) x 5 doses (i.e day 2-4)
            - aprepitant 80 mg PO day 3
            - prochlorperazine 10 mg IV/PO q6hrs prn
    - dose reduction / delay of chemotherapy dose should be considered for:
        - Cytopenia
            - Absolute neutrophil count (ANC)
                - 1-1.4 x 10e9/L: consider delay for 1 week, or 75% dose reduction
                - <1.0 x 10e9/L: delay cycle, and recheck bloodwork 1 week
        - Renal impairment
            - >60 ml/min: 100% dose; 45-59 ml/min: consider 50-75% dose; <45 ml/min omit cisplatin
        - Weight loss: less than 10% from baseline: 100% dose; > 10% loss: consider 75% dose, or discontinuation at physician's discretion
        - Neurotoxicity and Ototoxicity: Dose modification or discontinuation may be required
    - Other precautions:
        - Potential mutagen: Women of childbearing age must practice an appropriate form of contraception while being treated.
        - Neutropenia: fever of other evidence of infection should be investigated promptly and treated aggressively
        - Hepatitis B: For patients who are Hepatitis B surface antigen positive, consider anti-viral prophylaxis and lower dose of dexamethasone to lower the risk of viral reactivation

- CONCURRENT RADIOTHERAPY + TARGETED THERAPY
    - Cetuximab 400mg/m^2 loading dose week prior to radiotherapy, then 250mg/m^2 weekly concurrent with radiotherapy
    - SETTING:
        - outpatient chemotherapy suite
    - Pre-treatment Assessment:
        - Bloodwork: CBC, lytes, creatinine, liver function
        - Vital signs
    - Pre-Medication / Hydration
        - Diphenhydramine 50mg IV, 30-60 mins prior to each dose
        - Dexamethasone 10mg IV, 30-60 mins prior to each dose

    - CETUXIMAB
        - supportive care:
            - Allergic/Anaphylactic reaction:

        - Grade 1: decrease infusion rate to 50%
        - Grade 2: hold cetuximab, administer bronchodilators/antihistamine/corticosteroid as indicated; once resolved to grade 1 or less, resume at 50% infusion rate for the first occurrence. If second occurrence, discontinue cetuximab
        - Grade 3 or 4: stop cetuximab; administer epinephrine/bronchodilators/antihistamine/corticosteroid/O2/IV fluids/vasopressors as indicated; discontinue cetuximab
    - SKINCARE:
        - For management of rash, there is no evidence based recommendation.
        - Consideration can be given to clindamycin 2% and hydrocortisone 1% to be applied topically tid prn.
        - Severe rash (e.g. grade 3 rash) can be managed with dose delay 1-2 weeks and/or adding minocycline 100 mg PO bid.
        - Consideration can be given to treat patients prophylactically with minocycline 100 mg po bid.

- OTHER CHEMOTHERAPY TREATMENT OPTIONS: CONCURRENT RADIOTHERAPY and WEEKLY CISPLATIN
    - Consider for patients not suitable for high-dose cisplatin
    - SETTING:
        - Out-patient chemotherapy suite
    - Pre-treatment Assessment:
        - Bloodwork: CBC, lytes, creatinine, liver function
    - Pre-Medication / Hydration
        - Anti-emetics:
            - dexamethasone 8mg PO or IV
            - granisetron 1mg IV
    - CHEMO:
        - CISPLATIN 40 mg/m^2 IV in 500 cc normal saline, over 1 hrs
    - Post-chemo supportive care:
        - Hydration 500 cc normal saline over 30-60 minutes
        - Granisetron 2 mg PO day 2
        - Dexamethasone 8mg BID PO days 2-3
        - Prochlorperazine 10mg Q6H PRN
    - dose reduction / delay of chemotherapy dose should be considered for:
        - Cytopenia
            - Absolute neutrophil count (ANC)
                - 1-1.4 x 10e9/L: consider delay for 1 week, or 75% dose reduction
                - <1.0 x 10e9/L: delay cycle and recheck bloodwork 1 week

        - Renal impairment
            - Creatinine clearance >60 ml/min: 100% dose; 45-59 ml/min: consider 50-75% dose; <45 ml/min omit cisplatin
        - Weight loss: less than 10% from baseline: 100% dose; > 10% loss: consider 75% dose or discontinuation at physician's discretion
        - Neurotoxicity and Ototoxicity: Dose modification or discontinuation may be required
    - Other precautions:
        - Potential mutagen: Women of childbearing age must practice an appropriate form of contraception while being treated.
        - Neutropenia: fever of other evidence of infection should be investigated promptly and treated aggressively

6.3 Radiation Therapy

Pre-Treatment Assessment

- Dental assessment
- Nutritional assessment and consultation (pre-treatment, or during first weeks of treatment)
- Prophylactic feeding G-J tube
    - All patients receiving chemo-radiotherapy or accelerated fractionation schedules should be considered
    - Patients with existing nutritional impairment (due to swallowing dysfunction etc), planned for radical treatment
- Pharyngeal function assessment (speech/swallow) if indicated
- Audiology
    - Pts receiving platinum-type chemotherapy
    - Pts receiving high-dose adjacent to auditory apparatus
- Medical Oncology assessment (in patients potentially eligible for chemotherapy)
- Ophthalmology consult as needed
- Written consent to be obtained prior to simulation
- Pre-radiotherapy review: patients are reviewed by the radiation oncologist in the week prior to commencing treatment for assessment and to review the treatment plan

CONTOURING:

- DEFINITION / DELINEATION of TARGETS:
    - PRIMARY
        - GTV: Gross disease
        - CTV:

- High-dose GTV + 0.3cm (may be expanded to 0.5cm where there is uncertainty regarding disease extent)
- Low-dose GTV + 1.0cm

▪ PTV = CTV + 0.5cm

○ NECK:

▪ GTV(s)

▪ CTV

- High-dose: GTV (nodes) + 0.5cm
  - Standard dose / fractionation 70Gy
  - HARDWINS 64Gy
- Intermediate-dose (indeterminate lymph nodes < 1cm)
  - Standard dose / fractionation 63Gy
  - HARDWINS 56Gy
- Low-dose (elective neck, levels 2-4)
  - Standard dose / fractionation 56Gy
  - HARDWINS 46Gy

▪ PTV = CTV + 0.5cm

TREATMENT

- CLINICAL CARE DURING RADIOTHERAPY:
  - Pts shall be reviewed by the RO at least weekly during RT
  - ASSESSMENT:
    - acute toxicities (RTOG criteria) documented in MOSAIQ
    - Weight and nutritional review (weekly nutritional rv for pts with G-tube, or as clinically indicated)
    - Bloodwork prior to each cycle of chemoRx, or as clinically indicated
  - Management of acute toxicities: refer to Nursing / Supportive Care guideline

6.4 Oncology Nursing Practice

Refer to Head and Neck Nursing Care

7. Supportive Care

7.1 Patient Education

Refer to general patient education practices

7.2 Dental Care

Refer to dental care for Head and Neck Cancers

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Refer to palliative management of Head and Neck Cancers

7.6 Speech Pathology

Refer to speech language pathology for Head and Neck Cancers

8. Follow-up Care

- Setting: Assessment in multidisciplinary clinic
- Schedule:
    - 2-6 weeks post radiotherapy
    - Q3 months or more frequent for two years
    - Q4 months or more frequent for third year
    - Q6 months or more frequent for years 4-5
    - Annually for years 6-10

- Investigations and assessment (follow-up):
    - Fibre-optic nasendoscopy
    - Imaging
        - CT head and neck at 10-12 weeks post-treatment
        - Other imaging as clinically indicated
    - Pharyngeal function (speech/swallow), if indicated
    - Dental assessment where applicable
    - Audiometry or ophthalmology where applicable

ASSESSMENT and MANAGEMENT of PERSISTENT / RECURRENT DISEASE (SALVAGE)

- Biopsy / histological confirmation
- Record site of failure (local, regional, distant)
- Date of failure/recurrence
- Determine site of recurrence relative to the initial target volume
- RE-STAGE
    - CT Head, neck, thorax
    - Other imaging as clinically indicated
- salvage options:
    - refer to NECK DISSECTION policy above (*Surgery, 6.1*) for management of suspected / confirmed persistent regional disease
    - RE-IRRADIATION: refer to guideline for re-treatment of pts with H&N malignancy for re-irradiation
        - RT volumes
        - Fractionation
        - Use of concurrent Rx